NOTES FROM THE ASSOCIATION OF MEDICAL SCHOOL PEDIATRIC DEPARTMENT CHAIRS, INC.

OPPORTUNITIES FOR SCHOLARLY ACTIVITIES DURING SUBSPECIALTY EDUCATION:
A SCORECARD FOR PEDIATRIC FELLOWSHIP PROGRAMS
George Lister, MD, and David K. Stevenson, MD, Dallas, Texas

EDITORIALS

MANY FACES OF PORTOPULMONARY HYPERTENSION
Michael J. Krowka, MD, Rochester, Minnesota

THE EVIDENCE MOUNTS AGAINST USE OF PURE OXYGEN IN NEWBORN RESUSCITATION
Nigel Paneth, MD, MPH, East Lansing, Michigan

WHERE SHOULD BABY BE PUT BACK TO SLEEP?
Bradley T. Thach, MD, St. Louis, Missouri

TREATMENT OPTIONS FOR SEVERE UPPER AIRWAY OBSTRUCTION IN PIERRE-ROBIN SEQUENCE
Ravindra G. Elluru, MD, PhD, Cincinnati, Ohio

MEDICAL PROGRESS

A CRITICAL APPRAISAL OF EVIDENCE SUPPORTING A BARIATRIC SURGICAL APPROACH TO WEIGHT MANAGEMENT FOR ADOLESCENTS
Thomas H. Inge, MD, PhD, Meg H. Zeller, PhD, M. Louise Lawson, PhD, and Stephen R. Daniels, MD, PhD, Cincinnati, Ohio

ORIGINAL ARTICLES

PORTOPULMONARY HYPERTENSION IN PEDIATRIC PATIENTS
Adria A. Condino, DO, D. Dunbar Ivy, MD, Judith A. O’Connor, MD, Michael R. Narkewicz, MD, Sarah Mengshol, MD, John R. Whitworth, MD, Lori Claussen, BSN, RN, Aimee Doran, RN, MSGPNP, and Ronald J. Sokol, MD, Denver, Colorado

50 YEARS AGO IN THE JOURNAL OF PEDIATRICS—A CLINICAL TRIAL OF ALEVAIRE IN PULMONARY DISTRESS OF THE NEWBORN INFANT
Alan H. Jobe, MD, PhD, Cincinnati, Ohio

CHILDHOOD CANCER FOLLOWING NEONATAL OXYGEN SUPPLEMENTATION
Logan G. Spector, PhD, Mark A. Klebanoff, MD, MPH, James H. Feusner, MD, Michael K. Georgieff, MD, and Julie A. Ross, PhD, Minneapolis, Minnesota, Rockville, Maryland, and Oakland, California
50 YEARS AGO IN THE JOURNAL OF PEDIATRICS—PEDIATRIC EVALUATION OF BRAIN-DAMAGED CHILDREN
Pasquale Accardo, MD, Richmond, Virginia

BEDSHARING, ROOMSHARING, AND SUDDEN INFANT DEATH SYNDROME IN SCOTLAND: A CASE-CONTROL STUDY
David Tappin, MD, MPH, Russell Ecob, Scrt Stat, MSc, and Hazel Brooke, MA, Yorkhill, Scotland

THE USE OF A BEDSIDE ASSAY FOR PLASMA B-TYPE NATRIURETIC PEPTIDE AS A BIOMARKER IN THE MANAGEMENT OF PATENT DUCTUS ARTERIOSUS IN PREMATURE NEONATES
Patrick A. Flynn, MD, Ralph L. da Graça, MD, Peter A. M. Auld, MD, Mirjana Nesin, MD, and Charles S. Kleinman, MD, New York, New York

CONTINUOUS FEEDING PROMOTES GASTROINTESTINAL TOLERANCE AND GROWTH IN VERY LOW BIRTH WEIGHT INFANTS
Ann Dsilna, RN, BASc, Kyllike Christensson, RNM, PhD, Lars Alfredsson, PhD, Hugo Lagercrantz, MD, PhD, and Mats Blennow, MD, PhD, Stockholm and Eskilstuna, Sweden

50 YEARS AGO IN THE JOURNAL OF PEDIATRICS—THE PSYCHOLOGIC DEVELOPMENT OF A GROUP OF CHILDREN BROUGHT UP IN A HOSPITAL TYPE RESIDENTIAL NURSERY
Rolanda Maxim, MD, St. Louis, Missouri

VAGAL ACTIVITY, GASTRIC MOTILITY, AND WEIGHT GAIN IN MASSAGED PRETERM NEONATES
Miguel A. Diego, MA, PhD, Tiffany Field, OTR, MS, PhD, and Maria Hernandez-Reif, MS, PhD, Miami, Florida

BREASTFEEDING AND OVERWEIGHT: LONGITUDINAL ANALYSIS IN AN AUSTRALIAN BIRTH COHORT
Valerie Burke, MD, FRACP, Lawrie J. Beilin, MD, FRACP, Karen Simmer, PhD, FRACP, FRCPCH, Wendy H. Oddy, MPH, PhD, Kevin V. Blake, PhD, Dorota Doherty, PhD, Garth E. Kendall, PhD, MPH, John P. Newnham, MD, FRANZCOG, Louis I. Landau, MD, FRACP, and Fiona J. Stanley, MD, FRACP, FRACOG, Perth, Australia

METABOLIC, HORMONAL, OXIDATIVE, AND INFLAMMATORY FACTORS IN PEDIATRIC OBESITY-RELATED LIVER DISEASE
Claudia Mandato, MD, PhD, Stefania Lucariello, PhD, Maria Rosario Licenziati, MD, Adriana Franzese, MD, Maria I. Spagnuolo, MD, Romina Ficarella, PhD, Maria Pacilio, PhD, Michele Amitrano, MD, Grazia Capuano, MS, Rosario Meli, PhD, and Pietro Vajro, MD, Naples, Italy

MICROALBUMINURIA AND ABNORMAL AMBULATORY BLOOD PRESSURE IN ADOLESCENTS WITH TYPE 2 DIABETES MELLITUS
Leigh M. Ettinger, MD, MS, Katherine Freeman, DrPH, Joan R. DiMartino-Nardi, MD, and Joseph T. Flynn, MD, MS, Bronx, New York

THE RELATIONSHIP BETWEEN THE LOCATION OF PEDIATRIC INTENSIVE CARE UNIT FACILITIES AND CHILD DEATH FROM TRAUMA: A COUNTY-LEVEL ECOLOGIC STUDY
Folafoluwa O. Odetola, MD, William C. Miller, MD, PhD, Matthew M. Davis, MD, MAPP, and Susan L. Bratton, MD, MPH, Ann Arbor, Michigan, and Chapel Hill, North Carolina

A POLYMORPHISM IN PLASMA PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE IS INVOLVED IN RESISTANCE TO IMMUNOGLOBULIN TREATMENT IN KAWASAKI DISEASE
Takaomi Minami, MD, Hiroyuki Suzuki, MD, PhD, Takashi Takeuchi, MD, Shigeru Uemura, MD, PhD, Junko Sugatani, PhD, and Norishige Yoshikawa, MD, PhD, Wakayama and Shizuoka, Japan

continued on page 6A
INSTITUTIONAL REVIEW BOARD GUIDANCE ON PEDIATRIC RESEARCH: MISSED OPPORTUNITIES

Leslie E. Wolf, JD, MPH, Jolanta Zandecki, BA, and Bernard Lo, MD, San Francisco, California

GRAND ROUNDS

DEFINING THE CLINICAL SPECTRUM OF DELETION 22q11.2

Nathaniel H. Robin, MD, and Robert J. Shprintzen, PhD, Birmingham, Alabama, and Syracuse, New York

50 YEARS AGO IN THE JOURNAL OF PEDIATRICS—HYALINE MEMBRANE DISEASE OF NEWBORN PREMATURE LUNGS: A NEW APPROACH

Alan H. Jobe, MD, PhD, Cincinnati, Ohio

CLINICAL AND LABORATORY OBSERVATIONS

NEW TECHNIQUE FOR AIRWAY CORRECTION IN NEONATES WITH SEVERE PIERRE ROBIN SEQUENCE

Arlen Denny, MD, and Christian Amm, MD, Milwaukee, Wisconsin

RADIOLOGICAL EVIDENCE OF EARLY CEREBRAL MICROVASCULAR DISEASE IN YOUNG CHILDREN WITH FABRY DISEASE

Mario A. Cabrera-Salazar, MD, Erin O'Rourke, MS, CGC, Gustavo Charria-Ortiz, MD, and John A. Barranger, MD, PhD, Miami, Florida

MIXED DONOR CHIMERISM AND LOW LEVEL IDURONIDASE EXPRESSION MAY BE ADEQUATE FOR NERUODEVELOPMENTAL PROTECTION IN HURLER SYNDROME

Jennifer Conway, MD, Sarah Dyack, MD, FRCPC, FCCMG, Bruce N. A. Crooks, MB, ChB, BSc, MRCP, and Conrad V. Fernandez, MD, FRCPC, Halifax, Nova Scotia

HIGHER PREVALENCE OF VITAMIN D DEFICIENCY IN MOTHERS OF RACHITIC THAN NONRACHITIC CHILDREN

Adekunle Dawodu, FRCP, FRCPCH, Mukesh Agarwal, MD, Matt Sankarankutty, FRCS, Denis Hardy, FRCP, FRCPCH, Jose Kochiyil, MS, and Padmanabhan Badrinath, PhD, MFPH, Al-Ain, United Arab Emirates, and Southend-on-Sea, Essex, United Kingdom

KOILONYCHIA, DOME-SHAPED EPIPHYSES, AND VERTEBRAL PLATYSYNDYLYIA

Victoria Nguyen, BA, Robert L. Buka, MD, JD, Brandie Roberts, MD, Marilyn Jones, MD, and Sheila Fallon Friedlander, MD, San Diego, California

SEVERE HOLOCARBOXYLASE SYNTHETASE DEFICIENCY WITH INCOMPLETE BIOTIN RESPONSIVENESS RESULTING IN ANTENATAL INSULT IN SAMOAN NEONATES

Callum J. Wilson, FRACP, Michael Myer, FRACP, MRCP, MD, Brian A. Darlow, MD, FRACP, Thorsten Stanley, FRCP, Glen Thomson, FRANZCR, E. Regula Baumgartner, MD, Denise M. Kirby, BSc(Hons), and David R. Thorburn, PhD, Auckland, Christchurch, Wellington, New Zealand, Basel, Switzerland, and Melbourne, Australia

COMMENTARY

PITFALLS IN NEWBORN SCREENING

Eric Crombez, MD, Richard Koch, MD, and Stephen Cederbaum, MD, Los Angeles, California
CONGENITAL LATEROCERVICAL COMPLEX MASSES: ARE THEY ALL LYMPHANGIOMAS?
Antonio Messineo, MD, Daniela Codrich, MD, Alessandro Franchi, MD, Maria Serenella Pignotti, MD, and Giuseppe Spinelli, MD, Florence, Italy

OBJECTIVE ASSESSMENT OF PancreATIC FUNCTION IN ALL PATIENTS WITH CYSTIC FIBROSIS
Leena Patel, MD, MRCP, FRCPCH, MHPE, Manchester, United Kingdom

DOES THE EFFECT OF BREAST-FEEDING ON ATOPIC DERMATITIS DEPEND ON FAMILY HISTORY OF ALLERGY?
Christine Stabell Benn, MD, PhD, and Kim Fleischer Michaelsen, MD, DMS, Copenhagen and Frederiksberg, Denmark

CEREBRAL INFARCTION IN DIABETIC KETOACIDOSIS
George F. Carl, PhD, Afshin Ameri, MD, and William H. Hoffman, MD, Augusta, Georgia

GUIDE FOR AUTHORS
INFORMATION FOR READERS
ANNOUNCEMENTS
CHANGE OF ADDRESS FORM
OPPORTUNITIES FOR SCHOLARLY ACTIVITIES DURING SUBSPECIALTY EDUCATION: A SCORECARD FOR PEDIATRIC FELLOWSHIP PROGRAMS

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In 2001, the American Board of Pediatrics (ABP) convened leaders from the various subspecialties, organizations, and other constituencies of pediatrics to discuss the nature and quality of the education of subspecialty residents (or fellows). An explicit purpose of this evaluation was to examine whether the education was properly aligned with the purpose of fellowship training, "to develop future academic pediatricians," as stated in 1996 and reaffirmed in 2004 by the Federation of Pediatric Organizations.1 Important questions were raised as to whether "the meaningful accomplishment in research" was the only or best means of achieving the goal of providing a foundation in critical thinking, which was judged to be an essential component of academic preparation; whether the work product that was required was an effective means for ensuring that the fellow had indeed accomplished something meaningful; and whether there was sufficient flexibility in the training to recognize the diverse roles of contemporary subspecialty pediatricians in academic settings.

It had become apparent that the determination of compliance with this requirement was nearly impossible to adjudicate at the level of the credentials committees of the various subboards, which judged achievement in this regard based on written material of highly variable quality. Furthermore, there was little way to ensure that the quality of individual research training was substantially supported at an institutional level through specified local commitments and supervision.

After an extended process during which new guidelines were developed, reviewed, and revised, a document was widely distributed in the summer of 2003, with the intent that these be put into effect by the summer of 2004.2 There were a number of substantive changes that offered options for the educational experience of individual subspecialty fellows and necessitated organizational redesign of programs. Some of the most important components of the guidelines are as follows:

1. Programs can offer new tracks for training that provide various combinations of general and subspecialty education.
2. Formal education in preparation for an academic career must be incorporated into the subspecialty program.
3. Each subspecialty resident must participate in scholarly activity that results in a specific written work product.
4. Assistance, oversight, and verification for the scholastic activity will rest with a committee of faculty at the institution where the subspecialty training takes place.
5. The program bears responsibility for monitoring and assessing the success of its educational milieu and for attesting to the nature and quality of the scholarship of its trainees, as is the case with any other graduate program.

This last requirement offers an opportunity for training programs to gain systematic insight into the suitability and adequacy of their training resources, infrastructure support, operations, and individual trainee mentoring and supervision, through both internal and external review. However, at present, such a process may not be routine, and some programs may never have undergone such an evaluation. Traditionally, the respective subspecialty subboard of the ABP, aided by an evaluation from a program director, materials submitted by a candidate and formal testing, judged whether individuals fulfilled the spirit and requirements for clinical competence and research experience. The Residency Review Committee (RRC), on the other hand, evaluated whether the program had sufficient (ie, minimally acceptable) resources (faculty, patients, and institutional) and administrative structure to serve as an acceptable site for clinical education in the respective discipline. However, the RRC is not currently poised to examine either the array of opportunities for research or other scholarly activities in an individual program or the success of a program’s graduates. Moreover, prospective subspecialty residents are not necessarily equipped to assess the opportunities and merits of programs and often judge the training milieu based on very limited information.

We believe that it is essential for programs to evaluate the quality of their educational resources on a regular basis. We have developed a voluntary “score card” that includes many of the elements necessary for assessing short-term opportunities and longer term success of a program (Table...
available online at www.us.elsevierhealth.com/jpeds). We have deliberately tried to put this in a relatively simple format that permits regular additions with a minimum amount of incremental work. We propose that this can serve as a template for a database with common elements for all training programs, and provide a history of each program.

Our score card has at least 3 main purposes: (1) to serve as a basis for self-assessment, (2) to serve as a guideline for formal evaluation by invited intramural or extramural reviewers, and (3) to serve as a means for candidates to assess the available educational opportunities, the experience and accomplishments of previous fellows in the programs of interest, and the differences among potential training programs. We are particularly concerned that potential candidates might not currently have access to this information to assist them in exploring educational opportunities to support their scholarly activities during fellowship, nor would they know what data were of most use toward this end. This tracking of information regarding continued scholarly activities for at least 10 years postfellowship should be the responsibility of the training program. Although this requires that programs maintain continued contact with former fellows, it is an important opportunity to gain understanding of the consequences of the training.

Data regarding clinical education is of equal importance. However, the number and type of patients encountered, the variety of technical and cognitive experiences, and the faculty and institutional resources to support the education is already tracked by the regular RRC reviews of a program. Furthermore, there is no generic template that would readily apply to all subspecialties. Accordingly, we encourage interested applicants to request such information about the clinical education when considering a program and when comparing opportunities.

We fully recognize the potential problems inherent in voluntary reporting. Program directors could choose to not use this approach. There are no means to ensure that data are valid. However, if the reporting mechanism proves to be useful for applicants, they will request it from programs; the request and response will in turn help validate the data and may even refine or adapt the tool such that it is more useful. Just as there is an expectation that a product will be assessed by a consumer report, there could be the anticipation that a program will provide these data if the “consumer” (ie, the applicant) finds the information to be of value. Thus we offer this score card as a modest attempt to provide a tool that will be useful to program directors and potential fellows. For the benefit of the fellows, we have included a column to describe the purpose of the information related to previous fellows, even though in practice this might be deleted.

Important questions were raised whether “the meaningful accomplishment in research” was the only or best means to achieve the goal of providing a foundation in critical thinking.

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REFERENCES

Many faces of portopulmonary hypertension

Years of portal hypertension, dyspnea with exertion, a new murmur, syncopal episodes, and sudden death. These elements comprise only part of our experiences in caring for patients with the entity characterized as portopulmonary hypertension (POPH)—the evolution of pulmonary artery hypertension as a consequence of portal hypertension pathophysiology.1 Sadly, we are reminded in this issue of The Journal of Pediatrics by Condino et al2 that POPH is not an exclusive syndrome affecting only adults with liver disease and portal hypertension. These authors succinctly summarize the varied clinical courses of 7 pediatric patients with severe POPH (mean pulmonary artery pressure >50 mm Hg). Indeed, POPH is an uncommon syndrome (4% to 14.5% frequency at major liver transplantation centers), at times confusing even the best clinicians who have to deal with overlapping signs and symptoms of advanced liver disease and progressive pulmonary artery hypertension. The specific liver-lung mediators of this syndrome are not clearly identified.1 My comments focus on screening, treatment, and orthotopic liver transplantation (OLT).

**SCREENING**

From adult experience in the era of pre-OLT evaluation, we have learned that the diagnosis of POPH was frequently missed. In a retrospective review of 43 patients with POPH from 18 peer-reviewed studies, 65% of cases were first diagnosed in the operating room during the liver transplantation. Intraoperative death directly caused by cardiopulmonary events followed in 2 patients.3 Condino et al2 correctly point out that chest radiography and electrocardiography are insensitive screening tools if we are hoping to recognize this syndrome (or any cause of pulmonary artery hypertension for that matter) in its earliest stages. Screening transthoracic Doppler echocardiography (DE) in the setting of advanced liver disease is noninvasive, quantitative (estimate of right ventricle (RV) systolic pressure), and qualitative (assesses RV size and function). Importantly, DE provides a guide as to who should undergo right-sided heart catheterization to confirm the diagnosis of POPH.4 Currently at my institution, RV systolic pressure >50 mm Hg suggests POPH until proven otherwise and right-sided heart catheterization is advised. No doubt, most patients with portal hypertension, and up to 25% with RV systolic pressures >50 mm Hg, simply have a hyperdynamic, high flow state, documented by high cardiac output and low calculated pulmonary vascular resistance. As expected from the spectrum of disease noted in POPH (endothelial and smooth muscle proliferation, in situ thrombosis, and plexogenic lesions), an increase in pulmonary arterial resistance to flow from the right ventricle is a key hemodynamic feature of POPH.3 Right-side heart failure is the end result of unrelenting obstruction to pulmonary arterial flow.

**TREATMENT**

Continuous intravenous epoprostenol has been the “drug of choice” for patients with POPH considered for OLT at my institution on the basis of empiric experience.5 Acute and long-term improvement in pulmonary hemodynamics has been related to vasodilation, antiplatelet aggregating effect, inotropic effect, and presumed vascular remodeling. Published POPH treatment experiences are limited for the most part to case reports. The evolving use of intravenous prostanooids,5-7 inhaled iloprost,8,9 endothelin receptor antagonists,10-14 and phosphodiesterase inhibitors15 in highly selected patients with POPH provides encouraging options. However, no randomized or open-label multicenter trials have been conducted specifically for POPH to date.

**OLT**

Intraoperative and postoperative mortality rates remain high in the setting of adult POPH, in spite of efforts to screen and deny OLT to some patients with POPH with the most severe hemodynamic situations.16 Pre-OLT use of prostanooids (or any other agent) has not been studied systematically in any age group. Which pre-OLT pulmonary vasomodulating agent to select, duration of treatment, and hemodynamic therapy goals that would favor successful OLT are topics that are evolving. Whether POPH is “cured” or simply improved with a combination of OLT and vasomodulating agents remains a question to be answered. Finally, we must be aware that pulmonary artery hypertension can occur clinically after successful OLT.17

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**DE** Doppler echocardiography  
**OLT** Orthotopic liver transplantation  
**POPH** Portopulmonary hypertension  
**RV** Right ventricle

See related article, p 20.

Reprint requests: Michael J. Krowka, MD, 200 1st Street SW, Rochester, MN 55905. E-mail: krowka@mayo.edu. J Pediatr 2005;147:3-4. 0022-3476/$ - see front matter Copyright © 2005 Elsevier Inc. All rights reserved. 10.1016/j.jpeds.2005.04.014

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Should we seek living-donor OLT or a higher priority for OLT if less than severe POPH exists (ie, higher pediatric end-stage liver disease score)? The answer should depend on Institutional Review Board–approved investigation that demonstrates OLT in selected subgroups of POPH can result in normalized/improved pulmonary hemodynamics and favorable long-term survival. It is time to make future POPH management decisions from more than our anecdotal case reports.

We had hoped to see very few young faces with POPH. That may not happen. So, as we have done for adults when OLT is considered, we should strive to identify an earlier face of POPH. The report of Condino et al² clearly paints the picture of dismal outcome, despite best efforts, following the diagnosis of severe POPH. Institutional Review Board–approved studies to address screening Doppler transthoracic echocardiography, hemodynamic subgroups via right–side heart catheterization, “earlier” treatment (including a higher PELD score or living-donor OLT in selected patients?) and research-oriented patient registries make sense. Maybe then we can improve quality of life and survival rates for all age groups after the diagnosis of POPH.

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REFERENCES


THE EVIDENCE MOUNTS AGAINST USE OF PURE OXYGEN IN NEWBORN RESUSCITATION

The hardest exposures to indict as health hazards are common ones. Few will worry too much if an obscure dietary practice or a chemical found in only a handful of water supplies is implicated in disease, but the sometimes justified charge that epidemiologists are the “Chicken Littles” of biomedicine—repeatedly telling us that the sky is falling—usually emerges when the phenomenon labeled hazardous is familiar, routine, and ordinary. Such was the fate of smoking, whose risks took decades to become accepted, and it took quite some time too before the pediatric community as a whole was convinced that aspirin was a real cause of Reyes syndrome. The same can be said of oxygen, used for generations by physicians for a wide variety of therapeutic purposes.

See related article, p 27.
pursuits. Anyone who doubts that oxygen is a popular element with the lay public should visit the oxygen bars now installed in many of our airports and shopping malls.

In this issue of The Journal, the analysis of Spector et al of the venerable data of the National Collaborative Perinatal Project (NCPP) describes a slightly higher risk of cancer in children exposed to >3 minutes of oxygen in the delivery room than in children without oxygen exposure. From the perspective of the individual, the excess risk is quite small. The NCPP data suggest that a population of 10,000 unexposed children will have about 6 cancers by the age of 5, whereas 10,000 children exposed to >3 minutes of O₂ in the delivery room might experience 17 or 18 cases. The overwhelming majority of exposed children will not have cancer, which is the usual scenario when common exposures are implicated in disease, and the reason for popular skepticism. Everyone knows someone who is exposed to the risk, and it is overwhelmingly likely that the person you know will not have the disease in question. For example, 90% to 95% of smokers are never diagnosed with lung cancer.

From a public health perspective, of course, the numbers look different. Of the 48 cancers in the study, I calculated that 7, or nearly 15% of the total, might have been prevented if oxygen had not been used in resuscitation. To my knowledge, we have no other means available to remove about 1 in 7 cancers from the childhood population.

By now readers should be saying, “Stop! How do we know that this purported relationship between oxygen and cancer isn’t spurious?” The short answer is, of course, that we don’t. Absolute assurance is never available from relationships that emerge from observational research, but at the same time we cannot afford to ignore statistically significant observations made in large studies. The proper path between skepticism and faith in research is paved with careful scrutiny of the observation and its context. Applying that scrutiny in the discussion that follows, I use the term oxygen to indicate exposure to 3 or more minutes of oxygen, the exposure level where a cancer risk is indicated by the data, and follow some of the criteria that epidemiologists use in weighing observational evidence.

The study is one of the largest prospective studies of child health ever mounted, and the data on events in the delivery room were carefully collected and recorded years before most cancer diagnoses were established. Cancer in children is unlikely to be either missed or misclassified. Unfortunately, we cannot know exactly what concentration of oxygen these children were exposed to in the late 1950s and 1960s.

A range of variables were examined, and none seemed capable of explaining the association by confounding. Low Apgar score at 1 minute (but oddly, not at 5 minutes) was also associated with cancer risk, but less convincingly than oxygen. It is not unreasonable to suppose that if oxygen is a cancer risk, a low Apgar score would appear to be also, because the 2 phenomena necessarily cluster together, but the article does not tell us if controlling for oxygen eliminates the low Apgar association. But on the grounds of both biologic plausibility and strength of association, oxygen seems a more likely determinant of cancer than birth depression. The relationship of oxygen to cancer—as judged by a hazard ratio of nearly 3—was of moderate strength, but with little evidence of a dose-response relationship, a criterion usually taken as favoring causality. Two other perinatal exposures have been assessed in relation to cancer in this cohort—maternal smoking in pregnancy and vitamin K administration in the newborn period—and both were exonerated, with nary a suggestion of elevated risk. These negative results lend a degree of specificity to the oxygen-cancer relationship. At a time when the consensus view is that the impending National Children’s Study, with 100,000 births, will be too small to contribute to cancer epidemiology, the NCPP, with about 50,000 births, is in fact doing so.

The data are consistent with a recent large Swedish case-control study (>500 childhood leukemia cases), which found a significant odds ratio of 2.6 for resuscitation with 100% oxygen with a facemask and bag after birth, which increased to 3.5 if manual ventilation lasted for 3 minutes or more. In that study as well, low Apgar scores at 1 and 5 minutes were associated with leukemia, but not significantly so. The largest fraction of cancer cases in the study in this issue of the journal were leukemias.

Most readers will probably be interested in the biologic plausibility of the connection between oxygen exposure early in life and cancer later. The authors make 2 kinds of linkages. The first is to persistence of several indexes of oxidative stress in the serum of infants as late as a month after brief exposures to 100% oxygen in the delivery room. The second is to the multiplicity of ways in which reactive oxygen species can damage DNA and otherwise contribute to the carcinogenic process, at several stages. This kind of evidence has led to the hope that antioxidants might protect against cancer. Unfortunately the failure of antioxidant vitamins to prevent cancer (or heart disease for that matter) in randomized trials has proven a recurrent disappointment in epidemiology.

Even if we did not worry about the carcinogenic potential of 100% oxygen (and the authors are admirably cautious in drawing conclusions), we would have good reasons to resuscitate most babies with room air. Increasingly we find that levels of Pao₂ in premature infants not previously considered hyperoxic may be dangerous to eyes, lungs, or brain. Two recent meta-analyses of the relatively small number of trials comparing room air with 100% oxygen have concluded that room air resuscitation is superior, on several measures, including mortality, in asphyxiated babies. At the same time, one less-than-ideal follow-up of a randomized trial of room air versus 100% oxygen did not find significantly worse neurodevelopment in room air recipients at age 18 to 24 months.

On balance, we do not have to be certain that the findings of Spector et al are true. Added to the existing evidence, they tip the balance toward using room air, and not 100% oxygen, as the first line of treatment for most depressed newborns in the delivery room. Oxygen must be available
in the delivery room, and there are some circumstances (eg, persistent fetal circulation, diaphragmatic hernia) where 100% oxygen should perhaps be first-line treatment. But even brief neonatal exposures to pure oxygen should no longer be considered familiar, routine, and ordinary.

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REFERENCES

WHERE SHOULD BABY BE PUT BACK TO SLEEP?

A vehement debate currently exists regarding the merits as opposed to the dangers of infant parent bedsharing.1-3 The stakes are high as studies suggest that up to 50% of sudden infant death occur in infants sleeping on adult beds or the equivalent (about 2000 deaths per year in the United States) with an even higher percent of these deaths (67%) occurring in the African-American population.4-6 It is difficult to remember a clash of this magnitude between pediatricians and lay advocates. Also seemingly unprecedented is the publicly acknowledged rift between the investigators of a prominent research team who conducted a large multinational sudden infant death syndrome (SIDS) epidemiological study.7 The basis for the disagreement concerns the study’s finding on bedsharing. It is described as a “serious disagreement among the study authors about the statistical methods employed, the significance of these findings and their implications for parents.”8 The debate exists primarily because a coalition of lay and professional groups that promotes breastfeeding maintains that bedsharing is essential for optimal breastfeeding and in addition enhances mother infant bonding.3 Opposing this view are pediatric researchers who have documented the risks associated with bedsharing.4,9

Public health agencies caught between these often warring factions have taken a middle position. The Academy of Pediatrics Task Force on Infant Positioning and SIDS has advised that “while bed sharing may have certain benefits (breast feeding) there are no scientific studies demonstrating the risks associated with bedsharing.”4,9

See related article, p 32.
occuring while bedsharing. Therefore, a strong argument can be made for making bedsharing warnings more emphatic.

One big issue in this debate is that the breastfeeding advocates are promoting the concept that bedsharing can be made safe. For those on the other side of the debate it is perceived that this is virtually impossible in the United States and Europe. To make bedsharing safe the anti-bedsharing faction contends a mother would have to sleep on a thin floormat without pillows or blankets as is still practiced by some traditional societies. Important in this regard is that until now both the pro and con groups have been in general agreement that bedsharing by mothers who do not smoke is relatively safe. In fact numerous studies have found no evidence of bedsharing risk among nonsmoking mothers.

Accordingly, the most important finding of the study reported in this issue of the Journal is that there is a substantial SIDS risk associated with bedsharing in nonsmoking mothers even in those who also breastfeed. Because the controversies regarding bedsharing often center on the methods and data analysis in studies, it is noteworthy that a group of experts with pre-publish access to the manuscript found no serious flaws in the design or data analysis techniques employed in the study. Relevant to the mechanism of bedsharing deaths the authors conclude that the risk occurs when the parent is sleeping and hence putting an infant back into a crib before the parent falls asleep should make bedsharing virtually risk free. The present report comes on the heels of the controversial collaborative European Study showing a risk for SIDS in infants of nonsmoking bedsharing mothers, albeit much lower than reported in the present study. Doubtless a debate will ensue concerning why these two studies are so dissimilar in their assessment of the magnitude of bedsharing risk. Do Scots have more risk modifiers when they bedshare (eg, alcohol consumption, pillows or bulky comforters in the bed) than European bedsharers? Certainly, further studies of bedsharing risks in different ethnic, socioeconomic, and cultural groups are warranted.

Without doubt the bedsharing controversy will continue, yet we feel certain that the present study will provide much needed sound scientific evidence. Such evidence is essential for the ongoing bedsharing debate and perhaps one day will facilitate a coming together of the various parties involved.

REFERENCES


TREATMENT OPTIONS FOR SEVERE UPPER AIRWAY OBSTRUCTION IN PIERRE-ROBIN SEQUENCE

In this issue of The Journal, Denny and Ann report 5-year outcomes regarding initial and late control of airway obstruction, feeding results, growth, and maintenance of correction of mandibular deficiency after physiological growth in a cohort of 11 patients with severe Pierre-Robin sequence (PRS) who underwent mandibular distraction osteogenesis (MDO). Children selected for MDO had failed traditional management, including prone positioning, tongue-lip adhesion, or nasopharyngeal airway intubation.

See related article, p 97.

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Furthermore, tongue posture due to a small mandible was the primary source of airway obstruction, no other sites of airway obstruction were present, and respiratory symptoms were significant enough to justify a tracheotomy. All patients were extubated 3 to 6 days after distractor activation. Ten out of 11 patients were complete oral feeders within 45 days of extubation, whereas the remaining patient needed 1 year to become a complete oral feeder. Six of the 11 patients had both preoperative and postoperative polysomnograms demonstrating complete resolution of obstructive sleep apnea after MDO. Growth charts revealed that 10 of the 11 patients surpassed the 50th percentile for height and weight after the surgery and remained above the 50th percentile until the 5-year follow-up. Finally, the distracted mandible grew appropriately, in terms of size and shape, in all patients. Based on these and other published data, the authors concluded that “the indications for traditional corrective surgery techniques (eg, tongue/lip adhesion, subperiosteal tongue release, and tracheotomy) are being redefined.”

The report by Denny and Amm is one of several retrospective studies in the literature exploring the efficacy of MDO in the treatment of children with PRS. However, Denny and Amm’s study is unique in that the study cohort consisted predominantly of children who had severe PRS and had failed conservative treatment modalities. Furthermore, the authors carefully define and measure the most relevant short- and long-term outcomes in the treatment of children with PRS, including avoidance of tracheotomy, feeding, growth, and resolution of obstructive sleep apnea. Although this study suffers from the unavoidable shortcoming of a small cohort, it offers solid and objective data regarding the efficacy of MDO in severe PRS.

PRS was first described by Pierre and Robin in 1923 as a triad of micrognathia, U-shaped cleft palate, and glossoptosis. Children born with symptomatic PRS and severe upper airway obstruction are at risk for airway collapse and failure to thrive. Approaches advocated for treatment of airway obstruction in neonates with PRS include positioning, tongue-lip adhesion, mandibular distraction, and tracheotomy. Unfortunately, there are few scientifically established guidelines regarding which approach will best suit a particular patient and situation. The difficulty in developing guidelines arises for several reasons, including the following:

1. The phenotype of PRS is highly variable, presenting as an isolated entity or as part of a syndrome along with multiple other congenital anomalies.
2. Identifying and quantifying the specific level of airway obstruction is difficult in a child with PRS.
3. A subset of children with PRS will resolve their upper airway obstruction with time and mandibular growth, and therefore need only temporizing measures.

The phenotypic variability of infants who present with micrognathia, cleft palate, and neonatal respiratory distress was illustrated by a study of Printzlau and Andersen. The authors performed a retrospective population-based epidemiologic study on all Danish live births from 1990 through 1999 using the inclusion criteria of micrognathia, cleft palate, and neonatal respiratory distress; 50 children were identified, yielding an incidence of 1 in 14,000 live births for this disease entity. Importantly, 19 of the 50 patients had 1 or more malformations. In 5 of the 50 patients, the triad of PRS was a minor feature of a complex syndrome. Children with isolated PRS are otherwise normal, with generally less severe airway obstruction and a more optimistic prognosis for self-resolution, because many experience mandibular “catch-up” growth during the first year of life. Upper airway obstruction is generally more severe, and the prognosis for “catch up” growth less likely, in syndromal children with PRS. Therefore, it is the syndromal children with PRS who will more likely need surgical intervention to achieve a stable airway. Interestingly, in most published series examining outcomes of MDO, the preponderance of the cohort has consisted of children with isolated PRS, with only a few syndromal children with PRS. The question arises as to whether the excellent outcomes purported by those studies are a function of patient selection bias or a reflection of the surgical intervention. The phenotypic variability of PRS is compounded by the fact that there is no validated method for identifying and quantifying the level of airway obstruction leading to respiratory insufficiency in children with PRS. This fact is illustrated by studies demonstrating that a subset of children with PRS who undergo MDO cannot be decannulated despite resolution of the presumed site of upper airway obstruction.

To date, methods used to evaluate the upper airway in children with PRS have included analysis by cephalometrics, computed tomography (CT) scans, and flexible laryngoscopy. Cephalometric analysis and CT scans are limited in that they offer only a static, 2-dimensional image of a dynamic, 3-dimensional process constituting upper airway obstruction in children with PRS. Although flexible laryngoscopy offers a dynamic picture of the upper airway if performed with the patient under light sedation, this technique still offers only a 2-dimensional image. Furthermore, syndromal children with PRS may have multiple levels of obstruction that may not be completely appreciated with the aforementioned techniques. Techniques exist to evaluate the upper airway, such as cine magnetic resonance imaging (MRI), which yields both dynamic and 3-dimensional data. But cine MRI is not available at all institutions, and its role in evaluating children with PRS has not yet been evaluated.

Finally, given that some children with PRS will have mandibular “catch-up” growth in the first year of life, treatment options with an absolute minimal morbidity should be developed. The dictum of “causing no harm” has been adhered to in developing methods to manage airways in children with PRS. However, because MDO is a relatively new procedure, many of the associated short- and long-term complications have yet to be defined. Most MDO-associated complications are minor and correctable (eg, fracture of the transport segment, difficulties in finishing osteotomy, incorrect direction of distraction, suture dehiscence, mucosal perforation, and bone formation defects). A few rare, but significant complications have also been reported after MDO,
including pain not related to the operation, functional disturbances in the movement of the jaw, weight loss, temporary unilateral facial nerve palsy, and transient unilateral hypoesthesia of the inferior alveolar nerve. Finally, I potentially severe but unexplored complication of MDO is the long-term effect of this procedure on the temporomandibular joint. Several animal studies have demonstrated that MDO can lead to degeneration of the temporomandibular joint, displacement of the condyle in an upward and backward direction, and resorption of the condyle. Clearly, to develop guidelines for treatment of severe PRS, the potential morbidities of MDO will need to be completely evaluated and reconciled with the severity and prognosis of the disease being treated.

Although initial studies such as these offer promising treatment options for severe PRS, it should be clear that MDO is in its infancy. Before establishing a clear role for MDO in the treatment algorithm for severe PRS, there is a need for carefully designed prospective studies. These studies should be designed so that results from different groups can be easily compared. Patient selection for these studies should be standardized, preoperative evaluation methods should allow for objective assessment and reporting, and outcome measures should be standardized and uniformly reported. Outcome measures that should be reported include avoidance of tracheotomy, resolution of obstructive sleep apnea, resolution of dysphagia, height and weight gain, mandibular growth and shape, and dental occlusion. Finally, both the short- and long-term complications of MDO should be carefully assessed and reported. Given the scarcity of severe PRS and centers performing MDO, only through a standardized study design and a meta-analysis approach will the role of MDO in the treatment of PRS be validated.

REFERENCES

A CRITICAL APPRAISAL OF EVIDENCE SUPPORTING A BARIATRIC SURGICAL APPROACH TO WEIGHT MANAGEMENT FOR ADOLESCENTS

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Weight regulation is influenced by a complex interplay of environmental and biological factors. The combined effect of these factors has led to an increased prevalence of obesity worldwide. Obesity is rapidly emerging as a leading cause of morbidity in all age groups. As a result, bariatric surgical procedures that are considered safe and effective in obese adults are now being performed in a select group of extremely obese adolescents. As this trend continues, pediatricians and internists alike will require a more in-depth understanding of the highly specialized field of bariatric surgery.

Although guidelines for using a surgical approach in adolescents with extreme obesity have been published, there has been relatively little discussion in the pediatric literature of various surgical weight loss procedures or of the specific scientific findings that substantiate such an approach. The purpose of this review is to present a comprehensive critical appraisal of pertinent information and research findings. It is hoped that this overview will serve as a useful general resource for clinicians faced with the challenge of caring for severely obese adolescent patients.

DEFINITIONS AND EPIDEMIOLOGIC TRENDS

Measures of body mass index (BMI) (weight in kg/height in m²) provide a reasonably accurate, reproducible screening tool for obesity in both adults and children. BMI-based definitions of varying degrees of obesity (Table I) that are in common use for adults may also be useful for adolescents who have completed their linear growth. The health risks that have been linked to higher classes of obesity have not yet been defined for adolescents, however.

Over the past decade and a half, BMI trends in the adult population have been startling. The prevalence of BMI ≥30 kg/m² has increased 2-fold, that of BMI ≥40 kg/m² has increased 4-fold, and that of BMI ≥50 kg/m² has increased 5-fold. Unfortunately, similar trends have been noted in pediatric age groups as well.

Adolescents considered to be extremely obese (BMI ≥40 kg/m²) are generally at least 100 pounds overweight or at least 100% over ideal body weight. Particularly alarming, obese teenagers are unlikely to outgrow their obesity. Some estimates indicate that more than 1 million adolescents and young adults in the United States may be affected with extreme obesity. Because comorbidities and resulting health care expenditures are much higher in severely obese individuals, these trends warrant special attention and serious consideration of surgical intervention.

ADVERSE EFFECTS OF OBESITY

For adults (nonsmokers) with no history of disease, the relative risk of death from any cause increases abruptly above a BMI of 30 kg/m², whereas increased risk of death due to cardiovascular disease begins at a BMI of 25 kg/m². A number of longitudinal studies have also shed light on the serious consequences of obesity in adolescence. Follow-up of more than 200,000 children over a 30-year period showed that those with a BMI above the 95th percentile (mean, 31 kg/m²) were twice as likely to die during the follow-up period. Additionally, a clear dose-response relationship between BMI during adolescence and the risk of death in adulthood was demonstrated. There is a link between years of life lost and extreme obesity (BMI ≥45 kg/m²) in young adults age 20 to 30 years, with black men and women losing more than 20 years and 5 years, respectively, and white men and women losing 13 years and 8 years, respectively.
Research indicates that childhood and adolescent obesity are associated with risk factors for coronary artery disease. Childhood obesity also confers a significantly increased risk of hypertension, hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, and atherosclerosis compared with normal-weight cohorts. In addition, the incidence of type 2 diabetes mellitus is also increasing in adolescents, particularly in obese adolescents, with a recent 10-fold increase in incidence reported. Obese adolescents are also at substantial risk for metabolic syndrome; 33% to 50% of obese adolescents have been identified with this dangerous clustering of risk factors for cardiovascular disease. Obstructive sleep apnea syndrome occurs more frequently in obese children and has serious adverse effects on daytime learning and quality of life. Obese children are also at increased risk for pseudotumor cerebri, skeletal complications, and polycystic ovary syndrome. Cancer risk, particularly for gynecologic and gastrointestinal malignancies, has also been closely linked to obesity, specifically to BMI during the teenage years. Nonalcoholic fatty liver disease, as evidenced by elevated aminotransferase levels, occurs at high rates (30% to 66%) in overweight youth and may prove to be an important cause of end-stage liver disease in the future.

The psychosocial consequences of severe pediatric obesity are equally profound. Obese adolescents are more stigmatized and victimized by peers and have fewer friendships than do lean adolescents. Studies of obese adult women have found that obesity in the emerging adult years (age 18 to 23) is associated with completion of fewer years of advanced education, lower family income, lower rates of marriage, and lower life satisfaction with work and interpersonal relationships. Finally, compared with normal-weight adolescents, obese adolescents have been associated with psychological symptoms that are internalized, with poor self-concept, a greater expectation of not finishing high school or college, and a health-related quality of life indistinguishable from that of children with cancer.

WEIGHT LOSS PROCEDURES

All contemporary bariatric surgical procedures (Figure) dramatically restrict dietary intake and result in a period of negative energy balance, which is achieved by either hypocaloric intake or malabsorption. This usually results in a loss of 25% to 35% of body weight, preferentially lost as fat mass in both adults and adolescents. Subsequently, equilibrium of energy balance occurs, favoring weight stabilization at the reduced weight.

Malabsorptive Procedures

Because of their profound adverse metabolic consequences, the intestinal bypass operations introduced in the 1960s are no longer performed. The malabsorptive procedures done today include biliopancreatic diversion with or without duodenal switch. These operations prevent absorption by allowing ingested nutrients to mix with bile and pancreatic secretions and to be absorbed in only a very short (50- to 100-cm) segment of the distal small intestine (Figure). These operations result in significant macronutrient and micronutrient malabsorption, flatus, and variable degrees of diarrhea, and thus generally are not well suited for adolescents.

Gastric Bypass

Gastric bypass has become the most commonly performed operation worldwide for clinically severe obesity and is currently considered the “gold standard” for effectiveness with which all other bariatric procedures are compared. This operation entails the creation of a 15- to 30-mL gastric pouch just beyond the gastroesophageal junction. This small pouch severely restricts meal size (Figure). A roux limb of jejunum is anastomosed to the gastric pouch using a 1 to 1.5 cm anastomosis, which impairs rapid emptying of the pouch. Gastric bypass can be performed using an open laparotomy or a laparoscopic technique. Clinical trial data suggest that the laparoscopic technique may have some distinct advantages over open surgery, but it should be performed only by surgeons with advanced training and expertise in laparoscopic surgery. This operation results in appetite reduction and is an inherent deterrent to the ingestion of carbohydrates. In adult gastric bypass patients, follow-up indicates an average loss of 1/3 of initial body weight (Tables II and III). Preliminary data from an adolescent population shows that body composition significantly improves after gastric bypass, with mean body fat content decreasing from 47% to 36% and mean BMI decreasing from 59 kg/m² to 38 kg/m² by 1 year postoperatively.

Disadvantages of gastric bypass are outlined in Tables II and IV. They include potential micronutrient deficiencies of iron, calcium, and B vitamins and slightly greater mortality and morbidity risk than that of purely restrictive operations. Major complications include death,
gastrointestinal leakage, pulmonary embolism, and bleeding. Finally, late weight regain is a potential concern in the adolescent population and has been observed in up to 15% of patients.55

Vertical Banded Gastroplasty

Vertical banded gastroplasty (VGB) is performed by creating a small gastric pouch just below the gastroesophageal junction, with an outlet at the inferior aspect of the pouch that empties into the more distal stomach (Figure). The pouch outlet is banded with a synthetic material to prevent enlargement over time. Although this procedure was once popular and has been used in adolescents,56-58 it is now performed in only a few centers. Several prospective, randomized trials and many retrospective studies comparing VGB and gastric bypass have demonstrated the superiority of gastric bypass for sustained weight reduction.59-61

Adjustable Gastric Banding

Adjustable gastric banding has been increasingly used worldwide since the early 1990s, but has been approved in the United States for use in adults only since 2001. In this operation, a prosthetic band with an adjustable inner diameter is placed around the proximal stomach;62 this restricts the entry of food into the stomach, with the food instead filling a small proximal gastric pouch. The adjustable gastric band is connected to a subcutaneous port, which is accessed with a needle through which saline solution is injected to alter the inner diameter of the band. This procedure is the least invasive of all common bariatric operations and is reversible. There are no staples, no transection, no exclusion of any portion of the gastrointestinal tract, and no anastomoses—all of which decrease the morbidity and mortality of this procedure (Tables II and IV). Another potential benefit of the band is that patients require a physician visit to have the band adjusted, which may enhance compliance with regular medical and weight loss surveillance.

As shown in Tables II and III, weight loss occurs more slowly with adjustable gastric banding than with other procedures.63 Maximal loss occurs 2 to 3 years postoperatively,63,64 compared with 12 to 18 months postoperatively for gastric bypass. Short-term results suggest that laparoscopic adjustable gastric banding is as effective as gastric bypass and VBG, but the long-term efficacy of adjustable gastric banding remains unproven.54 Properly designed clinical trials will be needed before the FDA grants approval for the use of adjustable gastric banding devices in adolescents.

Implantable Gastric Stimulation

Implantable gastric stimulation, also called gastric pacing, does not involve gastric restriction or malabsorption and
requires no alteration of gastrointestinal anatomy. Instead, electric stimulation is used to alter stomach contractions much in the same way that an implantable cardiac pacemaker is used to control myocardial contraction. The device is believed to cause myoelectric dysrhythmias within the gastric wall, but whether gastric pacing primarily alters gastric emptying or induces fundic relaxation is not clear. Implantable gastric stimulators have been studied for about a decade and have been found to be safe in humans. Unfortunately, however, responses of obese subjects are heterogeneous, data pertaining to its efficacy are insufficient, and to date there have been no studies of this device in adolescents.

**RATIONALE FOR SURGICAL INTERVENTION**

One oft-raised question is whether extreme obesity in the teenage years justifies consideration of bariatric surgery rather than delaying surgery until adulthood when the individual may be more capable of making an informed decision. Although some health risks of extreme obesity in adolescence will not manifest as disease states for years, many weighing 100% or more over ideal weight manifest obesity-related diseases as teenagers that will predictably worsen over time. Bariatric treatment guidelines for adolescents have been developed that take these considerations into account. Furthermore, it is clear that once a preteen or teenager has become extremely obese and has failed traditional and available weight loss options, there is little chance that a healthy weight will be achieved and maintained in the absence of drastic intervention. Finally, although adolescents cannot legally “consent” to any medical or surgical treatment plan, there is general consensus among pediatric professionals that those who are capable of assent should have a voice in their health care decision making, especially as it relates to elective surgical procedures. There is little empiric evidence that an 18-year-old adolescent is more capable of making an informed decision than an appropriately counseled 15-year-old. But it is quite possible that denying an effective weight loss intervention to an extremely obese teen until he or she reaches the age of majority may well have adverse consequences both by impairing physical and emotional health and by increasing operative risks when the procedure is performed at a later date, at an even higher BMI.

The major medical rationale for considering surgical weight loss for adolescents is the demonstrated durability of weight loss and the effectiveness in treating obesity-related comorbidities. In general, the frequency and degree of comorbidity resolution vary with the percentage of weight reduction achieved with the various surgical procedures. Procedures associated with greater weight loss, such as gastric bypass and biliopancreatic diversion, carry a greater likelihood of resolution or improvement of most medical comorbidities than do purely restrictive procedures. Most of the outcome data have been derived from gastric bypass follow-up studies in adults.

There is also an increasing body of evidence suggesting that surgical weight reduction results in reduced mortality. For morbidly obese diabetic adults, mortality after 9 years of observation was 28% in patients who did not undergo bariatric surgery, compared with 9% in those who underwent surgery. These findings have been corroborated in the United States. In the largest study to date, rates of death were calculated for 1035 morbidly obese Canadians who underwent gastric bypass and 5746 similarly obese nonsurgical patients; surgical weight loss was found to reduce the mortality risk by 8-fold over

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**Table II. Adult bariatric surgery outcomes**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Morbidity (n)*</th>
<th>Mortality (n)*</th>
<th>Mortality (n)‡</th>
<th>Change in BMI (n)†</th>
<th>% Weight loss ‡</th>
<th>% EWL ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYGBP‡¹</td>
<td>27.4% (7,977)</td>
<td>0.5% (9,258)</td>
<td>0.5% (5,644)</td>
<td>–17 kg/m² (2,205)</td>
<td>35%</td>
<td>62%</td>
</tr>
<tr>
<td>AGB¹</td>
<td>11.3% (6,693)</td>
<td>0.05% (5,780)</td>
<td>0.1% (2,297)</td>
<td>–11 kg/m² (1,959)</td>
<td>NR</td>
<td>47%</td>
</tr>
<tr>
<td>VBG</td>
<td>23.6% (3,907)</td>
<td>0.31% (2,858)</td>
<td>0.1% (749)</td>
<td>–14 kg/m² (942)</td>
<td>24%</td>
<td>68%</td>
</tr>
<tr>
<td>BPD</td>
<td>ND</td>
<td>ND</td>
<td>1.1% (3,030)</td>
<td>–18 kg/m² (984)</td>
<td>39%</td>
<td>70%</td>
</tr>
</tbody>
</table>

ND, not determined; EWL, excess weight loss; NR, not reported; RYGBP, Roux-en-Y gastric bypass; AGB, adjustable gastric band; VBG, vertical-banded gastroplasty; BPD, biliopancreatic diversion.
*Data based on systematic review by Chapman et al.¹³⁴
†Data based on systematic review and meta-analysis by Buchwald.⁴⁵
‡Includes open and laparoscopic procedures.
§Includes only laparoscopic procedures.

**Table III. Single-center adult and adolescent series by highly experienced surgeons**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Procedure Population</th>
<th>Change in BMI at 1 year (n)</th>
<th>Change in BMI, final (n; max f/u)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYGBP‡¹</td>
<td>Adult</td>
<td>–36% (506)</td>
<td>–36% (10; 14 years)</td>
</tr>
<tr>
<td>AGB¹¹³¹</td>
<td>Adult</td>
<td>–24% (120)</td>
<td>–33% (12; 4 years)</td>
</tr>
<tr>
<td>RYGBP‡¹⁵⁵⁴</td>
<td>Adolescent</td>
<td>–31% (31)</td>
<td>–27% (6; 14 years)</td>
</tr>
<tr>
<td>AGB‡¹²⁸</td>
<td>Adolescent</td>
<td>–27% (17)</td>
<td>–31% (11; 2 years)</td>
</tr>
</tbody>
</table>

RYGBP, Roux-en-Y gastric bypass; AGB, adjustable gastric band.
*Study reported results from cohort of 608 patients, of whom only 506, 407, 337, 158, and 10 subjects were eligible for reassessment at years 1, 2, 4, 10 and 14, respectively.
†Study reported results from cohort of 302 patients, of whom only 120, 43, and 12 subjects were eligible for reassessment at years 1, 2, and 4, respectively.
5 years. Epidemiologic approaches have also shown improved 15 year survival rates in patients who underwent gastric bypass in the United States.

Improvement in dyslipidemias has been seen in approximately 80% of surgical patients overall. A comparison of 2010 patients who underwent bariatric surgery with 2037 matched controls who underwent dietary management found a 10-fold lower incidence of hyperlipidemia at 2 years in the surgical treatment group. Although hypertension resolves after surgical weight loss in 65% of patients and improves in 80%, long-term evidence suggests that improvement is not long-lasting. Nevertheless, echocardiography has demonstrated a 14.5% decrease in left ventricular mass after surgical weight loss in adults.

Regarding type 2 diabetes mellitus, 75% of adults experience remission postoperatively, whereas 85% experience significant improvement in disease burden. Interestingly, the duration of diabetes significantly predicts poorer resolution after weight loss surgery. This may be an important factor when considering the timing of bariatric surgery for younger diabetic patients.

Obstructive sleep apnea resolves in 66% of obese adults after bariatric surgery, and the mean apnea-hypopnea index falls from 26 to 64 events per hour. Similar resolution or improvement in cardiac dysfunction, nonalcoholic fatty liver disease, gastroesophageal reflux, pseudotumor cerebi, arthritis, infertility, stress incontinence, and venous stasis disease has also been documented.

After surgical weight loss intervention, obese adults report improved psychosocial status, higher health-related quality of life, decreased stigmatization and discrimination, an improved social life, and improved educational and occupational status. Our own recent data demonstrate that before undergoing bariatric surgery, extremely obese adolescents displayed moderate to severe levels of depressive symptoms, low self-worth, and significant impairment in health-related quality of life. With loss of as few as 12 BMI units 3 months postoperatively, the majority of patients reported depressive symptoms within the normal range for youth. A 31% improvement in self-concept and a 21% improvement in health-related quality of life scores were also seen.

In summary, although bariatric surgery certainly carries both risks and costs, in adults these factors appear to be outweighed by the benefits to overall health and the long-term reduction in the enormous financial burden that results from obesity-related medical, physical, and psychological problems. It is reasonable to hypothesize that major and sustained weight reduction for some extremely obese teenagers will also result in an improved overall health and quality of life compared with no surgical intervention. Although short-term results appear to indicate positive outcomes, these findings have not yet been rigorously verified. The task at hand is thus to make a careful assessment of the potential risks and benefits of surgical weight loss intervention for each individual patient. This should be done by a multidisciplinary team of providers with experience and expertise in treating adolescents.

### CAVEATS

Despite the reported health- and cost-related benefits, bariatric surgery is a high-risk endeavor. Clinical evidence demonstrates that complications are directly related to the experience of the surgical team caring for patients. Population-based data from Washington suggest a mortality rate of up to 6% during a surgeon’s first 20 bariatric procedures, with this rate decreasing significantly, to < 0.4%, beyond 100 operations performed. Others have noted that the operative time and rates of leak and other major complications decrease markedly after a learning curve of ~100 cases. Surgical weight loss procedures have come under intense public and scientific scrutiny but nevertheless have gained acceptance as a realistic approach for treating patients with clinically severe obesity. Although a multicenter bariatric research consort-
tium that will provide adult outcome data in the near future was funded by the National Institutes of Health in 2003, a similar study in pediatric patients is only now being organized. Clinicians treating severely obese adolescents must therefore rely on currently available clinical and scientific evidence of safety and effectiveness to make rational clinical judgments about the appropriateness of bariatric operations for these patients.

MECHANISM OF WEIGHT LOSS AFTER BARIATRIC SURGERY

In patients who have undergone gastric bypass, early satiety is experienced after ingestion of very small (1 to 2 cups) portions, because of a ~95% reduction in gastric reservoir size. It is generally agreed that macronutrient malabsorption does not occur to any significant degree after gastric bypass.\(^\text{105}\) If surgical weight reduction occurred by dietary restriction alone, then homeostatic systems that oppose weight loss should attempt to restore a patient to his or her preoperative BMI by increasing meal frequency or caloric intake in response to weight loss\(^\text{106}\) or by decreasing energy expenditure beyond what would be expected. Interestingly, this does not occur.\(^\text{48}\) Other physiological mechanisms to explain the sustained effect of gastric bypass on body weight are currently being investigated.

Although levels of insulin and leptin, 2 major obesity-promoting molecules, do decrease significantly after surgically induced weight loss, these hormones are not thought to be responsible for appetite reduction. Alternatively, ghrelin is a candidate peptide that may be responsible for appetite reduction after bariatric surgery.\(^\text{107}\) Diet-induced weight loss is associated with a moderate increase in ghrelin levels.\(^\text{107,108}\) Although the findings remain somewhat controversial, some investigators have reported dramatically decreased ghrelin concentrations after gastric bypass surgery. Thus, it is conceivable that increases in plasma ghrelin concentration after diet-induced weight loss may contribute to the long-term failure of weight loss and that, conversely, depression of ghrelin levels after gastric bypass may contribute to long-term efficacy.\(^\text{44}\) Similar studies in patients after adjustable gastric banding have not corroborated these findings and indeed have found increased serum ghrelin levels after gastric banding compared with gastric bypass.\(^\text{109}\) This and other similar data\(^\text{110}\) support the possibility that differences in the efficacy of weight loss after purely restrictive procedures may due in part to the lack of suppression of this orexigenic hormone.

NUTRITIONAL CONSIDERATIONS

Because dietary vitamin and mineral intake is restricted after bariatric surgery, maintaining adequate levels of micronutrients necessitates daily supplementation.\(^\text{111}\) Deficiencies of vitamins B\(_1\), B\(_6\), B\(_12\), and E and iron have been described after bariatric surgery in adults.\(^\text{111-113}\) Beriberi has also been reported in adolescents after gastric bypass.\(^\text{114}\) It is recognized that vitamin and mineral intake after bariatric surgery in adolescents is suboptimal, with 73% reporting regular compliance but only 13% taking supplements regularly as prescribed.\(^\text{58}\) Compliance with prescribed vitamin intake by adolescent patients is critical to ensure good nutritional outcomes of weight loss surgery. The long-term effects are unknown in adolescents with poor compliance with supplementation.

Persons achieve up to 60% of their total bone mass during the adolescent growth spurt; 90% of peak bone mass is acquired by age 18 in girls and by age 20 in boys. Critical determinants of bone mineral accretion include availability of dietary calcium and active vitamin D, and adequacy of intestinal absorptive capacity. Adult bone mass and thus the subsequent risk of osteoporosis and fracture are largely dependent on the peak bone mass achieved during the active phases of bone mineral accretion and skeletal growth during adolescence. Bariatric operations necessarily reduce the ingestion or absorption of micronutrients, including calcium and vitamin D. Thus, there is concern regarding the possibility of negatively impacting bone mineral accretion.\(^\text{115-117}\) Longitudinal monitoring of adult bariatric patients has not demonstrated an increased fracture risk in later life compared with obese peers (I. Naslund, personal communication, May 2004). These data suggest that decreases in bone density and content commensurate with major body mass loss after surgery may represent a physiological rather than pathological change.

Bariatric surgeons have long speculated that females who undergo bariatric surgery should avoid pregnancy until they have reached a stable weight, typically 1 to 2 years after surgery. For those subsequently wanting to conceive, compliance with nutritional goals is paramount, especially during the periconceptional period and first trimester, to avoid fetal undernourishment and embryopathy. Folate is most important for preventing fetal malformations, including neural tube defects and perinatal complications such as low birth weight, prematurity, and placental abruption and infarction.\(^\text{118}\) Clinicians caring for these women must stress the importance of daily micronutrient supplementation and monitor serum vitamin levels (eg, folate) when uncertainty about compliance exists. Importantly, population-based data\(^\text{119}\) and case series\(^\text{120-123}\) have demonstrated that once weight is stable, women who have undergone bariatric surgery are entirely capable of healthy pregnancies with no greater incidence of fetal malnutrition or malformations or obstetrical/perinatal complications than that seen in nonobese patients.

WHICH OPERATION IS BEST FOR ADOLESCENTS?

Given the nutritional and gastrointestinal consequences of malabsorptive procedures, it is unlikely that such operations as biliopancreatic diversion or duodenal switch will be ideal for most adolescents. The limited available evidence indicates that both gastric bypass and adjustable gastric banding may be acceptable surgical treatments for highly selected adolescents.\(^\text{55,57,58,123-128}\) Both procedures are considered relatively safe, and there is little evidence of the superiority of one
procedure over another with respect to comorbidity treatment.\textsuperscript{129} It must be stressed, however, that less than a decade of experience is available regarding the long-term effectiveness of adjustable gastric banding.\textsuperscript{62,130,131} From the standpoint of experience is available regarding the long-term effectiveness of adjustable gastric banding from VBG, with the major exception that the former allows the amount of restriction to be titrated. Nevertheless, the consumption of calorically dense liquids in obese adolescents\textsuperscript{132} raises a concern that restriction alone may not be sufficient for the extremely obese adolescents. From a safety standpoint, adjustable gastric banding is associated with a 5- to 10-fold lower mortality rate and a 3-fold lower complication rate than gastric bypass in adults, and hence seems to be an attractive option for adolescents.

The greater risk of postoperative surgical and nutritional complications after gastric bypass as compared to gastric banding must be assessed, and patients and their families must be adequately informed. The objective determination of which operation better serves adolescents requires prospective, controlled trials and the participation of surgeons who are expert at each procedure.

RESEARCH CONSIDERATIONS AND FUTURE DIRECTIONS

Adolescents are now being considered for bariatric surgery with very little scientific data available on which to base decisions. Although bariatric procedures offer the greatest likelihood of major weight loss, the long-term outcomes remain uncertain, and the need for further research is crucial. Research efforts aimed at elucidating the physiological mechanisms by which weight loss procedures affect alterations in appetite, feeding behavior, and energy balance may ultimately lead to treatments for obesity that optimize these mechanisms. It is conceivable that such knowledge may lead to the development of noninvasive treatments alone or in combination with minimally invasive surgical options that carry less risk of short- and long-term complications.

When considering weight loss surgery in adolescents, clinicians must imagine the magnitude of the competing risks of carrying hundreds of pounds of excess weight from adolescence to middle age. Evidence suggests that surgical intervention earlier in the course of extreme obesity provides the best chance to reverse comorbidities, especially derangements of carbohydrate metabolism and diabetes.\textsuperscript{7,135} Given the central role of insulin resistance in the pathogenesis of many obesity-related disorders and the dramatic improvement in insulin resistance after bariatric surgery, longitudinal assessment of these patients may help improve our understanding of the biology of numerous disease processes linked to insulin resistance, including diabetes, cardiovascular disease, liver disease, polycystic ovary syndrome, metabolic syndrome, and sleep apnea.

Finally, properly designed clinical studies may elucidate other benefits of early (adolescent) versus late (adulthood) intervention for extreme obesity. It is entirely possible that other consequences of juvenile extreme obesity (eg, cardiovascular remodeling and atherosclerosis, endocrinopathy, psychosocial impairments) may be more reversible in their early stages. Until these research strides are made, careful consideration of the risk–benefit ratio in light of known scientific findings is of utmost importance for ensuring the highest degree of safety for severely obese adolescents seeking treatment.

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PORTOPULMONARY HYPERTENSION IN PEDIATRIC PATIENTS

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Objectives To investigate the clinical presentation, manifestations, and response to therapy of portopulmonary hypertension (PPHTN) in pediatric patients.

Study design This study was a retrospective chart review describing the evaluation and course of 7 patients with PPHTN.

Results Causes of portal hypertension (HTN) included biliary atresia (3 cases), cavernous transformation of the portal vein (2 cases), and primary sclerosing cholangitis and cryptogenic cirrhosis (1 case each). The median interval from the diagnosis of portal HTN to PPHTN was 12.1 years. Four patients presented with a new heart murmur, 4 presented with syncope, and 3 presented with dyspnea. Although electrocardiograms (ECGs) and chest x-rays were normal in 3 and 2 patients, respectively, echocardiograms diagnosed pulmonary HTN in all 7 patients. Five patients had cardiac catheterizations; the average mean pulmonary arterial pressure was 68 ± 20 mm Hg. Response to therapy was variable, and 4 patients died. Postmortem lung tissue examination revealed plexiform lesions and pulmonary arteriopathy.

Conclusions Because symptoms are subtle and may be overlooked, pediatric patients with portal HTN who develop a new heart murmur, dyspnea, syncope, or who are being evaluated for liver transplantation require evaluation for PPHTN. ECG and chest x-ray are insensitive screens for PPHTN. An echocardiogram and cardiology evaluation is essential for the diagnosis. (J Pediatr 2005;147:20-6)

Portopulmonary hypertension (PPHTN) is one of the pulmonary vascular disorders complicating chronic liver disease. In 1998 the World Health Organization (WHO) classified PPHTN as pulmonary arterial hypertension (HTN) associated with liver disease or portal HTN. PPHTN is defined by elevated mean pulmonary arterial pressure (PAP) (> 25 mm Hg at rest), increased pulmonary vascular resistance (PVR) (>3 Wood units · m⁻²), and normal pulmonary capillary wedge pressure (<15 mm Hg) in the presence of portal HTN. Both hepatic and extrahepatic causes of portal HTN may lead to PPHTN. The prevalence of PPHTN in adult patients with cirrhosis is 0.25% to 0.73% based on autopsy series and 3.5% to 8.5% in liver transplant candidates. The diagnosis of PPHTN is usually made 4 to 7 years after the diagnosis of portal HTN in adults.

There are only limited numbers of case reports of children with PPHTN. Pediatric patients with biliary atresia, portal vein thrombosis, focal nodular hyperplasia, and congenital hepatic fibrosis have been reported with pulmonary arterial HTN. To more fully characterize the clinical presentation, cardiopulmonary abnormalities, and clinical course, we report our experience with 7 children who developed PPHTN.

METHODS

A retrospective review of patient records in the Pediatric Liver Center, Children’s Hospital identified 7 pediatric patients with PPHTN diagnosed between 1995 and 2004 (Table 1). All of these children had been previously enrolled in an institutional review board–approved protocol for prospective longitudinal evaluation of childhood pulmonary hypertension.
HTN, for which written informed consent was obtained from the parents or guardians. Data obtained from the medical record included age at diagnosis of portal HTN and PPHTN, cause of portal HTN, symptoms and/or signs precipitating the evaluation for pulmonary HTN, and additional review of chest x-ray, electrocardiogram (ECG), Doppler echocardiogram, right heart catheterization results, lung and liver histology (if available), response to treatment, and overall outcome for each patient. Review of patient records was approved by the institutional review board and was exempted from written consent.

### Case Summaries

Patient 1, a Caucasian female, presented with splenomegaly and esophageal hemorrhage at age 3.5 years. Portal venogram demonstrated cavernous transformation of the portal vein. The patient underwent partial splenic embolization at age 7 years due to esophageal variceal bleeding refractory to sclerotherapy. At age 16 she developed syncope, which over the next 2 years progressed to shortness of breath, dyspnea on exertion, and orthopnea. Cardiac evaluation included an abnormal chest x-ray, electrocardiogram (ECG), echocardiogram, right heart catheterization results, lung and liver histology (if available), response to treatment, and overall outcome for each patient. Review of patient records was approved by the institutional review board and was exempted from written consent.

### Table 1. Clinical information on patients with PPHTN

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Age at portal HTN</th>
<th>Age at PPHTN</th>
<th>Liver disease</th>
<th>Associated diseases</th>
<th>Liver biopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27 yrs</td>
<td>3.5 yrs</td>
<td>18.2 yrs</td>
<td>CTPV</td>
<td>None</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>13.8 yrs</td>
<td>10.11 yrs</td>
<td>13.8 yrs</td>
<td>BA</td>
<td>None</td>
<td>Portal fibrosis</td>
</tr>
<tr>
<td>3</td>
<td>20.4 yrs</td>
<td>2 yrs</td>
<td>20.4 yrs</td>
<td>CC</td>
<td>CP, scoliosis, prematurity</td>
<td>Portal fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>13 yrs</td>
<td>10 mths</td>
<td>11.9 yrs</td>
<td>CTPV</td>
<td>Juvenile polyposis</td>
<td>Steatohepatitis</td>
</tr>
<tr>
<td>5</td>
<td>11 yrs</td>
<td>8.11 yrs</td>
<td>3 mths</td>
<td>PSC</td>
<td>ASD</td>
<td>Portal fibrosis</td>
</tr>
<tr>
<td>6</td>
<td>18 yrs</td>
<td>4 mths</td>
<td>17.3 yrs</td>
<td>BA</td>
<td>None</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>7 mths</td>
<td>8 mths</td>
<td>7 mths</td>
<td>BA</td>
<td>Complex CHD</td>
<td>Portal fibrosis</td>
</tr>
</tbody>
</table>

*BA, biliary atresia; CC, cryptogenic cirrhosis; PSC, primary sclerosing cholangitis; CHD, congenital heart disease; CP, cerebral palsy; ASD, atrial septal defect; ND, not done; CTPV, cavernous transformation of the portal vein.

*Age at death.

Patient 2 underwent a Kasai portoenterostomy for biliary atresia at age 59 days. At age 10 years, after an exercise-induced syncopal episode, she was found to be anemic with splenomegaly. An upper intestinal endoscopy revealed esophageal varices, which were treated with endoscopic sclerotherapy. Despite attempted variceal ablation and prophylactic propranolol, she continued to have episodic variceal bleeding. At age 13 years she was admitted to the intensive care unit with hematemesis, treated with an octreotide infusion, and found to have portal hypertensive gastropathy without actively bleeding esophageal varices. A soft systolic ejection murmur was noted. Cardiac evaluation included an abnormal chest x-ray and echocardiogram and a normal ECG (Table II). She acutely became hypotensive and suffered a fatal cardiorespiratory arrest. Postmortem examination demonstrated pulmonary arteriopathy with plexiform lesions.

Patient 3, a Caucasian female with cerebral palsy secondary to prematurity, developed jaundice and rectal...
bleeding at age 2 years. A percutaneous liver biopsy revealed cryptogenic cirrhosis. At age 14 she developed hematemesis and was found to have splenomegaly and a gastric ulcer without esophageal varices. At age 16 a severe gastric variceal hemorrhage prompted placement of a transjugular intrahepatic portosystemic shunt complicated by polymicrobial sepsis and ascites. As part of her initial evaluation for liver transplantation, she had a normal chest x-ray and ECG. At age 17 an accentuated pulmonic component of the second heart sound was auscultated. Cardiac evaluation revealed an

Table II. Evaluation of patients with PPHTN

<table>
<thead>
<tr>
<th>Patient</th>
<th>Chest X-ray</th>
<th>ECG</th>
<th>Echocardiogram</th>
<th>Echocardiogram-RVSP</th>
<th>VQ scan</th>
<th>Hypercoagulability workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prominent PA</td>
<td>RVH</td>
<td>RVH</td>
<td>95.8 mm Hg</td>
<td>Normal</td>
<td>Low free/total protein S</td>
</tr>
<tr>
<td>2</td>
<td>Prominent PA</td>
<td>Normal</td>
<td>RVH</td>
<td>105 mm Hg</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>Normal</td>
<td>RVH</td>
<td>45 mm Hg</td>
<td>Not done</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>Prominent PA</td>
<td>RVH</td>
<td>RVH</td>
<td>51.4 mm Hg</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>RVH</td>
<td>RVH</td>
<td>85.7 mm Hg</td>
<td>Not done</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>Prominent PA</td>
<td>Normal</td>
<td>Normal</td>
<td>52.8 mm Hg</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>Cardiomegaly</td>
<td>RVH</td>
<td>RVH</td>
<td>41.5 mm Hg</td>
<td>Normal</td>
<td>Not done</td>
</tr>
</tbody>
</table>

PA: pulmonary artery; RVH: right ventricular hypertrophy; RVSP: right ventricular systolic pressure (estimate of tricuspid regurgitation + assumed right atrial pressure); ECG: electrocardiogram; VQ: ventilation perfusion.

Hypercoagulability workup included lupus inhibitor, factor V Leiden, AT III, protein C/S, and cardiolipin IgG/IgM.

Table III. Cardiac catheterization data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Status</th>
<th>PAP (mm Hg) (Normal, &lt;25)</th>
<th>AOP (mm Hg) (Normal, 67-105)</th>
<th>CI (L·min⁻¹·m⁻²) (Normal, 2.5-3.5)</th>
<th>PVRI (U·m²⁻¹) (Normal, &lt;2)</th>
<th>PVR/SVR (Normal, &lt;0.1)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.2</td>
<td>Room air</td>
<td>85</td>
<td>104</td>
<td>3.0</td>
<td>28.2</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO+O₂</td>
<td>62</td>
<td>95</td>
<td>2.9</td>
<td>26.8</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Room air</td>
<td>65</td>
<td>93</td>
<td>3.0</td>
<td>18.6</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NO+O₂</td>
<td>55</td>
<td>93</td>
<td>2.6</td>
<td>17</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>O₂</td>
<td>73</td>
<td>75</td>
<td>4.9</td>
<td>12.65</td>
<td>0.91</td>
<td>EPO</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>NO+O₂</td>
<td>64</td>
<td>82</td>
<td>4.4</td>
<td>12.01</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18.8</td>
<td>Room air</td>
<td>72</td>
<td>82</td>
<td>3.0</td>
<td>19.68</td>
<td>0.76</td>
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<tr>
<td></td>
<td></td>
<td>NO+O₂</td>
<td>62</td>
<td>83</td>
<td>2.8</td>
<td>17.33</td>
<td>0.62</td>
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<tr>
<td>4</td>
<td>11</td>
<td>Room air</td>
<td>52</td>
<td>65</td>
<td>6.8</td>
<td>6.8</td>
<td>0.7</td>
<td>EPO</td>
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<tr>
<td>5</td>
<td>0.3</td>
<td>Pre-ASD</td>
<td>50</td>
<td>72</td>
<td>See text</td>
<td>1.48</td>
<td>0.32</td>
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<tr>
<td></td>
<td>4</td>
<td>Post-ASD</td>
<td>44</td>
<td>57</td>
<td>3.3</td>
<td>10.2</td>
<td>0.77</td>
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<tr>
<td>6</td>
<td></td>
<td>Room air</td>
<td>64</td>
<td>78</td>
<td>4.9</td>
<td>12.78</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>NO+O₂</td>
<td>62</td>
<td>77</td>
<td>4.4</td>
<td>10.3</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Room air</td>
<td>57</td>
<td>62</td>
<td>6.3</td>
<td>10.9</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>NO+O₂</td>
<td>54</td>
<td>60</td>
<td>5.5</td>
<td>8.4</td>
<td>0.87</td>
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</tr>
<tr>
<td>10</td>
<td></td>
<td>Room air</td>
<td>53</td>
<td>100</td>
<td>3.8</td>
<td>12.29</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>NO+O₂</td>
<td>40</td>
<td>101</td>
<td>3.5</td>
<td>9.56</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>O₂</td>
<td>65</td>
<td>66</td>
<td>8.4</td>
<td>4.1</td>
<td>0.87</td>
<td></td>
</tr>
</tbody>
</table>

AOP: mean arterial pressure; CI: cardiac index; PVRI: pulmonary vascular resistance index; SVR: systemic vascular resistance; U: Wood units; EPO: epoprostenol; ASD: atrial septal defect; PAP: pulmonary artery pressure.

*Started on EPO after cardiac catheterization.
abnormal echocardiogram suggesting mild pulmonary HTN (Table II). End-stage liver disease developed with hyperammonemia and grade 1-2 encephalopathy, and the patient underwent liver transplantation. During induction for liver transplantation, she suffered a fatal cardiac arrest. Postmortem examination showed plexiform pulmonary arteriopathy with multiple acute pulmonary arterial thrombi.

Patient 4, an African-American female, developed abdominal distension, ascites, and anemia at age 10 months. Esophageal varices were found on endoscopy, and angiography identified cavernous transformation of the portal vein (CTPV). Her father had CTPV and juvenile polyposis coli. At age 4 a colonoscopy and upper intestinal endoscopy showed duodenal and colonic juvenile polyps. Evaluation for a hypercoagulable state was negative. At age 11 she was hospitalized for fever, vomiting, diarrhea, and ascites and was found to have nocturnal hypoxia and new heart murmur. Chest x-ray, ECG, and echocardiogram were abnormal. A ventilation-perfusion scan was negative for PE (Table II). Severe pulmonary HTN was demonstrated by cardiac catheterization, with a hepatic vein wedge pressure of 8 mm Hg (Table III). Her family refused epoprostenol therapy. A trial of diltiazem was continued for 4 months, until symptoms progressed and she experienced multiple syncopal episodes. Continuous intravenous epoprostenol therapy was initiated, but she developed fatigue, ascites, and abdominal discomfort associated with a gallop and peripheral edema, prompting albumin and furosemide infusions. Repeat cardiac catheterization showed worsening pulmonary HTN (Table III). At age 13 years she developed lower extremity paralysis secondary to spinal cord ischemia and hemorrhage. Gastrointestinal hemorrhage ensued, and the patient expired. Postmortem examination showed plexiform pulmonary arteriopathy (Figure 2).

Patient 5, a Caucasian male, was born with an atrial septal defect that was surgically closed at age 3 months. His PAP was elevated before surgical repair, with a pulmonary to systemic flow ratio of 2.1 on room air and 3.3:1 on oxygen. The pulmonary to systemic resistance ratio was 0.32:1 on room air and 0.20:1 on oxygen. At age 4, cardiac catheterization demonstrated persistent pulmonary HTN that was nonreactive to hyperventilation and 100% oxygen. He developed exercise intolerance with occasional dyspnea at age 8 years, and a repeat cardiac catheterization demonstrated worsening pulmonary HTN (Table III). He was enrolled in a trial of an endothelin receptor antagonist, bosentan, at age 8.5 years.17 Before initiating bosentan, liver tests were within twice-normal values, increased 2– to 3-fold during the 5 days of therapy, and peaked at 1 month (aspartate aminotransferase, 94; alanine aminotransferase, 325; γ-glutamyltransferase, 656). Liver tests normalized by 2 months after discontinuation of therapy, and an abdominal ultrasound revealed a normal liver with mild splenomegaly. Evaluation for infectious, autoimmune, and metabolic liver disease was negative. Liver biopsy revealed severe portal inflammation, early bridging fibrosis, and bile ductular proliferation. Magnetic resonance cholangiopancreatoscopy showed no evidence of large duct strictures or obstruction. Hematochezia developed, and ulcerative colitis was found at colonoscopy. The patient was diagnosed with primary sclerosing cholangitis and was treated with ursodeoxycholic acid, sulfasalazine, and prednisone. Despite aggressive therapy for primary sclerosing cholangitis and ulcerative colitis, pulmonary HTN worsened (Table III). Continuous intravenous epoprostenol therapy was initiated at age 11, and the patient is able to attend school with a WHO classification of III.

Patient 6, a Caucasian female, underwent a gallbladder Kasai portoenterostomy for biliary atresia at age 96 days with revisions to a Roux-en-Y jejunocystoenterostomy due to poor biliary drainage. At age 16 years she experienced 3 syncopal events and was found to have a prominent pulmonic component of the second heart sound. ECG and echocardiogram were normal. At age 17, due to continued self-limited physical activity, a chest x-ray identified a prominent main pulmonary artery. A ventilation-perfusion scan was negative for PE. A repeat echocardiogram was abnormal (Table II). Cardiac catheterization demonstrated pulmonary arterial HTN with a hepatic vein wedge pressure of 15 mm Hg (Table III). Despite treatment with nifedipine and furosemide, the patient developed a gallop and persistent peripheral edema. Continuous epoprostenol infusion was recommended. She is currently 18 years old and under consideration for liver transplantation with a WHO classification of III.

Patient 7 was diagnosed in utero with complex congenital heart disease. A postpartum echocardiogram showed abnormal systemic venous return with interrupted inferior vena cava and azygous continuation, atrial septal defect, right heart dilatation, a left aortic arch with an aberrant right subclavian artery, and bilateral superior vena cava. She was subsequently diagnosed with biliary atresia and underwent a Kasai portoenterostomy at age 71 days. At age 4 months she was hospitalized with respiratory syncitial viral bronchiolitis and had a central
venous line placed for nutritional support. At age 7 months she developed sudden respiratory failure requiring mechanical ventilation. Cardiac catheterization revealed systemic-level PAPs that were not reactive to oxygen, nitric oxide, or prostacyclin (Table III). Due to refractory persistent pulmonary HTN, severe lung disease, and her cardiac anomalies, she was found to be an unacceptable candidate for liver transplantation. Supportive care was withdrawn, and she expired.

RESULTS

Our patient group comprised 6 females and 1 male with a median age at diagnosis of portal HTN of 24 months (range, 4 to 131 months) and a median age for the diagnosis of pulmonary HTN of 164 months (range, 3 to 244 months). One of the 7 patients was diagnosed with pulmonary HTN before diagnosis of portal HTN. In the remaining 6 patients, the median interval between the diagnosis of portal HTN to PPHTN was 154 months (range, 3 to 220 months) (Table I).

Syncope was present in 4 patients, occurring before the diagnosis of PPHTN in 3 and after the diagnosis of PPHTN in 1. A new heart murmur or prominent pulmonic component of the second heart sound prompted cardiac evaluation in 4 patients. Shortness of breath was found in 2 patients, and dyspnea on exertion was reported in 3 patients.

Chest x-rays were abnormal in 5 of the 7 patients, with either a prominent pulmonary artery or cardiomegaly. Two patients had completely normal chest x-rays. Three patients had normal ECGs, whereas right ventricular hypertrophy was present in 4 patients. Echocardiograms revealed pulmonary HTN in all 7 patients, with a mean baseline right ventricular systolic pressure of 67.4 mm Hg (range, 41.5 to 105 mmHg) (Table II). Five patients underwent cardiac catheterizations which demonstrated a markedly elevated mean PAP of 65 mm Hg (range, 50 to 85 mm Hg), of whom only 1 patient demonstrated vasoreactivity to nitric oxide, suggesting that most of these patients were poor candidates for calcium-channel blocker therapy (Table III).

Three patients were initially treated with calcium channel blockers that did not improve pulmonary hemodynamics, and were subsequently placed on epoprostenol infusions. One patient was initially treated with bosentan, because liver disease was unknown, but then was converted to epoprostenol because of significantly elevated liver function tests.

Of the 3 surviving patients, 1 is homebound and 2 are able to attend school; 1 is married. Four patients died of progressive PPHTN despite aggressive medical management. Two of the 4 patients were considered to have PPHTN that was too severe to allow for safe liver transplantation. Thus, PPHTN showed variable degrees of response to medical management depending on the severity at diagnosis.

DISCUSSION

PPHTN is a serious complication of portal HTN that, when left untreated, is fatal. Once diagnosed, mean survival in adults is 15 months, with a median survival of 6 months. Disease progression can be rapid, ranging from 3 weeks to 5 years. Patients are classified as mild, moderate, or severe depending on the elevation of the mean PAP and PVR, which provides both prognostic and therapeutic considerations. Clinical symptoms are nonspecific and often subtle. This disorder requires a high index of suspicion for diagnosis. The ultimate treatment is reversal of portal HTN, which may require liver transplantation. However, patients with severe PPHTN have a high mortality with liver transplantation unless PAP can be lowered into a safe range. Placement of a Swan-Ganz catheter is recommended in patients with PPHTN undergoing liver transplantation.

Our 7 patients are representative of the liver conditions associated with pulmonary arterial HTN in pediatric patients. Unfortunately, when the diagnosis of PPHTN was made based on clinical symptoms, the pulmonary arterial HTN was severe in all cases. We found that our patients’ initial clinical presentation was often subtle. Therefore, our patients had moderate to severe pulmonary HTN at the time of diagnosis of PPHTN resistant to many first-line medications, making them poor candidates for liver transplantation.

In our series, only 3 patients had symptoms of syncope or dyspnea that were recognized before diagnosis of PPHTN. Syncope was the only symptom clearly linked to this condition, occurring in 3 patients prediagnosis and in 1 patient post-diagnosis. A new heart murmur or accentuated P2 by auscultation were physical findings that prompted evaluation. Even despite our high index of suspicion in 2 of the patients, chest x-ray and ECG were normal, which led to deferment of further evaluation for PPHTN. These cases clearly show that an echocardiogram must be performed before excluding the diagnosis of PPHTN. It should be pointed out, however, that even echocardiograms may not detect mild degrees of PPHTN and may underestimate the degree of pulmonary arterial HTN. Thus, cardiac catheterization is necessary for the diagnosis and further treatment of most patients with PPHTN.

The goal of treatment of PPHTN is to transform a borderline candidate for liver transplantation into an acceptable one, through aggressive treatment of the pulmonary arterial HTN. A thorough evaluation of causes of pulmonary arterial HTN is crucial to the diagnosis and management of this entity. Treatment may include providing supplemental oxygen to maintain saturation above 92%, diuretics to control volume overload, and calcium-channel blockers if the patient has demonstrated good reactivity to vasodilators during cardiac catheterization. Similar to adults, few patients with PPHTN in our series responded to calcium channel blocker therapy. Continuous prostacyclin improves survival in adults and children with idiopathic pulmonary HTN. Unfortunately, prostacyclin currently must be given by continuous intravenous infusion, necessitating central venous catheterization with its associated complications.

If the diagnosis of PPHTN is made early before the development of irreversible pulmonary vasculopathy, then liver transplantation can be successfully performed and may reverse the process of PPHTN.
bypass has been proposed to restore intrahepatic portal flow and reduce portal HTN in children with CTPV. In children with CTPV and normal liver histology and anatomy, this procedure has been effective in reversing portal HTN and its sequelae, although this procedure has not been reported in children with significant PPHTN.

PPHTN, by definition, involves deleterious effects of portal HTN on pulmonary vasculature. Portal HTN causes increased cardiac output that may induce shear stress from increased pulmonary blood flow, resulting in endothelial damage. It has also been postulated that portal HTN causes release of humoral mediators, cytokines, and endotoxins, which may stimulate increased flow and shear stress in the pulmonary circulation. The net result is an increased vascular resistance caused by vasoconstriction, which can lead to pulmonary vascular remodeling and proliferation of pulmonary arterial endothelial cells, resulting in pulmonary HTN.

A previous study has shown that patients with end-stage liver disease and PPHTN undergoing liver transplantation have high mortality compared with transplant patients without PPHTN. The current Mayo Clinic Intraoperative guidelines in patients with PPHTN recommend pursuing liver transplantation in patients with a mean PAP < 35 mm Hg or in patients with a mean PAP between 35 and 50 mm Hg with a PVR of < 3 Wood units \( \cdot \) mm\(^2\). One study reported a 100% mortality rate in adult patients with a mean PAP of > 50 mm Hg who underwent liver transplantation and a 50% mortality rate in adult patients with mean PAP between 35 and 50 mm Hg with a PVR > 3 Wood units \( \cdot \) mm\(^2\). Unfortunately, up to 60% of patients with PPHTN do not have the condition detected before induction of anesthesia for liver transplantation.

Our geographic referral base represents a population living at moderate elevation (1600 meters above sea level in Denver). This relative hypoxia may complicate an already diseased pulmonary vasculature, accelerating the appearance of symptoms. However, hypoxia is not a required stimulus for the development of PPHTN in children, because PPHTN has been described at sea level, and 1 of our 7 patients developed PPHTN while living at sea level.

Currently there is no accepted universal screening protocol for PPHTN in patients with portal HTN or in those undergoing evaluation for liver transplantation. This raises the question of how pediatric patients should be screened. Is it justifiable to screen all pediatric patients with chronic liver disease or wait until they are candidates for liver transplantation? We believe that delayed diagnosis predisposes to more severe disease and potentially may preclude liver transplantation. We agree that echocardiography should be the recommended screening test for PPHTN because of the lack of sensitivity of chest x-ray and ECG. We also agree with the European Respiratory Task Force’s recommendations to screen all patients before liver transplantation with transthoracic echocardiography to detect PPHTN before induction. We propose the development of a national database for PPHTN in pediatric patients that could define the natural history and response to therapy of this entity, facilitate multicenter trials, and ultimately lead to evidence-based recommendations for screening and treatment.

REFERENCES

A CLINICAL TRIAL OF ALEVAIRE IN PULMONARY DISTRESS OF THE NEWBORN INFANT

Clinical trials are demanding, expensive, and may put patients at risk. Therefore they should be performed only when based on a reasonable hypothesis and when there is the potential for change in clinical care practice. In 1955 the pathophysiology of respiratory distress syndrome (RDS) was not known, and no treatments were known to be effective. Avery and Mead did not identify surfactant deficiency as the primary developmental abnormality causing RDS until 1959. The first experimental demonstration in animal models that surfactant replacement could correct the deficiency was reported by Enhorning and Robertson in 1972. The first report of the clinical efficacy of surfactant treatments in preterm infants was by Fujiwara et al in 1980, and the first randomized-controlled trial of surfactant was reported by Enhorning and Robertson in 1985. In 1955 Briggs randomized 62 infants to an aerosol of Alevaire, a nonionic detergent now called Tyloxapol, or no intervention. Tyloxapol aerosols were being used at the time to deliver streptomycin to children with cavitary tuberculosis and to decrease the viscosity of saliva and pus. Tyloxapol also was being used to treat RDS on the basis of care reports. Detergents have one property in common with pulmonary surfactant—the ability to lower surface tensions at an air-water interface. Detergents also can transiently improve the compliance of the surfactant-deficient lung, but they also can cause lung injury. The hypothesis that a detergent aerosol would improve RDS is not reasonable in retrospect. The trial showed no benefit, which resulted in the clinical benefit in that this therapy was not used subsequently for RDS. Fortunately for these infants in 1955, aerosols deliver very little material to the lungs of infants with RDS, and no harm was done. Tyloxapol appeared again in neonatology as a component in Exosurf, the first synthetic surfactant used to treat RDS. Of note, 26 infants in this trial from 1955 died, and all had autopsies. We envy a 100% autopsy rate in 2005.

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10.1016/j.jpeds.2005.03.012
Objective: To evaluate the relationship between neonatal oxygen supplementation (O₂) and childhood cancer in the Collaborative Perinatal Project (CPP).

Study design: The CPP consisted of 54,795 children born between 1959 and 1966 and followed to age 8 years. We used Cox proportional hazards modeling to examine the association between history of neonatal O₂ and cancer (n = 48).

Results: The hazard ratio (HR) for any O₂ was 1.77 (95% confidence interval [CI] = 0.94 to 3.35). The HR for continuous duration of O₂ was near 1 and not significant. However, the HRs were 0.69 (95% CI = 0.17 to 2.88) and 2.87 (95% CI = 1.46 to 5.66) when comparing 0 to 2 and 3 or more minutes of O₂, respectively, to no O₂. The latter association was weaker (HR = 2.00; 95% CI = 0.88 to 4.54) and not significant (P = .10) when analysis was restricted to cancers diagnosed after age 1 year (n = 41).

Conclusions: These findings are consistent with an association between O₂ for 3 minutes or longer and cancer in childhood, and should serve as a basis for further study. (J Pediatr 2005;147:27-31)

A small body of evidence suggests that neonatal oxygen supplementation (O₂) may slightly increase the risk of childhood cancer. A Swedish case-control study found a dose–response association between length of O₂ and risk of childhood lymphatic leukemia.¹ Two small Japanese studies also found an association between duration of O₂ and hepatoblastoma among premature infants.²,³ Given the epidemiologic evidence for an association and its plausibility,⁴,⁵ we analyzed data on O₂ and childhood cancer in a United States cohort study.

METHODS

The Collaborative Perinatal Project (CPP) enrolled approximately 48,000 women, who had about 60,000 pregnancies, at 12 university-affiliated medical centers between 1959 and 1966; study design and data collection procedures have been described elsewhere.⁶ Briefly, trained observers in delivery rooms recorded the details of 54,795 live births using a standardized methodology. Children received multiple physical examinations in the first year of life and again at age 7 years. Parents were interviewed several times in the first 2 years and annually thereafter until their children were age 7 or 8 years (depending on site).

Fifty-one cancers were identified in the cohort and subsequently confirmed by 2 pediatricians as described by Klebanoff et al.⁷ Previous analyses using these cases have examined exposure to vitamin K prophylaxis,⁷ maternal smoking during pregnancy,⁸ and simian virus 40.⁹ Three infants who were diagnosed with cancer within the first week of life were excluded from the analysis. Table I summarizes the types and ages at diagnosis of cancers in the CPP.

Supplemental O₂ was recorded with respect to the mode of delivery (“open oxygen” or “positive-pressure oxygen”), with the duration of each recorded in whole minutes. Newborns were considered to be exposed to O₂ if there was an affirmative response to either variable. Length of O₂ was the sum of the 2 durations. We defined dichotomous
(any/no O$_2$), continuous (duration of O$_2$ in minutes), and categorical (none, < median duration O$_2$, ≥median duration O$_2$) exposure variables. History of O$_2$ was missing for 1818 children (3.3%; none with cancer), whom we excluded from analysis. There were also 869 children (none with cancer) for whom O$_2$ was indicated but no duration was recorded. The latter group was considered exposed to O$_2$ in the dichotomous analysis but was excluded from the analysis of O$_2$ duration.

We used Cox proportional hazards modeling to examine the relation between history of O$_2$ and cancer at either 0 to 8 or 1 to 8 years of age. This method of survival analysis is commonly used because it allows for varying lengths of follow-up and robustly describes most underlying probability distributions. Person-time was calculated as the number of months from birth (or age 1 year) to the date of cancer diagnosis or the date of the last follow-up visit in computerized records, for a maximum of 96 months. We considered family socioeconomic status (in 5 categories), maternal education (< high school graduate, high school graduate, >high school), maternal age (> 35 years), sex of child, race of child (black, white, other), birth weight (< 2500 g, 2501 to 4000 g, ≥4001 g), and gestational age (< 37 weeks) to be potential confounders, because of their known associations with some childhood cancers. We also adjusted for Apgar score at 1 minute (0 to 6), Apgar score at 5 minutes (0 to 6), and the presence of meconium at birth as markers of neonatal distress. Adjustment for each was made in turn, rather than simultaneously, because cases were few. Because Down syndrome and certain other congenital anomalies are known risk factors for childhood cancer, we repeated the analyses excluding 101 children with Down syndrome and 209 children with other, unspecified syndromes, none of whom developed cancer during follow-up.

RESULTS

Table II summarizes the number of cases, child-months, and hazard ratios (HRs) for the potential confounders. There were no statistically significant associations of cancer with family socioeconomic index, maternal education or age, or child’s race, birth weight, or gestational age. Only 1-minute Apgar score < 7 was significantly associated with childhood cancer (HR = 2.22; 95% confidence interval [CI] = 1.19 to 4.13).

Table III summarizes the number of cases, child-months, and HRs for dichotomous O$_2$. The HR for any receipt of O$_2$ was 1.77 (95% CI = 0.94 to 3.35; $P = .08$) for all cancers and 1.34 (95% CI = 0.64 to 2.81; $P = .43$) for those cancers diagnosed after infancy. HRs adjusted for family socioeconomic status, maternal education, maternal age, sex of child, race of child, birth weight, gestational age, 5-minute Apgar score at 1 minute.
Apgar score, or the presence of meconium at birth were 1.74 to 2.16 in the former analysis and 1.31 to 1.59 in the latter. Adjustment for 1-minute Apgar score gave HRs of 1.19 in the first analysis and 0.81 in the second.

The duration of O₂ ranged from 0 to 196 minutes for those who received it, although 90% of the children received O₂ for 14 minutes or less. Among cases, the duration of O₂ was between 0 and 10 minutes. HRs for O₂ as a continuous variable were near unity, regardless of adjustment, and were not significant (data not shown).

Children who received O₂ were classified into those exposed for less than the median time, 3 minutes, and those exposed for 3 or more minutes (Table III). There were no significant associations comparing children who received O₂ for 0 to 2 minutes with those who received no O₂. However, there was a significantly increased risk of cancer among children who received O₂ for 3 minutes or longer (HR = 2.87; 95% CI = 1.46 to 5.66; *P* = .002). When restricted to cancers diagnosed after age 1 year, this HR was 2.00 (95% CI = 0.88 to 4.54; *P* = .10). HRs comparing O₂ for 3 minutes or longer with O₂ and adjusted for family socioeconomic status, maternal education and age, or child’s sex, race, birth weight, or gestational age ranged from 2.81 to 3.11 for all cancers and from 1.94 to 2.22 for those cancers diagnosed after age 1 year.

Table III also presents the results of analyses adjusting for markers of neonatal distress. There was little evidence of an association between O₂ for 3 minutes or longer and childhood cancer when adjusted for low 1-minute Apgar score. However, missing data for the 1-minute Apgar score resulted in the

<table>
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<th>No. of cases</th>
<th>HR</th>
<th>95% CI</th>
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<th>No. of cases</th>
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* Analyses of cancer at ages 0-8 and 1 to 8 years excluded 869 children (59,185 child-months, 0 cancers) and 642 children (50,556 child-months, 0 cancers), respectively, for whom O₂ was indicated but no duration was recorded.
† Excluding 3 infants diagnosed in the first week of life.
‡ Excluding 4,952 children, 4 with cancer, for whom 1-minute Apgar score was missing.
§ Excluding 4,205 children, 2 with cancer, for whom 5-minute Apgar score was missing.
¶ Excluding 1,245 children, 1 with cancer, for whom presence of meconium was missing.

Table III. Hazard ratios and 95% confidence intervals for neonatal supplemental oxygen exposure in the CPP cohort.
disproportionate exclusion of childhood cancer rate data among children who received O_2 for 3 minutes or longer (20,954 child-months, 1 cancer) compared with children who received no O_2 (215,923 child-months, 3 cancers). Adjustment for low 5-minute Apgar score increased the HRs comparing O_2 for 3 minutes or longer with no O_2 for both cancers diagnosed at age 0 to 8 years and those diagnosed at age 1 to 8 years, whereas adjustment for the presence of meconium at birth affected HRs only minimally. Exclusion of children with Down syndrome or other syndromes did not materially change the results.

**DISCUSSION**

We found a significantly increased rate of childhood cancer diagnosed between the first week of life and age 8 years among children who received O_2 for 3 minutes or longer. This finding was robust to adjustment for various risk factors for childhood cancer. The HR for receipt of 3 or more minutes of O_2 was not significant (P = .10) but was still elevated when analysis was restricted to cancers diagnosed after age 1 year, to rule out the possibility that O_2 was given in response to the symptoms of cancer present at birth. This study’s major strength is its prospective design; its major weakness is its small number of cases. Several other caveats also apply in the interpretation of these results.

O_2 was not significantly associated with childhood cancer when analyzed as a continuous variable. There was a long right tail to the distribution of O_2 exposure duration such that 14.5% of exposed children (n = 1115) had durations greater than 10 minutes, the maximum duration of O_2 among children with cancer. The fact that no cancers occurred among the children with the very longest durations of exposure diminishes the argument for an association of O_2 with cancer in childhood.

The percentage of O_2 that the newborn children in the CPP cohort received was not documented. Also, we counted infants as exposed if O_2 was delivered by hose or loose mask, either of which can administer a lower fraction of inspired oxygen than is intended. Thus we could not verify the concentration of O_2 received by each infant. In contrast, Naumburg et al found a significant association of leukemia specifically with administration of 100% oxygen by bag and mask.

An alternate explanation for these results is that O_2 may be a proxy for a poor transition to extrauterine life. We adjusted for markers of neonatal distress to examine this possibility. The association of prolonged O_2 with childhood cancer remained when adjusted for low 5-minute Apgar score and the presence of meconium at birth. Adjustment for low 1-minute Apgar score attenuated the association, but this may have been a function of missing data. Our findings appeared to be independent of at least 2 markers of neonatal distress.

Finally, the magnitude of the association that we observed was low and thus could be due to confounding by a factor that we did not examine. We also cannot rule out the possibility that our findings were due to chance. However, our findings do corroborate those of a few previous case-control studies, and there is some plausibility to the idea that such a brief exposure as O_2 could have long-term sequelae. Reactive oxygen species (from many sources) are known to cause DNA damage. Moreover, a study that randomly assigned moderately asphyxiated infants to receive either O_2 or pressurized room air found that biomarkers of oxidative stress were significantly elevated 4 weeks after birth in the former group compared with both the latter group and infants who did not require resuscitation. Importantly, the former group of infants received O_2 for a mean of only 7.5 minutes (standard deviation, 1.8).

Special consideration may be given to the effect of O_2 on preterm infants. One might expect an association of O_2 with childhood cancer to be particularly pronounced in preterm infants, who are exposed for long periods of time and who have reduced antioxidant defenses. Children born at birth weight < 2500 g, many of whom are preterm, have a greatly increased risk of developing hepatoblastoma. Two small studies (12 cases and 75 controls and 5 cases and 285 controls) from Japan suggest that greater duration of O_2 exposure may be a risk factor for hepatoblastoma among low birth weight infants. Only isolated reports have found associations between low birth weight or prematurity and various childhood cancers. The fact that no obvious association of prematurity with childhood cancer has emerged (apart from that with hepatoblastoma) may be evidence against a true association of childhood cancer with O_2 exposure. In the CPP data, the association that we noted was independent of low birth weight and short gestational age.

A comparatively common exposure such as O_2 could explain a significant proportion of cases even if it only modestly increased the risk of cancer in childhood. Congenital syndromes, in contrast, drastically increase the risk of childhood cancer but, because of their rarity, explain few cases. It is thus important to articulate fully any risk associated with O_2. Many studies of childhood cancer have obtained delivery records as part of data collection. We encourage any investigators who have such data to examine the history of oxygen supplementation.

The findings of this analysis do not unambiguously support an association between O_2 and childhood cancer and should not be interpreted as connoting causality. No change in pediatric practice should be made on the basis of these results, although they may be a datum of interest in the ongoing debate over the toxicity of O_2 and the possibility of using room air in its stead.

**REFERENCES**


50 Years Ago in The Journal of Pediatrics

PEDiatric EVALUATION OF BRAIN-DAMAGED CHILDREN


Clinical data on 133 children monitored in the cerebral palsy program at the Children’s Hospital in San Francisco in the early 1950s was reviewed to emphasize the complexity of children with brain damage and to highlight the use of both an interdisciplinary team approach and an expectant attitude. There was a male predominance (n = 74), and more than three quarters of the children were less than 5 years of age. The incidence of seizures (n = 17) was low presumably because of the young age of the study population. More than 70% of the children were below the third percentile in height and weight. In most of these cases the bone age was severely delayed, but children with growth delay and normal bone age actually tended to be the most severely motor impaired. The timetable for tooth eruption tended to be on time even in the presence of retarded bone age. More severe motor impairment was associated with bruxism, flattening of the teeth, and a high arched palate. The last was attributed to involuntary motor pulls. These brain-damaged children were noted to have feeding difficulties, respiratory problems, and frequent infections that contributed to an elevated mortality rate. Their medical fragility was attributable directly to neurogenic or specific brain factors. The author warned caution when interpreting intelligence levels because infant IQ tests so frequently depend on motor responses and psychomotor experiences. Delay and more long-term observation were advised in the place of early and often incorrect labeling of mental retardation. Only 39 of this population were categorized as mentally retarded. The burden of increased medical and social costs was noted even then. A team approach with early therapeutic intervention was suggested as offering the best opportunity for improved outcomes.

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Childhood Cancer Following Neonatal Oxygen Supplementation
Objective To examine the hypothesis that bedsharing with an infant is associated with an increased risk of sudden infant death syndrome (SIDS).

Study design A 1:2, case-control study in Scotland UK, population 5.1 million, including 123 infants who died of SIDS between January 1, 1996 and May 31, 2000, and 263 controls. The main outcome measure was sharing a sleep surface during last sleep.

Results Sharing a sleep surface was associated with SIDS (multivariate OR 2.89, 95% CI 1.40, 5.97). The largest risk was associated with couch sharing (OR 66.9, 95% CI 2.8, 1597). Of 46 SIDS infants who bedshared during their last sleep, 40 (87%) were found in the parents’ bed. Sharing a bed when <11 weeks (OR 10.20, 95% CI 2.99, 34.8) was associated with a greater risk, \( P = .010 \), compared with sharing when older (OR 1.07, 95% CI 0.32, 3.56). The association remained if mother did not smoke (OR 8.01, 95% CI 1.20, 53.3) or the infant was breastfed (OR 13.10, 95% CI 1.29, 133).

Conclusions Bedsharing is associated with an increased risk of SIDS for infants <11 weeks of age. Sharing a couch for sleep should be strongly discouraged at any age. (J Pediatr 2005;147:32-7)

There is considerable debate about the potential benefits and risks of bedsharing with an infant. Case-control studies from the 1980s\(^1\) and early 1990s\(^2\) failed to demonstrate an association with sudden infant death if the parent was a nonsmoker; had not taken alcohol or other medication, and was not unusually tired. Bedsharing is now promoted to aid breastfeeding.\(^3\) However, the increase in bedsharing in the United States\(^4\) has coincided with reports from pathologists of an increasing prevalence of bedsharing among sudden unexpected deaths in infancy.\(^5\) Pediatricians have agreed that, “there is insufficient data to conclude that bedsharing under carefully controlled conditions is clearly hazardous or clearly safe.”\(^6\)

This study was designed to look at two hypotheses generated from our previous study.\(^7\) The first regarding used infant mattresses and sudden infant death syndrome (SIDS) has been addressed in a recent publication.\(^8\) The second hypothesis was that bedsharing with an infant is associated with an increased risk of SIDS.

METHODS

Ethics

Ethics committees for the 15 Health Boards in Scotland gave approval.

Population

Between January 1996 and May 2000, pathologists notified us of all sudden unexpected infant deaths that history, police death scene investigation, and initial postmortem dissection had failed to explain. A standard necropsy protocol\(^9\) with agreed diagnostic criteria was used to provide consistent classification, and 94% of cases were examined by an expert pediatric pathologist. Parental home visits were arranged for 156 cases, with notification in time to attempt an interview within 28 days of death. One hundred and thirty-one (84%) visits were completed; others proved impossible within 28 days. Two controls were identified for each case: the births immediately before and after in the same

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Table I. Sleep place and sharing during last sleep

<table>
<thead>
<tr>
<th>Sleep place and sharing last sleep</th>
<th>Cases (%)</th>
<th>Control (%)</th>
<th>Univariate (95% CI)</th>
<th>Multivariate* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room with parent(s) not sharing</td>
<td>44 (36)</td>
<td>167 (63)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Room with parent(s) some bedsharing</td>
<td>46 (37)</td>
<td>44 (17)</td>
<td>3.97 (2.34, 6.74)</td>
<td>3.49 (1.54, 7.92)</td>
</tr>
<tr>
<td>Separate room not sharing</td>
<td>15 (12)</td>
<td>43 (19)</td>
<td>1.32 (0.67, 2.60)</td>
<td>3.26 (1.03, 10.35)</td>
</tr>
<tr>
<td>Separate room some bedsharing</td>
<td>0 (0)</td>
<td>6 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Share couch</td>
<td>14 (11)</td>
<td>2 (1)</td>
<td>26.57 (5.82, 121)</td>
<td>66.95 (2.81, 1596)</td>
</tr>
<tr>
<td>Share chair</td>
<td>2 (2)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Share cot with twin</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>123 (100)</td>
<td>263 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Multivariate model included: maternal age; quadratic function of maternal age; birth weight; infant age; parity; either parent smoked; laid prone to sleep; laid on side to sleep; found with head covered in the past; found with head covered after last sleep; infant routinely slept on a used infant mattress.

**Parents perceived their child to have slept for most of last sleep in a separate room. These infants were brought into parent(s) room and their bed to share during last sleep, 5 for <2 hours and 1 for 2-5 hours.

†The number of cases or controls is too small for meaningful odds ratios to be calculated.

maternity unit. No other matching was employed. By the 28-day cutoff, 278 of 312 (90%) control parents were interviewed. Cases and controls with and without interview had similar maternal age and socioeconomic status.10 Eight of 131 interviewed cases were re-classified as explained deaths when final postmortem test results became available: subdural hemorrhage, cerebral edema, meningitis and septicemia, pulmonary hemorrhage, and four overlaying/accidental asphyxiation (of which two were found on a couch with an adult, one on a bean bag and one where position was not known). The infant in which pulmonary hemorrhage was diagnosed was bedsharing between two parents. These and the associated 15 controls were removed from the study leaving 123 SIDS cases and 263 controls.

Data Collection

The questionnaire provided core medical and social data, and infant-care practices used routinely and for the night before interview for controls and day/night of death for SIDS (hereafter referred to as last sleep).

Socioeconomic status was assessed by seven individual factors: mother’s marital status, mother living alone, mother and father currently employed, age parents left full-time education, mother in paid employment before the infant’s birth, and one measure (Deprivation Category [DEPCAT]) that assesses deprivation on the basis of mailing address in seven categories in ascending order of severity.10 These categories take cognizance of overcrowding, male unemployment, low socioeconomic status, and the lack of a car.

Data collection did not include ethnic background. Although in other countries, eg, the United States, race/ethnicity is an important descriptor of social class, this is not the case in Scotland, where ethnic minority groups are small. The economically and socially deprived are usually white Caucasians.

Exposure to smoking was assessed by yes/no response when questioned about current smoking habit for parents and other household members. We did not collect data on smoking during pregnancy as our previous study7 had shown that nearly all the people who smoked did so both during and after pregnancy.

Roomsharing was assessed by asking: “In which room was your baby for most of the last sleep?” To assess normal sleep place, parents were asked: “What was baby’s normal sleep place (day and night)?” Possible answers were: cot, carrycot, pram, crib, Moses basket (dressed maize bassinette with padded interior), parent’s bed, other.

Questions about sharing a sleep surface during last sleep included: where (bed, couch, chair); for how long (<2 hours, 2-5 hour, >5 hour); with whom; how close (snuggled up/at arms length); and, if on bed, whether between parents or at the edge of the bed.

For control infants, last sleep was designated as last night. For SIDS infants, last sleep was that before being found dead which was “night” (last seen alive between 8 PM and 8 AM) or “day” (last seen alive between 8 AM and 8 PM).

We did not collect data on alcohol consumption as our previous experience11 had demonstrated the difficulty of obtaining accurate information, possibly because of fear of censorship. Also, the New Zealand Cot Death Study had shown no interaction between bedsharing and maternal alcohol consumption.5

Data Analysis

The full dataset, 123 cases and 263 controls, was analysed using the random effects logistic regression procedure (xlogit) in the software package STATA (Stata Press, College Station, Tex),12 which allows the inclusion of all data, including cases with no controls. All variables significantly (P < .05) related to SIDS on univariate analysis were treated as potential confounders. They were entered sequentially in groups (socioeconomic, not easily modifiable, possibly modifiable) into the logistic regression of case versus control and removed singly in a stepwise manner starting with the least significant until all remaining variables showed statistical significance P < .10. The next group of variables was then added. Quadratic functions were included for continuous and multicategorical variables and retained if nonlinear effects
**Table II. Bedsharing for infants <11 weeks**

<table>
<thead>
<tr>
<th>Infant age at last sleep</th>
<th>Room with parent(s) Bedsharing</th>
<th>Cases (%)</th>
<th>Control (%)</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariate OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11 weeks</td>
<td>Not share</td>
<td>16</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bedshare</td>
<td>33</td>
<td>13</td>
<td>9.36 (4.01, 21.83)</td>
<td>10.20 (2.99, 34.8)</td>
</tr>
<tr>
<td>How long</td>
<td>&lt;2 hours</td>
<td>6</td>
<td>2</td>
<td>11.06 (2.04, 60.13)</td>
<td>29.15 (3.62, 235)</td>
</tr>
<tr>
<td></td>
<td>2-5 hours</td>
<td>12</td>
<td>6</td>
<td>7.38 (2.39, 22.7)</td>
<td>2.97 (0.48, 18.6)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 hours</td>
<td>15</td>
<td>5</td>
<td>11.06 (3.49, 35)</td>
<td>13.92 (2.80, 69)</td>
</tr>
<tr>
<td>How close</td>
<td>Close not touching</td>
<td>14</td>
<td>4</td>
<td>12.91 (3.73, 45)</td>
<td>12.11 (2.11, 69)</td>
</tr>
<tr>
<td></td>
<td>Snuggled up</td>
<td>16</td>
<td>7</td>
<td>8.43 (2.96, 24)</td>
<td>9.45 (2.17, 41)</td>
</tr>
<tr>
<td>Where</td>
<td>Outside edge 1 parent</td>
<td>6</td>
<td>4</td>
<td>5.53 (1.39, 22)</td>
<td>7.63 (1.27, 46)</td>
</tr>
<tr>
<td></td>
<td>Outside edge 2/3 people</td>
<td>12</td>
<td>4</td>
<td>11.06 (3.14, 39)</td>
<td>7.06 (1.16, 43)</td>
</tr>
<tr>
<td></td>
<td>Between 2 or 3 people</td>
<td>14</td>
<td>3</td>
<td>17.21 (4.40, 67)</td>
<td>28.64 (4.17, 197)</td>
</tr>
</tbody>
</table>

Totals for analysis: How long 123 cases, 263 controls; How close 119, 260; Where 122, 260.
Of infants <11 weeks, 2 SIDS case patients were in a separate room not sharing compared with nine controls; 6 case patients shared a couch compared with 1 control; and 1 case patient shared a chair. One control shared a cot with a twin compared with no case patients.

Where: for all 14 case patients, “between 2 or 3 people” were in fact between 2 parents; for 1 control a sibling also was in the bed, and whether the infant was between sibling and parent or between two parents is not known. For “outside edge 2 or 3 people”: 3 case patients were in bed with father, mother, and sibling; 3 case patients were with sibling and mother; and 6 case patients were with father and mother; all 4 controls were in bed with just father and mother. “Edge 1 parent” was mother for 5 cases and father for 1; all 4 controls were with mother.

Data from infants <11 weeks is available online (Table B) (www.us.elsevierhealth.com/jpeds).

*Multivariate model included: maternal age; quadratic function of maternal age; birth weight; infant age; parity; either parent smoked; laid prone to sleep; laid on side to sleep; found with head covered in the past; found with head covered after last sleep; and infant routinely slept on a used infant mattress.

were present. The model that best described the difference between cases and controls without sharing sleep surface variables (Table A, available online at www.us.elsevierhealth.com/jpeds) was maternal age and its quadratic function; birth weight continuous; infant age (date of death minus date of birth for cases, date of interview minus date of birth for controls); parity linear; either parent smokes (yes/no); laid prone; laid on side; found with head covered in the past; found with head covered after last sleep; and routinely slept on a used infant mattress. To this model was added the last sleep sharing bed, couch, or chair or cot variable.

Interactions were examined for in room with parent(s) bedsharing versus in room with parents not bedsharing with all other variables in the multivariate model.

The interaction with infant age was demonstrated by examining age groups (0-6 weeks, 6-11 weeks, >11 weeks). All analyses used the complete dataset and the full multivariate model, which included infant age, to allow for residual differences between cases and controls within age groups. The modifying effect on in room with parent(s) bedsharing, length of bedsharing, proximity to parents, and location in bed were examined in two groups: infants <11 weeks of age and infants >11 weeks of age at last sleep. Similar age group comparisons were made for infants exposed to maternal smoking and those breastfed at last sleep.

**RESULTS**

Last sleep was “night” for 107 of 119 (90%) SIDS cases and “day” for 12 (10%) SIDS cases; 4 were not recorded. “Day” deaths were all found between 9:30 AM and 6:30 PM. Only 2 of 12 (17%) “day” deaths co-slept (both bed).

Parental bed was the normal sleep place (the infant did not normally sleep in a cot or elsewhere) for 11% (13/123) of SIDS infants and 5% (13/263) of controls. Overall, 64 of 123 (52%) SIDS infants shared the same sleep surface (bed, couch, chair or cot) during their last sleep compared with 53 of 263 (20%) of controls (OR 2.89 95% CI 1.40, 5.97), P = .004. Fourteen (11%) of SIDS infants shared a couch at last sleep (Table I) compared with 2 (1%) controls (OR 66.95 95% CI 2.81, 1596), 8 of these 14 SIDS infants were ≥11 weeks of age. Sharing a bed during last sleep also was significantly associated with SIDS (OR 3.49 95% CI 1.54, 7.92). Of 46 SIDS infants who bedshared during their last sleep, 40 (87%) were found in the parents’ bed, 2 in a cot, 3 in a Moses basket, and 1 not known. Two SIDS infants and 1 control shared a cot with a twin for last sleep, and 2 SIDS infants shared a chair with an adult; no SIDS infants or controls bedshared with an older sibling alone. Sharing with siblings and parents is described in the footnote to Table II.

For six control infants (Table I), the parents’ perception of “where baby slept for most of last sleep” was a separate room, but these infants did in fact share the parental bed at some point during last sleep, five for <2 hours and one for 2 to 5 hours. All were >11 weeks of age. When these six infants were added to the bedsharing controls who slept all night in the parents’ room, and analysis was performed comparing bedsharing and not bedsharing, results were little different and the interaction with infant age remained the same.

Separate room not sharing (Table I) was not associated with a risk of SIDS on univariate analysis (OR 1.32 95% CI 0.67, 2.60) but became a risk on multivariate analysis (OR 3.26 95% CI 1.03, 10.35). Variables were removed singly to ascertain which were important in converting a nonsignificant univariate model to a significant multivariate model. The main factor was parental smoking. Further stratified analysis showed that separate room was associated with a significant
risk of SIDS only if a parent smoked (OR 12.2 95% CI 2.25, 66.4) and not if parents were nonsmokers (OR 1.25 95% CI 0.16, 10.06).

The strongest interaction with in room with parents bedsharing during last sleep compared with in room with parents not bedsharing was infant age ($P = .035$), even after control for preterm gestation ($P = .042$) (Table III). The largest difference in associated risk comparing younger with older infants was seen when the data were divided at 11 weeks (OR 9.51 95% CI 1.68, 53.8), $P = .01$. Of 46 bedsharing deaths, 33 (72%) occurred in infants <11 weeks. For arbitrarily chosen age groups, the associated risk of bedsharing was: <6 weeks: 59% cases, 17% controls (multivariate OR 17.49, 95% CI 1.93, 158); 6 to 11 weeks: 48% cases, 15% controls (OR 7.64, 95% CI 1.31, 42.44); >11 weeks: 18% cases, 17% controls (OR 1.07, 95% CI 0.32, 3.56).

No significant interaction was found between maternal smoking and bedsharing (Table III). Table II examines bedsharing details for infants <11 weeks of age. A strong association was seen for young infants regardless of how long they bedshared, their proximity to parents, or location in the bed. Sleeping between parents was associated with a particularly high risk (OR 28.6 95% CI 4.17, 197).

Sixteen SIDS infants who bedshared for some time during their last sleep were still being breastfed, 11 were found in the parents’ bed, 4 in their cot, and 1 not known. All were <11 weeks of age. There was an association between bedsharing and SIDS for young babies who were breastfed at last sleep (OR 13.10, 95% CI 1.29, 133). Breastfeeders made up 43% (n = 6) of SIDS infants <11 weeks who slept between parents during their last sleep. For young infants, bedsharing was significantly associated with a risk of SIDS even if mother did not smoke (OR 8.01 95% CI 1.20, 53.28) (Table IV).

**DISCUSSION**

We confirm that sharing a couch to sleep is associated with an increased risk of SIDS and that sleeping in the same room as parents is associated with a lower risk compared with sleeping in a separate room. However we cannot confirm that bedsharing is only associated with SIDS if a parent is a smoker. As suggested by the recent ECAS study, we found an association between bedsharing and SIDS for young infants even if parents did not smoke. Novel findings from this study are that bedsharing was associated with SIDS for young infants particularly if their position in bed was between their parents, an association not significantly influenced by parental smoking or breastfeeding.

**Data Collection and Analysis**

Data collection and overall strategy for analysis were described in our previous paper from this study, which included examination of chance, bias, and confounding. We therefore believe the association between bedsharing and SIDS is valid. Infant age is of particular importance in case-control studies because of the unusual age distribution of SIDS and the difficulty of interviewing controls close to the age at night of death of SIDS cases. Calculation of infant age as date of death–date of birth for cases and date of interview–date of birth for controls avoided a systematic bias within age groups, and the random effects logistic
regression procedure (xtlogit) in the software package STATA dealt with any residual age difference between cases and controls. It also was reassuring to note that the rate of last sleep bedsharing in the control population remained static at 15% to 17% in the three age groups examined.

Twelve (10%) of SIDS infants died during the day and only two (17%) bedshared during their last sleep compared with 35% of all SIDS infants. Comparison with control infants where last sleep was always “night” is therefore likely to underestimate, rather than overestimate, any associated risk of night-time bedsharing.

The presence of parental smoking, birth weight, maternal age, and routinely used infant mattress in the final model resulted in the seven individual socioeconomic factors as well as DEPCAT becoming nonsignificant. This suggests that these four measures are surrogates for adverse socioeconomic circumstances within the statistical model.

Relatively few parents stated that the parental bed was the “normal” sleep place for their infant, but we suggest that considerably more infants may bedshare frequently as demonstrated by the higher proportions at last sleep for both cases and controls. It also was reassuring to note that the rate of last sleep bedsharing between cases and controls was greatest for those <60 days of age, as well as the findings of the recent ECAS study. Although our data suggest no risk from bedsharing for infants >11 weeks of age, the wide confidence intervals prevent us from drawing any conclusions about safety.

Most SIDS infants (87%) who bedshared during their last sleep were found dead in the parental bed. The average time interval between “last seen alive” and “found dead” for babies found in the parental bed was 4 hours 45 minutes, the minimum interval being 50 minutes and the maximum 10 hours. It seems unlikely that parents who were awake would not notice that their infant was dead, and we therefore believe it is safe to assume that parents were asleep when death occurred. Five SIDS cases occurred after <2 hours bedsharing, four of these infants were found in the parental bed. This may represent the parent waking to find the baby dead and, thus, a shorter duration of sharing.

The strong associated risk for young infants sleeping between two parents (43% of whom were breastfed at last sleep) suggests that infants may be exposed to extra stress in this position. Although we did not collect data on bedcovers in this study, we know from our previous study that 81% of infants bedsharing at death in an adult bed were covered with a duvet. If an infant is positioned between two parents it would seem possible that the infant could be covered by the duvet and in close proximity to pillows. This suggests a non-ideal sleeping environment that may lead to a greater risk of the infant’s head being covered or of overheating.

There remained a strong association with SIDS for breastfeeding mothers who bedshared with young babies. The CESDI study and a study from Ireland suggest no risk for infants put back into their cot after feeding, although neither study examined different age groups.

If mother was a nonsmoker, a strong associated risk persisted for young infants (OR 8.01, 95% CI 1.20, 53.28).
Previous studies failed to show an associated risk for bedsharing if mother was a nonsmoker.\textsuperscript{1,2} If bedsharing is not associated with a risk of SIDS for older infants, as suggested by our study (OR 1.07, 95\% CI 0.32, 3.56), examination of all ages together may conceal an associated risk for young infants. Also the increased incidence of bedsharing\textsuperscript{4} among nonsmoking parents will have raised the power of recent studies to demonstrate an association. The proportion of control mothers who were nonsmokers and bedshared was 5.8\% (139/2411) in the ECAS study from 1992 to 1996,\textsuperscript{14} and it rose to 11\% (29/263) in our study from 1996 to 2000.

\textbf{CONCLUSION}

Sharing a couch for sleep, sleeping in a room alone, and bedsharing with smoking parents are associated with an increased risk of SIDS. In Scotland, the association with bedsharing remains for young infants even if mother is a non-smoker or the infant is breastfed. We support the revised UK Department of Health advice that the safest place for your baby to sleep is in a cot in your room for the first six months.\textsuperscript{17}

Table A and Table B are available online at www.us.elsevierhealth.com/jpeds.

\textbf{REFERENCES}

Objective  To test the utility of the bedside plasma concentration of B-type natriuretic peptide (BNP) assay as a screen for patent ductus arteriosus (PDA) in premature neonates.

Study design  Newborn infants admitted to the neonatal intensive care unit (NICU) had paired echocardiography and BNP measurements at enrollment and every 4 to 5 days.

Results  Twenty neonates (gestational age ~28.6 weeks and birth weight ~1161 g) had 81 paired echocardiography and BNP determinations. BNP ranged from 5 to 3900 pg/mL. Fifty-six of 81 echocardiograms showed PDA. Significant correlations were found between BNP and ductal size and degree of shunting. Correlation was greater in infants >2 days of age. BNP >300 pg/mL predicted significant PDA, whereas BNP <105 pg/mL predicted absence of significant PDA.

Conclusion  Bedside measurement of BNP correlates with magnitude of PDA in premature newborns, particularly beyond day 2, and may be useful in guiding diagnostic and management strategies. (J Pediatr 2005;147:38-42)

Patent ductus arteriosus (PDA) has been recognized as a cause of significant comorbidity in premature infants since the 1970s.1,2 More than 80% of premature infants born <750 g have a persistent PDA beyond the third day.3 Aorticopulmonary shunting at the PDA is the main cause of congestive heart failure (CHF) in neonates. Excessive pulmonary blood flow results in increased ventilatory dependency and contributes to bronchopulmonary dysplasia.4 Additionally, feeding difficulty, necrotizing enterocolitis, and intracranial hemorrhage may result from diastolic runoff from the systemic circulation.4,9

Because physical examination may be unreliable in determining the presence and magnitude of PDA in premature neonates,10 echocardiography is employed to document PDA shunting.11,12 Routine echocardiography for evaluation of PDA in preterm newborns is not without disadvantages, including cost, discomfort, disruption of the neonatal environment, and limited availability in some centers.

Plasma B-type natriuretic peptide (BNP) is secreted by ventricular myocytes in response to pressure or volume overload of the cardiac ventricles. BNP regulates extracellular fluid volume and blood pressure by natriuresis, diuresis, vasodilation, and antagonism of the renin-angiotensin-aldosterone system.13-18 BNP is present in small amounts in healthy subjects, and in increased amounts in patients with cardiac disease.

BNP is of diagnostic and prognostic value in the assessment of CHF in adults and is used as a bedside screen for CHF19; to rapidly differentiate between cardiac and pulmonary causes of respiratory difficulty20; and as a screening tool for ventricular hypertrophy,21 ventricular diastolic dysfunction,22 transplant rejection,23 and risk for sudden death in adult CHF patients.24

In term neonates, BNP levels peak just after birth and decline over the first 3 months of life.25,26 Bioimmunoassay of plasma BNP has been correlated with the magnitude of PDA shunts in preterm infants.27,28 BNP levels can be measured rapidly at the bedside...
using an FDA-approved device that employs 0.25 mL of arterial, venous, or capillary blood.\textsuperscript{29} This system is used as a screen for CHF in adults.\textsuperscript{30}

We asked whether the rapid bedside determination of BNP level could be used to predict the presence and magnitude of PDA in preterm neonates.

\section*{Methods}

Premature neonates (<36 weeks gestation) admitted to the Neonatal Intensive Care Unit (NICU) of the Weill-Cornell Children’s Hospital of New York-Presbyterian Hospital were recruited, independent of clinical suspicion for PDA. Exclusion criteria included congenital heart disease other than PDA. Infants had transthoracic echocardiography and bedside determination of whole blood BNP concentration on the day of enrollment and every 4 to 5 days until documented closure of the ductus arteriosus on two consecutive echocardiograms or discharge from the nursery, whichever came first. Infants without PDA on initial echocardiography did not undergo repeat echocardiography.

This study was approved by the Institutional Review Board, and written informed consent for participation was obtained from the parents or guardians.

\subsection*{Measurement of Plasma B-type Natriuretic Peptide Levels}

Blood was drawn from indwelling catheters or in conjunction with other laboratory tests to avoid blood collection specifically for study purposes. BNP levels were determined using the Triage BNP assay (Biosite Diagnostics Inc., San Diego, Calif). This assay utilizes a disposable device approved by the FDA. Assays were performed at the bedside. After addition of 0.25 mL of whole blood to the sample port of the test device, blood cells are separated from the plasma by a filter. The plasma enters a reaction chamber containing murine polyclonal fluorescence-tagged BNP antibodies. The reaction mixture is incubated for 2 minutes. Capillary action results in migration of the reaction mixture through the diagnostic lane to a zone of immobilized murine monoclonal antibody against the ring structure of BNP, binding the BNP fluorescent antibody complex. The unbound fluorescent antibodies are washed away by excess plasma. The triage meter quantifies the fluorescence intensity of the BNP assay zone using an internal calibration curve. The assay takes approximately 15 minutes and can be performed by personnel after a brief in-service training. The first several assays were performed in duplicate, and no more than 10\% inter-assay variability was noted. This is consistent with the 9.9-12.2\% assay imprecision approved by the FDA (Biosite Diagnostics, Inc.).

\subsection*{Echocardiography}

Echocardiographic studies were performed using either an Acuson Sequoia\textsuperscript{®} C-256 Echocardiographic System (Siemens-Acuson, Mountain View, Calif) or a Phillips SONOS 5500\textsuperscript{®} Echocardiographic Scanner (Phillips Ultrasound, Andover, Mass). Studies were performed using standard, segmental, sequential scanning techniques, from subxiphoid, precordial, apical, and suprasternal imaging windows. All echocardiographic studies were performed by a single echocardiographer who was blinded to the results of the BNP measurements. Two-dimensional, M-mode imaging and pulsed Doppler information were recorded.

In each study, two sets of electrocardiographic variables were determined: (A) variables correlated with ventricular function and (B) with anatomically and/or physiologically significant PDA;

A) Measurements of left ventricular performance

1) Systolic contractility is represented by \textit{fractional shortening}; \(LVEDD-LVESD/LVEDD\), or the decrease in the dimension of the left ventricle from the beginning to end of systole, expressed as a percent of the end diastolic dimension.

2) Diastolic function is estimated using \(E:A\) ratio, the ratio of early (E) to late (A) transmitral inflow velocities. In a normally compliant ventricle, passive (early) diastolic inflow is greater than late inflow contributed by atrial contraction, and thus, the \(E:A\) ratio is >1; with diastolic dysfunction of the ventricle, the \(E:A\) ratio becomes <1.

3) The myocardial performance (Tei) index, which evaluates combined systolic and diastolic performance using pulsed-wave Doppler velocity spectra of left ventricular inflow and outflow, calculated by the sum of the isovolumic contraction time plus the isovolumic relaxation time divided by the ejection time.

B) Measurement of the anatomic and physiologic significance of PDA:

1) \(PDA\) diameter: absolute diameter of the PDA in millimeters.

2) \(PDA/PAB\): ratio of PDA diameter to the mean diameter of the infant’s pulmonary artery branches (PAB); this was recorded in order to index the ductal size to the patient size.

3) \(LA/Ao\): the ratio of left atrial diameter to aortic diameter: excessive pulmonary blood flow results in increased volume of pulmonary venous return to the left atrium, thus larger PDA corresponds to higher \(LA/Ao\) ratio

4) \(D\Delta\): an expression of magnitude of diastolic “steal” from the descending aorta, and thus systemic circulation, calculated by the area subtended by the diastolic waveform divided by the area subtended by the systolic waveform of the pulsed Doppler tracing. If the diastolic flow is in the retrograde direction, the ratio is assigned a negative number, and thus a negative score represents a clinically more significant ductal shunt.

5) \(S\Delta\): similar to above, a measure of diastolic runoff from the splanchnic circulation because of a sizeable PDA resulting in decreased or reversed diastolic flow in the superior mesenteric artery.

\textit{PDA Score}: To define the overall anatomic and physiologic magnitude of the PDA and correlate this with the
There was significant positive correlation between plasma BNP levels and the anatomic size of the PDA as illustrated by the PDA diameter and the PDA/PAB ratio. BNP is a sensitive marker of left heart dysfunction and renal dysfunction. In this study, we evaluated BNP for the presence of significant ductal left-to-right shunting in newborns. Serum BNP value a “PDA score” was defined. Results of the quantifiable variables (PDA diameter, PDA/PAB, LA/Ao, DAO, SMA) were grouped into quintiles and scored 0 through 4. The mean of those scores for available variables on each echocardiogram was assigned as the PDA score. A higher score correlated with an anatomic and physiologic PDA.

The presence and magnitude of a patent foramen ovale (PFO) also was recorded. Theoretically, a PFO could allow for decompression of the left heart in the setting of volume overload from a PDA, and this may affect the utility of BNP for predicting PDA.

### Statistical Analysis

Echocardiographic measurements as well as plasma BNP measurements are escalating continuous variables. Thus, each echocardiographic variable was correlated with the plasma BNP measurements using Pearson’s correlation coefficients. Subgroup analysis was performed based on age (greater than or less than 2 days), PDA score (less, or above 2) and magnitude of a PFO.

Receiver operating characteristic curves were constructed, and sensitivity, specificity, positive predictive value and negative predictive value for the bioassay (the plasma BNP) for the presence of significant ductal left-to-right shunting were calculated at two different cutoff points.

### RESULTS

A total of 81 echocardiographic studies were performed on the same day as BNP levels on 20 newborns ranging in gestational age from 24 to 35 weeks (mean 28.6 weeks; median 28 weeks) and birth weight 715 to 2200 g (mean 1161 g; median 1070 g). Plasma BNP ranged from <5 to 3900 pg/mL (mean 362 pg/mL; median 105 pg/mL). PDA was present on 56 of 81 echocardiograms, with 13 of 56 judged overall as small, 26 of 56 moderate, and 17 of 56 large.

The frequency of results, and the correlation of ascending PDA magnitude compared with plasma concentrations of BNP for each measured variable are presented in Table 1. There was significant positive correlation between the plasma concentration of BNP and the anatomic size of the PDA as illustrated by the PDA diameter and the PDA/PBA. There was also significant positive correlation between BNP and the expression of the physiologic impact of the PDA on the systemic circulation, as judged by diastolic runoff from the

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**Table I. Correlation Between Echocardiographic Parameters and Bedside BNP Level**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Age ≤2 days</th>
<th>Age &gt;2 days</th>
<th>Control for age</th>
<th>Control for PFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDA</td>
<td>0.626</td>
<td>&lt;.0001</td>
<td>0.493</td>
<td>0.103</td>
<td>0.634</td>
</tr>
<tr>
<td>PDA/PAB</td>
<td>0.634</td>
<td>&lt;.0001</td>
<td>0.521</td>
<td>0.082</td>
<td>0.635</td>
</tr>
<tr>
<td>LA/Ao</td>
<td>0.331</td>
<td>0.004</td>
<td>0.474</td>
<td>0.141</td>
<td>0.391</td>
</tr>
<tr>
<td>DAO</td>
<td>0.549</td>
<td>&lt;.0001</td>
<td>0.15</td>
<td>0.07</td>
<td>0.56</td>
</tr>
<tr>
<td>SMA</td>
<td>0.412</td>
<td>0.002</td>
<td>0.09</td>
<td>0.848</td>
<td>0.414</td>
</tr>
<tr>
<td>PDA score</td>
<td>0.464</td>
<td>0.001</td>
<td>0.217</td>
<td>0.576</td>
<td>0.574</td>
</tr>
</tbody>
</table>

**Table II. Predictive Value of BNP for Significant PDA**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDA diameter &gt;1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP ≥300 pg/mL</td>
<td>52</td>
<td>100</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td>BNP &gt;105 pg/mL</td>
<td>73</td>
<td>80</td>
<td>73</td>
<td>80</td>
</tr>
<tr>
<td>PDA total score &gt;2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP ≥300 pg/mL</td>
<td>60</td>
<td>94</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>BNP &gt;105 pg/mL</td>
<td>95</td>
<td>80</td>
<td>66</td>
<td>98</td>
</tr>
<tr>
<td>PDA/PAB &gt;.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP ≥300 pg/mL</td>
<td>63</td>
<td>98</td>
<td>93</td>
<td>85</td>
</tr>
<tr>
<td>BNP &gt;105 pg/mL</td>
<td>82</td>
<td>77</td>
<td>62</td>
<td>90</td>
</tr>
<tr>
<td>DROF DAO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP ≥300 pg/mL</td>
<td>57</td>
<td>100</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>BNP &gt;105 pg/mL</td>
<td>78</td>
<td>79</td>
<td>72</td>
<td>84</td>
</tr>
<tr>
<td>DROF SMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP ≥300 pg/mL</td>
<td>75</td>
<td>95</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>BNP &gt;105 pg/mL</td>
<td>100</td>
<td>73</td>
<td>73</td>
<td>100</td>
</tr>
</tbody>
</table>

**BNP, B-type natriuretic peptide; DROF DAO, presence of diastolic reversal of flow in descending aorta; DROF SMA, presence of diastolic reversal of flow in superior mesenteric artery; NPV, negative predictive value; PDA, patent ductus arteriosus; PDA/PAB, ratio of PDA diameter to pulmonary artery branch diameter; PPV, positive predictive value.**

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Flynn et al \( P < .05 \) is significant.

DAO, diastolic reversal of flow in descending aorta; E:A, ratio of early to late mitral inflow velocities; FS, fractional shortening; LA/Ao, ratio of diameter of left atrium to diameter of aorta; PCC, Pearson’s correlation coefficient; PDA, diameter of patent ductus arteriosus; PDA/PAB, ratio of patent ductus arteriosus diameter to pulmonary artery branch diameter; PDA score, cumulative measurement of anatomic and physiologic PDA; PFO, patent foramen ovale; SMA, diastolic reversal of flow in superior mesenteric artery; Tei, myocardial performance index.
DAO and SMA. There was a correlation between BNP and the echocardiographic assessment of pulmonary overcirculation from the PDA, as judged by the LA/Ao ratio. There was significant positive correlation between BNP and the overall anatomic and physiologic magnitude of the PDA as represented by the total PDA score. There was no correlation between BNP and the assessment of systolic, diastolic, or combined performance of the left ventricle. The correlation between BNP and PDA was not altered by controlling for continuous variables of age or the presence and magnitude of PFO. Subgroup analysis of BNP and PDA magnitude showed significantly better correlation beyond 2 days of age.

For infants >2 days of age, sensitivity, specificity, negative predictive value, and positive predictive value were calculated for a moderate plasma concentration of BNP of >105 pg/mL and a high level of ≥300 pg/mL as predictive for PDA diameter of >1.5 mm, PDA/PAB >.5, total PDA score >2, and the presence of diastolic reversal of flow in the abdominal descending aorta and superior mesenteric artery (Table II). Plasma BNP concentrations >300 pg/mL are predictive of anatomically and physiologically significant PDA. Using the lower cutoff of 105 pg/mL results in improved sensitivity and negative predictive value.

**DISCUSSION**

The rapid determination of BNP using a commercially available, FDA-approved bedside monitoring system correlated with the presence and magnitude of the PDA as determined by bedside echocardiographic measures. Whole blood BNP concentration correlated with progressive increase in the size of the PDA, the degree of pulmonary overcirculation, and the magnitude of steal from the systemic circulation, as well as a combined score reflecting all of those measurements. BNP concentrations >300 pg/mL were predictive of ductal size sufficient to result in clinically significant alterations in relative systemic and pulmonary blood flows. Using a lower cutoff of 105 pg/mL resulted in improved sensitivity and negative predictive value, yielding accuracy that compares favorably with that of many of the currently accepted clinical uses for BNP.

Lack of correlation was demonstrated between BNP and the measures of systolic, diastolic, and combined function of the left ventricle, consistent with the concept that the major clinical cardiac burden facing premature neonates is large volume aortopulmonary shunting rather than impaired myocardial performance.

The clinical applicability of the bedside BNP in the NICU remains to be determined. Bedside BNP could be used as a routine screen. The presence of a very high BNP level may indicate echocardiographic evaluation, resulting in improved identification of hemodynamically important PDA. On the other hand, a low BNP may not be accurate enough to avoid echocardiography in the newborn with a clinical status suggestive of large PDA. Thus, screening with BNP may result in increased number of preterm neonates receiving echocardiographic evaluation. However, once the presence of absence of PDA has been established, and other forms of congenital heart disease excluded, BNP may obviate the need for repeated echocardiography. Thus, the total number of echocardiograms and the cost of care may be diminished. Additionally, BNP may be useful in determining the indication for, and in evaluating the efficacy of, therapeutic interventions aimed at the PDA. In patients with high BNP and large PDA on echocardiogram who receive medical therapy for the PDA, a falling BNP in conjunction with clinical signs may avoid follow-up echocardiography. This would be especially valuable in NICU settings where routine echocardiography and pediatric cardiology consultation are not easily available.

In this study, the accuracy of BNP for predicting presence and magnitude of PDA was comparable to that of many other uses of BNP cited in the literature and accepted in clinical practice. However, a recent editorial by Bozkurt and Mann31 cautions against the overzealous reliance on laboratory tests like BNP as biomarkers for cardiac disease, based on somewhat suboptimal sensitivity and specificity and proven track record for reproducibility and clinical efficacy. BNP should not supplant echocardiography in the diagnosis of PDA in preterm neonates, but it should be used in conjunction with clinical judgment and echocardiography to aid in the care of these newborns.

**REFERENCES**


CONTINUOUS FEEDING PROMOTES GASTROINTESTINAL TOLERANCE AND GROWTH IN VERY LOW BIRTH WEIGHT INFANTS

ANN DSILNA, RN, BASC, KYLLE CHRISTENSSON, RNM, PhD, LARS ALFREDSSON, PhD, HUGO LAGERCRANTZ, MD, PhD, AND MATS BLENNOW, MD, PhD

Objective To compare the effects of continuous versus intermittent feeding on gastrointestinal tolerance and growth in very low birth weight (VLBW) infants.

Study design In a randomized, controlled trial conducted at 3 neonatal units, 70 premature infants with a gestational age 24 to 29 weeks and birth weight < 1200 g were assigned to 1 of 3 feeding methods: continuous nasogastric feeding, intermittent nasogastric feeding, or intermittent orogastric feeding. Feeding was initiated within 30 hours of birth. Daily enteral and parenteral volumes, caloric and protein intakes, growth, enteral intolerance, and clinical complications were recorded. Cox regression analysis was used to determine primary outcome, the time to achieve full enteral feeding.

Results The continuously fed infants achieved full enteral feeding significantly faster than the intermittently fed infants (hazard ratio [HR] = 1.86; 95% confidence interval [CI] = 1.07 to 3.22). In stratified analysis according to birth weight, the improvement was even more pronounced in the smallest infants, those with birth weight ≤850 g (adjusted HR = 4.13; 95% CI = 1.48 to 11.53). Growth rate was significantly faster in the continuously fed infants (P = .002).

Conclusion In VLBW infants, continuous feeding seems to be better than intermittent feeding with regard to gastrointestinal tolerance and growth. (J Pediatr 2005;147:43-9)

Feeding intolerance is a common problem in very low birth weight (VLBW) infants (birth weight <1200 g), necessitating partial parenteral nutrition (PPN) or total parenteral nutrition (TPN) with intravenous access. However, the use of PPN and/or TPN is associated with increased risk of delayed growth, chronic lung disease, hepatic dysfunction, and nosocomial infections.1-5 Delays to reaching full enteral feeding are probably due to both general physiological immaturity and disorganized gastrointestinal motility.6-9 Studies performed in both animals and humans have demonstrated that intraluminal nutrition is essential to avoid gastrointestinal atrophy and dysfunction.10,11 In previous studies of VLBW infants, early initiation of small volumes of enteral feeding with PPN promoted gastrointestinal maturation and development compared with TPN.12-14

But this feeding method necessitates administering PPN through intravenous lines for extended periods. Continuous feeding decreases energy expenditure in both adults and preterm infants.15,16 Blondheim et al17 found that compared to continuous feeding, intermittent feeding had adverse effects on pulmonary function in premature infants. Further, there is also evidence that feeding given at a slow rate of infusion enhances duodenal motor function compared with bolus feeding.18,19 Time to achieve full enteral feeding is an indicator for gastrointestinal tolerance and it was used as an endpoint in several studies.12,20-23 However, the definition of time to achieve full enteral feeding differs widely. The question of whether different feeding strategies have an effect on gastrointestinal tolerance and growth.

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gastrointestinal tolerance and growth has been raised by several authors, but the results of previous studies are limited and conflicting.\textsuperscript{12,20-24} To our knowledge, only 1 study\textsuperscript{23} has compared continuous versus intermittent feeding in infants with gestational age (GA) as low as 24 weeks. It is therefore of importance to know whether the mode of feeding (continuous versus intermittent) promotes gastrointestinal tolerance and growth in this specific group of very immature infants.

We conducted a randomized controlled trial with the most immature infants with regard to both GA and birth weight. The objective of this study was to compare the effects of continuous versus intermittent feeding on gastrointestinal tolerance, assessed as time to achieve full enteral nutrition, and growth in VLBW infants with a birth weight <1200 g and GA of 24 to 29 weeks.

**METHODS**

**Study Design and Population**

Infants were enrolled within 30 hours of birth and randomly assigned to 1 of the following tube feeding methods: continuous nasogastric feeding (CNG) (index group), intermittent nasogastric feeding every 3 hours (ING) (control group 1), and intermittent orogastric feeding every 3 hours (IOG) (control group 2). Two control groups were chosen to detect any differences of the placement of the feeding tube (oral or nasal) on gastrointestinal tolerance as well as on the infant’s behavior. The impact of different feeding methods on behavior will be the focus of a future report.

The infants remained in their assigned group from the time of randomization to a postmenstrual age of 32 weeks (intervention phase); then infants belonging to the IOG group were changed to nasogastric feeding tube placement. At the same time, the CNG infants were gradually weaned from continuous feeding to intermittent feeding every 3 hours over a period of 10 to 14 days. The sample size, 22 infants in each of the 3 groups, was chosen to permit detection of a 40% difference in the primary outcome, the time to achieve full enteral nutrition, and/or severe medical instability were noted, then the feeding was increased by 15 to 20 mL/kg/day in infants with birth weight < 1000 g and by 15 to 20 mL/kg/day in infants with birth weight 1000 to 1199 g during the first 2 days. Starting on the third day of feeding, if no clinical signs of enteral intolerance and/or severe medical instability were noted, then the amount was increased by 15 to 20 mL/kg/day in all infants. Gastric residuals were checked every 6 hours for ING and IOG and every 8 hours for CNG, or more frequently if signs of enteral intolerance appeared. If any clinical signs of enteral intolerance and/or severe medical instability were noted, then the feeding volume was reduced or the feedings were temporarily withheld according to clinical routines. Enteral intolerance was defined as showing signs of possible necrotizing enterocolitis (NEC), such as abdominal distension, visible bowel loops, bile-stained aspirates or emesis, increased gastric residuals > 50% of the previous meal (for IOG and ING), an exceeded hourly aspiration.

The total amounts of enteral feedings were gradually increased by 10 to 15 mL/kg/day in infants with birth weight < 1000 g and by 15 to 20 mL/kg/day in infants with birth weight 1000 to 1199 g during the first 2 days. Starting on the third day of feeding, if no clinical signs of enteral intolerance and/or severe medical instability were noted, then the amount was increased by 15 to 20 mL/kg/day in all infants. Gastric residuals were checked every 6 hours for ING and IOG and every 8 hours for CNG, or more frequently if signs of enteral intolerance appeared. If any clinical signs of enteral intolerance and/or severe medical instability were noted, then the feeding volume was reduced or the feedings were temporarily withheld according to clinical routines. Enteral intolerance was defined as showing signs of possible necrotizing enterocolitis (NEC), such as abdominal distension, visible bowel loops, bile-stained aspirates or emesis, increased gastric residuals > 50% of the previous meal (for IOG and ING), an exceeded hourly infusion rate (for CNG), or heme-positive stools. PPN with lipids (Intralipid; Fresenius Kabi AG, Germany) and amino acid solutions (EvaLac extempore; Apoteket AB, Sweden or Vaminolac; Fresenius Kabi AG) were started before 72 hours of postnatal age. Sodium, potassium, calcium, trace elements, and vitamins were given according to clinical routines. The total volume of enteral feedings was increased by 10 mL/kg/day to a target volume of 140 to 160 mL/kg/day. When enteral feedings reached 75% of the total target volume, PPN was discontinued. As soon as PPN/TPN was discontinued, fortification...
of human milk was begun for all infants. The protein, fat, lactose, and energy content in the human milk was analyzed in accordance with clinical protocols. Based on the individual breast milk analysis, fortification with addition of supplemental protein (HMF Presem; Semper AB, Sweden) calculated to a protein content of 3 to 4 g/kg/day and fat emulsions (Calogen or Liquigen; SHS International, UK) to a caloric content of 120 to 150 kcal/kg/day. To stimulate nonnutritive sucking, a pacifier was frequently used.

GA was determined by a combination of maternal data and early ultrasound. Information regarding the Clinical Risk Index for Babies (CRIB) score and treatment with antenatal steroids was obtained from the patient records. Small for GA was defined as a body weight at birth less than −2 standard deviations below the mean weight for gestational age. Body weight was measured to the closest gram using an electronic scale (TANITA BLB-12; Umedico AB, Sweden).

Outcome Measures

The primary outcome—time to achieve full enteral feeding—was defined as the time from birth to when enteral feedings fulfilled the total prescribed volume with respect to postnatal age and weight. Thus this could be achieved at volumes < 140 to 160 mL/kg/day. The primary outcome was calculated from the patient records. A minimum of 48 hours of exclusive enteral nutrition was required. Enteral and parenteral energy (kcal/kg/day) and protein (g/kg/day) intake during the intervention phase was calculated from the patient records. Time to regain birth weight was defined as the number of days from birth to regain birth weight. Lower leg growth rate was defined as the average growth of the lower leg, (in mm/day) during the periods from birth to 32 weeks (intervention phase) and from birth to 36 weeks postmenstrual age. To assess lower leg growth, knee–heel length was measured to the closest mm using a knemometer (Force Institute, Copenhagen, Denmark).

Gastric residuals were defined as a gastric residual volume > 50% of the previous meal (for IOG and ING) or as exceeding the hourly feeding infusion rate (for CNG). The total number of occasions with gastric residuals was calculated from the patient records. Emesis was defined as the vomiting of gastric contents. NEC was defined by typical clinical signs together with the presence of pneumatosis intestinalis on abdominal radiographs (Bell stage II). The diagnosis of septicemia required clinical symptoms, elevated C-reactive protein level, and 1 positive blood culture. Respiratory distress syndrome was diagnosed on the basis of characteristic radiographic findings, respiratory distress, and increasing FiO2 demand. The number of infants requiring respiratory support by inspiratory positive pressure ventilation (IPPV), high-frequency oscillatory ventilation (HFOV), continuous positive airway pressure (CPAP), and supplemental oxygenation were extracted from the patient records. Patent ductus arteriosus was defined by the presence of typical clinical findings and confirmed by echocardiography.

Statistical Analysis

Data analysis was performed by intention to treat; that is, all infants were included as randomized. To compare the primary outcome between the index and control groups, the hazard ratio (HR) and 95% confidence interval (CI) were calculated using Cox’s regression analysis. Because the 2 control groups (ING and IOG) did not differ regarding primary outcome, demographic and birth-related factors, and duration of feedings, the infants in the CNG group were compared with the 2 control groups taken together (ie, IOG and ING). One-way analysis of variance (including the Bonferroni post hoc test) was used to analyze demographic and birth-related factors, nutritional outcomes, and clinical morbidities on normal distributed variables. The nonparametric Kruskal-Wallis test was used for nonnormally distributed variables. Fischer’s exact test was used for dichotomous outcomes. Data are expressed as median (range) or mean (standard deviation). Statistical significance was set at 0.05.

RESULTS

Of all eligible VLBW infants born between February 1998 and November 2001, 70 infants (91%) were randomly assigned to 1 of 3 feeding groups. Seven eligible infants (9%) did not participate in the study; 5 were excluded due to a lack of parental consent to partake in the study, 1 was missed, and 1 was excluded because the mother died during caesarean section delivery. Two infants were excluded after randomization because of diagnosed malformations.

There were no statistically significant differences between the groups regarding demographic and birth-related factors (Table I). During the intervention phase, 3 infants from the control groups switched feeding methods because of severe medical problems. One infant in the IOG group switched to CNG for 14 days (35% of the intervention phase) because of severe apnea and bradycardia due to gastroesophageal reflux. Another infant in the IOG group switched to ING for 13 days (30.2% of the intervention phase) because of severe bradycardia occurring during tube insertions. One infant in the ING group switched to IOG for 6 days (9.5% of the intervention phase) because of CO2 retention resulting from nasal obstruction, probably caused by the feeding tube.

With regard to the primary outcome, the CNG infants achieved full enteral feeding faster than the control infants (HR = 1.86; 95% CI = 1.07 to 3.22). This result remained virtually unchanged after adjustment for demographic and birth-related factors (HR = 1.84; 95% CI = 1.03 to 3.27) (Table II). To investigate whether improvement differed according to birth weight, a stratified analysis on birth weight was carried out. Among infants with a birth weight of ≤ 850 g, the CNG infants achieved full enteral feeding considerably faster than the control infants and also after adjustment of confounding factors relating to demographic and birth-related factors (HR = 4.13; 95% CI = 1.48 to 11.53). Among the infants with birth weight > 850 g, the difference between compared groups was smaller and more uncertain in terms of the
Table I. Distribution of demographic and birth-related factors among study infants (n = 68), by group

<table>
<thead>
<tr>
<th>Continuous nasogastric index group (n = 22)</th>
<th>Intermittent nasogastric control group 1 (n = 22)</th>
<th>Intermittent orogastric control group 2 (n = 24)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)*</td>
<td>864 (172)</td>
<td>833 (177)</td>
<td>.449</td>
</tr>
<tr>
<td>Knee-heel length at birth (mm)*</td>
<td>77.2 (7.1)</td>
<td>75.4 (5.3)</td>
<td>.075</td>
</tr>
<tr>
<td>Gestational age (weeks)*</td>
<td>26.9 (1.3)</td>
<td>26.6 (1.2)</td>
<td>.735</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>10 (45.5)</td>
<td>13 (59.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar score, 5 minutes†</td>
<td>8.0 (5.0 to 10.0)</td>
<td>8.0 (3.0 to 10.0)</td>
<td>.660</td>
</tr>
<tr>
<td>CRIB score #*</td>
<td>5.5 (3.2)</td>
<td>6.2 (3.2)</td>
<td>.654</td>
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<tr>
<td>Small for gestational age, n (%)</td>
<td>7 (31.8)</td>
<td>6 (27.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment with antenatal steroids, n (%)</td>
<td>19 (86.4)</td>
<td>18 (85.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.
*Values are mean (standard deviation).
†Values are median (range).
‡Index versus control 1, \( P = .547 \); index versus control 2, \( P = .768 \); control 1 versus control 2, \( P = .774 \).
§Index versus control 1, \( P = 1.000 \); index versus control 2, \( P = .159 \); control 1 versus control 2, \( P = .159 \).
¶Index versus control 1, \( P = 1.000 \); Index versus control 2, \( P = .464 \); control 1 versus control 2, \( P = .469 \).

Table II. Crude and adjusted hazard ratio for achieving full enteral feeding together with 95% CI for infants with continuous feeding compared with infants with intermittent feeding, by birth weight

<table>
<thead>
<tr>
<th>Continuous versus intermittent feeding ‡</th>
<th>Crude*</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95.0% CI)</td>
<td></td>
<td>HR (95.0% CI)</td>
</tr>
<tr>
<td>Birth weight ≤ 850 g§</td>
<td>2.57 (1.15 to 5.76)</td>
<td>4.13 (1.48 to 11.53)</td>
</tr>
<tr>
<td>Birth weight &gt; 850 g grams‡</td>
<td>1.63 (0.75 to 3.53)</td>
<td>1.89 (0.80 to 4.42)</td>
</tr>
</tbody>
</table>

*Crude, no adjustments.
†Adjusted for birth weight, gestational age, small for gestational age, Apgar score at 5 minutes, CRIB score, antenatal steroids, knee-heel length at birth, and sex.
‡Continuous feeding, \( n = 22 \); intermittent feeding, \( n = 46 \).
§Birth weight ≤ 850 g, \( n = 35 \); Continuous feeding, \( n = 12 \); intermittent feeding, \( n = 23 \).
¶Birth weight > 850 g, \( n = 33 \); continuous feeding, \( n = 10 \); intermittent feeding, \( n = 23 \).

width of the confidence interval (HR = 1.89; 95% CI = 0.80 to 4.42) (Table II). No statistically significant difference was found between the 2 control groups, neither crude (HR = 1.22; CI = 0.66 to 2.24) nor after adjustment for demographic and birth-related factors (HR = 1.62; CI = 0.77 to 3.4).

Energy and protein intake during the intervention phase was similar between the groups, as was the time to regain birth weight (Table III). However, the lower leg growth rate during the intervention phase and from birth to 36 weeks postmenstrual age was significantly faster in the CNG infants than in the control groups (\( P = .002 \) and .012, respectively). The rates of feeding intolerance, gastric residuals, and vomiting were higher in the IOG group but did not differ significantly from those in the CNG and ING groups (\( P = .055 \) and .090, respectively). Only 2 infants (1 in the CNG group and 1 in the IOG group) regressed to PPN after reaching full enteral feeding.

The distribution of clinical morbidities is given in Table IV. All study infants needed respiratory support with supplemental oxygen. The need for supplemental oxygen and mechanical ventilatory support (IPPV/HFOV and CPAP) was comparable among the groups, as was the incidence of respiratory distress syndrome. Septicemia, the need for antibiotic treatment, patent ductus arteriosus, and NEC were similar among the groups. NEC was diagnosed in 3 infants. Two cases occurred early in the intervention phase, 1 IOG infant at day 13 and 1 CNG infant at day 14. One infant in the CNG group developed NEC 3 weeks after the intervention phase was completed, at a postmenstrual age of 35 weeks. The mortality rate also did not differ significantly among the 3 groups. Three infants, 1 in each feeding group, died early in the intervention phase due to respiratory and circulatory collapse. Two infants in the CNG group died after the intervention phase at postmenstrual ages of 33 and 47 weeks, due to septicemia in combination with severe respiratory and circulatory distress and chronic lung disease.

**DISCUSSION**

This study demonstrates that continuous feeding of infants with birth weight < 1200 g and GA of 24 to 29 weeks improved gastrointestinal tolerance and shortened the time needed to achieve full enteral feeding relative to bolus feeding. The study also indicates that continuous feeding might be even more physiologically suitable with regard to enteral tolerance in the extremely low birth weight infants ≤850 g, though the relatively low number of subjects hampers a definitive conclusion.

The primary outcome of the study—the time to achieve full enteral feeding—was measured with a high degree of
precision, because the infants were continuously monitored and the outcome was well defined and easily determined. Misclassification of outcome was unlikely, even though the study was not blinded with regard to the study group. The comparison between the continuously fed infants and the intermittently fed infants was adjusted for factors that might influence the primary outcome. We adjusted for sex, birth weight, GA, small for GA, knee–heel length at birth, Apgar score, CRIB score, and antenatal steroid treatment. We thus believe that the observed differences in time to full enteral feeding are real. The results of our study are in contrast to previously reported findings. One reason for this might be due to the fact that our study focused on more preterm infants with respect to both GA and birth weight. Moreover, the design of the present study, combining the exclusive use of human milk, the early start of enteral feeding within 30 hours of age, and the daily increase of enteral milk volumes, also differs from that of previously reported randomized trials. Even though the studies of Baker et al and de Ville et al indicated that a slow infusion rate of feedings may promote maturation of intestinal function in stable preterm infants, to our knowledge only 1 study has investigated continuous versus intermittent feeding in critically ill premature infants with a GA as low as 24 weeks and with a similar study protocol to ours. That study reported results in line with ours, although it was a retrospective study.

In agreement with findings of Akintorin et al and Silvestre et al, but inconsistent with those of Schanler et al,
we observed no statistically significant differences in feeding intolerance, such as frequency of gastric residuals and emesis between continuously fed and intermittently fed infants, even though the frequency of gastric residuals could have been influenced by the more restricted definition for the continuous group as compared with the control group. However, gastric residuals and emesis in the present study population were more common in the IOG group. Furthermore, the feeding method was switched because of severe medical problems associated with the feeding method only for the intermittently fed infants.

The CNG infants had significantly faster linear bone growth compared with the control infants during the intervention phase, from birth to 32 weeks of postmenstrual age; this difference remained at 36 weeks of postmenstrual age. These results are supported by previous findings focusing on the influence of feeding methods on bioenergetic and metabolic response. Heymsfield et al.\textsuperscript{15} reported a significant reduction in thermal losses in adults and suggested that energy requirements are lower during continuous feeding compared with meal ingestion. In a publication by Grant et al.\textsuperscript{16} increased energy efficiency was found in continuously fed premature infants compared with intermittently fed premature infants. In contrast with these results but in line with previous reports,\textsuperscript{12,21–23} we could not detect any differences between study groups regarding time to regain birth weight. However, one reason for the difficulty with using weight gain as a measurement for growth in these very immature infants is the fact that weight gain may be influenced by changes in fat and fluid deposition and thus may not necessarily reflect changes in true growth.\textsuperscript{33,34} Another explanation could be the problems with using a nonlinear variable, such as weight, to assess true growth.

We found no differences in adverse effects, such as mortality, NEC, and sepsis, among the 3 groups, however, the relatively small sample size limited the ability to detect such differences. The incidence of NEC (4.4\%) in our study population appeared to be lower than that reported in previous studies of early enteral feeding in populations with similar GA and birth weight.\textsuperscript{12,14} This may be due to the very early initiation of feeding, which probably avoids gastrointestinal atrophy and dysfunction,\textsuperscript{10,11} in combination with the protective effect against NEC associated with the use of human milk.\textsuperscript{12,35}

Even though the limited sample size in our study hampered the ability to detect any differences in the incidence of sepsis, several authors have correlated the use of PPN/TPN with an increased risk of sepsis.\textsuperscript{3–5} Moreover, Kilbride et al.\textsuperscript{36} recently suggested early introduction of trophic feeds, consistent advancing of feeding volumes, and removal of deep intravenous lines before 21 days of life as potentially better practices for decreasing neonatal nosocomial bacteremia.

It is of major concern that very immature infants reach full enteral feeding as soon as possible, not only to obviate the well-known negative effects connected with parenteral nutrition on morbidity,\textsuperscript{1–5,36} but also to minimize the negative sensorial experiences for the child linked to the use of intravenous lines. In conclusion, the results from the present study strongly indicate that continuous feeding promotes gastrointestinal tolerance and growth among infants with GA below 29 weeks and with birth weight <1200 g, and thus is preferable to intermittent feeding.

REFERENCES


50 Years Ago in The Journal Of Pediatrics

THE PSYCHOLOGIC DEVELOPMENT OF A GROUP OF CHILDREN BROUGHT UP IN A HOSPITAL TYPE RESIDENTIAL NURSERY

Du Pan M. J Pediatr 1955;47:124-9

At the beginning of the 20th century, the mortality rate in the United States was close to 100% in infants who remained institutionalized. In 1909 Dr Henry Chapin advocated that those infants needed to be placed in foster homes. In 1941 the association between failure to thrive and emotional deprivation was recognized in institutionalized infants. Subsequently, the majority of US residential institutions were closed, and children were placed in foster homes. Dr Martin Du Pan studied the developmental outcomes of 14 children admitted before the age of 4 months in a residential nursery in Switzerland. After 8 months of admission, their average developmental scores were normal. Contradicting previous studies their developmental quotients did not decrease after 14 months of admission. In agreement with previous and current research their average scores were higher in “motricity,” “adaptivity,” and lower on “sociability” and language. The parents of 10 of the 14 children did not report any developmental or behavioral concerns 1 to 2 years after discharge from the nursery. The author concluded that the development of children placed in a high-quality residential nursery with toys and staff that frequently interacted with the children was similar to that of children living with a family. The power of the study was limited due to the small number of cases, and current data do not support Dr Du Pan’s conclusions. Research has shown that institutionalized children with optimal care can maintain average developmental quotients, but they are lower when compared with matched low-income children living with biologic or foster parents. In spite of the best care, children raised in institutions are at high risk for attachment disorder. Current research on international adoption reveals that children adopted from deprived institutions had growth deficiency, cognitive and language delays, social and behavioral abnormalities, inattention, hyperactivity, and “quasi-autism.” Better outcomes were seen in children adopted before 6 months of age. Today we still agree with Dr Chapin’s statement: “The best conditions for the infant require a home and a mother,” with the observation that a mother can be substituted by another consistent and dedicated caregiver to whom the infant can form a stable attachment.

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Objective  Multiple studies have documented an increase in weight gain after 5 to 10 days of massage therapy for preterm neonates. The massaged preterm neonates did not consume more calories than the control neonates. One potential mechanism for these effects might involve massage-induced increases in vagal activity, which in turn may lead to increased gastric motility and thereby weight gain.

Study design  The present randomized study explored this potential underlying mechanism by assessing gastric motility and sympathetic and parasympathetic nervous system activity in response to massage therapy (moderate pressure) versus sham massage (light pressure) and control conditions in a group of preterm neonates.

Results  Compared with preterm neonates receiving sham massage, preterm neonates receiving massage therapy exhibited greater weight gain and increased vagal tone and gastric motility during and immediately after treatment. Gastric motility and vagal tone during massage therapy were significantly related to weight gain.

Conclusion  The weight gain experienced by preterm neonates receiving moderate-pressure massage therapy may be mediated by increased vagal activity and gastric motility. (J Pediatr 2005;147:50-5)

Randomized, controlled studies have consistently documented greater weight gain in preterm neonates receiving massage therapy (also known as tactile/kinesthetic stimulation).1-3 Preterm neonates receiving 5 to 10 days of massage therapy exhibited a 21% to 47% greater increase in weight gain during the study period and were hospitalized for 3 to 6 days less than control neonates receiving standard care. The question of how massage therapy facilitates weight gain in preterm neonates remains unanswered. One hypothesis was that massage leads neonates to consume more calories. However, preterm neonates who received massage did not consume more formula or calories than the control preterm neonates.4-9 Another hypothesis was that massaged neonates conserved more calories by increasing sleeping time. However, the massaged neonates were more alert and spent more time in active awake states than control neonates, suggesting that enhanced weight gain was not achieved by decreased activity.8

A third hypothesis is that moderate-pressure massage stimulates vagal activity, leading to more efficient food absorption through increased gastric motility and the release of food absorption hormones, such as insulin.10 This hypothesized mechanism is based on our work demonstrating increased vagal activity and insulin levels in preterm neonates after massage therapy,10 on a rat model showing that moderate-pressure stroking is critical for stimulating the release of ornithine decarboxylase (an index of growth hormone),11,12 and on both rat and human models showing that stimulation of pressure receptors in the intraoral cavity increases vagal activity and the release of food absorption hormones.13

We examined this potential mechanism by assessing indices of vagal activity and gastric motility in preterm neonates receiving moderate-pressure massage therapy. Based on previous findings and on our proposed pressure receptor stimulation model, we hypothesized that preterm neonates receiving moderate-pressure massage therapy would show greater weight gain and increased vagal activity and gastric motility, but not greater calorie intake than preterm neonates receiving light-pressure stimulation (sham/ placebo massage) or controls.

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Participants

After approval by the institutional review board of the University of Miami School of Medicine and parental consent, medically stable preterm neonates were recruited from the University of Miami/Jackson Memorial Hospital Neonatal Intensive Care Unit. Neonates were excluded from this study if they (a) required surgery; (b) received respiratory support, antibiotics, or phototherapy; (c) had genetic anomalies, congenital heart malformations, and/or central nervous system dysfunction; or (d) were HIV-positive or immunocompromised or (e) if their mothers had a history of syphilis, hepatitis B, or alcohol/illicit drug use. At study entry, all neonates were gavage-fed. There were no systematic differences in diagnoses between treatment groups.

A total of 115 preterm neonates met our inclusion criteria. Of these, 61 had parents who could not be contacted (n = 55) or refused to participate in the study (n = 6). Due to equipment malfunctions and unusable data, 6 neonates (3 control, 2 massage, and 1 sham) were excluded from the study. Our final sample comprised 48 hospitalized preterm neonates who were assigned to a control (n = 16), massage therapy (n = 16), or sham massage therapy group (n = 16) based on stratified randomization based on birth weight and a 1:1:1 allocation ratio implemented with a permuted block design based on a computer-generated randomization list and a 1:1:1 allocation ratio implemented to attain equal treatment group sizes.

Data collection was done by researchers blind to the neonates’ group assignments. Parents and clinical staff were also blind to the neonates’ group assignments and to the hypotheses of the study. Massage therapists were blind to the hypotheses of the study. Power analyses based on our previous neonatal vagal tone study suggested that a minimum of 10 to 15 participants per group would be needed to detect vagal tone differences between groups (80% power; \(P < .05\); 2-tailed test).

Throughout this 5-day massage therapy study, relevant medical history was gathered, and mean weight gain per day per neonate weight, mean calories consumed per day per neonate weight, and days from beginning of treatment to discharge (days to discharge) were recorded. Electrocardiograms (ECGs) and electrogastrograms (EGGs) were collected during the first treatment session (control/ massage/sham) of the study for a total of 45 minutes (15 minutes baseline, 15 minutes treatment, and 15 minutes posttreatment) at approximately the same time for all subjects (between 1:00 and 3:00PM) 1 hour after feeding. All subjects continued to receive standard nursery care during the course of the study.

Treatment Groups

Treatment was provided for 3 15-minute periods per day for 5 days, 1 hour after feeding by massage therapists trained in the study protocol. Training involved presentation of a structured video treatment protocol followed by a series of observation and practice sessions. Reliability was assessed by the authors before study commencement and reevaluated throughout the study period to ensure protocol compliance, especially with respect to the amount of pressure provided. Each neonate received treatment from several therapists to ensure that treatment effects were the result of the treatment protocol and not from any one particular therapist. Therapists providing the light-pressure sham massage did not perform moderate-pressure massage therapy and vice versa.

The massage therapy consisted of the 15-minute preterm neonate massage therapy protocol used by Field et al.\(^5\) The 15-minute stimulation sessions included 3 standardized 5-minute phases, with tactile stimulation in the first and third phases and kinesthetic stimulation in the middle phase. In the tactile stimulation phase, the neonate was placed in a prone position and stroked with moderate pressure (sufficient to produce a slight skin color change from pink to white in a Caucasian neonate or slight indentations in the skin for all neonates). The neonate is massaged for 5 1-minute periods (12 strokes at approximately 5 seconds per stroking motion) over each region in the following sequence: (1) from the top of the head to the neck and back to the top of the head, and back to the neck; (2) from the neck across the shoulders; (3) from the upper back to the waist and back to the upper back; (4) from the thigh to the foot to the thigh on both legs; and (5) from the shoulder to the hand to the shoulder on both arms. During the kinesthetic stimulation phase, the neonate is placed in a supine position and each arm, then each leg, and finally both legs together are flexed and extended (as in a bicycling motion). Each flexion/extension motion lasts 10 seconds, for a total of 5 1-minute segments.

The light-pressure sham massage followed the same Field et al.\(^5\) protocol. The scheduling and duration of the sham and massage therapy sessions were identical in the type, number, and rate of movements, with the exception that light-pressure stroking (producing no skin color change in a Caucasian neonate or skin indentation for all neonates) was used during the first and last 5-minute periods of the sham massage procedure. The middle 5-minute period of kinesthetic stimulation remained the same. The sham massage procedure served as a pressure stimulation control condition.

Physiological Measures

An ECG was obtained from each neonate using a UFI Model SRS2004/d-SP Electrophysiology Acquisition System (UFI, Morro Bay, CA) to derive measures of heart rate and autonomic nervous system function. ECGs were acquired by placing 3 disposable silver chloride electrodes on the neonate’s chest and back. The signal was filtered between 1 Hz and 100 Hz, amplified using a gain of 2000, and sampled at a rate of 1000 Hz. After manual artifact correction, ECG data were converted to R-wave intervals (interbeat intervals [IBIs]) to the nearest millisecond using data acquisition and analysis software (Acq Knowledge software, version 3.5; Biopac Systems). IBI data were then analyzed using CMETI software\(^14\) (freeware written by J.J.B. Allen, Department of Psychology, University of Arizona, Tuscon, AZ) to obtain measures of sympathetic nervous system activity (cardiac
sympathetic index (CSI) and vagal activity (cardiac vagal index [CVI] and vagal tone [respiratory sinus arrhythmia]).

EGGs were evaluated in each neonate using a UFI Model SRS2004/d-SP Electrophysiology Acquisition System (UFI) to assess gastric motility. EGGs were acquired by placing a ground electrode and 3 disposable silver chloride electrodes on the neonate’s abdomen and back. The EGG signal was filtered between 1 Hz and 45 Hz, amplified using a gain of 3000, and sampled at a rate of 4.267 Hz. After manual artifact correction, the EGG data were spectrally analyzed using fast Fourier transforms on 15-minute epochs of EGG data using Matlab (version 6.0) to derive power density estimates in 0.5-cpm-wide bins from 1 to 15 cpm. Neonate EGG activity occurring between 2 and 4 cpm is considered normogastric activity, that occurring between 4 and 9 cpm is considered tachygastric activity, and that occurring between 1 and 2 cpm is considered bradygastric activity. Inasmuch as each recording epoch lasted only 15 minutes, we could not obtain reliable bradygastric measurements.

Absolute EGG power comparisons between subjects are not reliable, because of the influence of several confounding factors (eg, abdominal wall thickness, skin preparation, electrode placement). As such, relative rather than absolute EGG power was analyzed. Relative power in the 2- to 4-cpm band (representing normal gastric activity) was computed as %2 to 4 cpm activity = (2 to 4 cpm power/1 to 15 cpm power) x 100. Tachygastria (representing abnormally fast gastric activity) was computed as %4 to 9 cpm activity = (4 to 9 cpm power/1 to 15 cpm power) x 100.

Statistical Analyses

Analysis of variance (ANOVA) and $\chi^2$ analyses were used to assess equivalence across groups on all demographic study entry variables. ANOVA was also used to assess for group differences in weight gain, calorie consumption, and days to discharge. Significant ANOVAs were followed by post hoc Bonferroni-corrected $t$-tests.

Group (control vs massage vs sham) by time (pre/during/post) repeated-measures ANOVAs were conducted on vagal (ie, CVI and vagal tone) and sympathetic activity and gastric motility (normal EGG and tachygastria) measures. Significant repeated-measures ANOVAs were followed by post hoc trend analyses to detect polynomial trend components, including positive or negative linear trends, suggesting an increase or decrease, respectively, in values during treatment and posttreatment periods, and U-shaped or inverted U-shaped quadratic trends, indicating an increase or decrease, respectively, of values during the treatment period. Finally, Pearson’s $r$ correlation analysis was used to assess the relationships between weight gain, vagal activity, and gastric motility.

| Table I. Means and standard deviations (range under means in parentheses) for demographics |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Control N = 16 | Massage N = 16 | Sham N = 16 | df/F or $\chi^2$, $\eta^2$ | $P$ |
| Gender* | | | | | | |
| Male 62.5% | 25.0% | 43.8% | $\chi^2(2) = 4.57$ | NS |
| Female 37.5% | 75.0% | 56.2% | | |
| Ethnicity | | | | | | |
| African-American 42.9% | 56.3% | 37.5% | $\chi^2(4) = 5.77$ | NS |
| Hispanic 50.0% | 43.8% | 37.5% | | |
| Caucasian 7.1% | 0% | 25.0% | | |
| Birth weight (g) 1265 ± 333 (560-1800) | 1091 ± 193 (790-1430) | 1184 ± 205 (890-1525) | F(2,47) = 1.9, .08 | NS |
| Gestational age 29.6 ± 2.7 (22-33) | 29.8 ± 3.4 (25-37) | 30.3 ± 1.7 (27-33) | F(2,47) = 0.27, .01 | NS |
| Ponderal index 2.0 ± 0.4 (1.2-2.6) | 2.1 ± 0.3 (1.4-2.6) | 2.2 ± 0.2 (1.8-2.4) | F(2,47) = 0.94, .04 | NS |
| Days since birth 29 ± 20 (9-76) | 34 ± 18 (12-75) | 32 ± 13 (13-56) | F(2,47) = 0.39, .02 | NS |
| Day 1 weight (g) 1504 ± 224 (1115-1865) | 1527 ± 236 (1085-1855) | 1503 ± 189 (1220-1860) | F(2,47) = 0.06, .08 | NS |

*Exploratory analyses failed to reveal any gender differences in weight gain, vagal activity, or gastric motility responses to massage therapy.

| Table II. Means (and standard deviations under means) for clinical outcomes |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Control | Massage | Sham | F, $\eta^2$, $P$ |
| Days to discharge 25.5 ± 11.1 | 20.1 ± 11.2 | 24.4 ± 13.2 | F = 0.93, .04, NS |
| Weight gain (kg/ day)* 15.5 ± 3.68 | 19.6 ± 3.96 | 16.2 ± 3.86 | F = 5.13, .19, < .01 |
| Caloric intake (kg/ day) 111 ± 12.4 | 111 ± 11.4 | 121 ± 9.2 | F = 0.24, .01, NS |

*Infants in the massage group gained significantly more weight than infants in the control or sham massage groups.

sympathetic index (CSI) and vagal activity (cardiac vagal index [CVI] and vagal tone [respiratory sinus arrhythmia]).

EGGs were evaluated in each neonate using a UFI Model SRS2004/d-SP Electrophysiology Acquisition System (UFI) to assess gastric motility. EGGs were acquired by placing a ground electrode and 3 disposable silver chloride electrodes on the neonate’s abdomen and back. The EGG signal was filtered between 1 Hz and 45 Hz, amplified using a gain of 3000, and sampled at a rate of 4.267 Hz. After manual artifact correction, the EGG data were spectrally analyzed using fast Fourier transforms on 15-minute epochs of EGG data using Matlab (version 6.0) to derive power density estimates in 0.5-cpm-wide bins from 1 to 15 cpm. Neonate EGG activity occurring between 2 and 4 cpm is considered normogastric activity, that occurring between 4 and 9 cpm is considered tachygastric activity, and that occurring between 1 and 2 cpm is considered bradygastric activity. Inasmuch as each recording epoch lasted only 15 minutes, we could not obtain reliable bradygastric measurements.

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Statistical Analyses

Analysis of variance (ANOVA) and $\chi^2$ analyses were used to assess equivalence across groups on all demographic study entry variables. ANOVA was also used to assess for group differences in weight gain, calorie consumption, and days to discharge. Significant ANOVAs were followed by post hoc Bonferroni-corrected $t$-tests.

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NS, not significant.
RESULTS

Study Entry Variables

Maternal and neonate demographic and study entry characteristics did not differ between groups (Table I).

Outcome Variables

Control versus massage versus sham ANOVAs revealed that even though the preterm neonates in the massage therapy group gained significantly more weight than neonates in the control or sham massage groups, they did not consume more calories (Table II). Intent-to-treat analyses revealed that even with the inclusion of the 6 neonates with missing physiological data, the neonates in the massage therapy group gained significantly more weight than those in the control or sham massage groups ($F(2, 15) = 6.93; P < .01; \eta^2 = .21$), but did not consume any more calories ($F(2, 15) = 0.10; P = \text{not significant}; \eta^2 = .01$).

EKG and EGG Analyses

Group by time (pre/during/post) repeated-measures ANOVAs conducted on ECG and EGG measures revealed significant group–time interactions for CVI and vagal tone (Figure 1) and normal EGG activity and tachygastria (Figure 2). To better understand these interactions, post hoc trend analyses were conducted and revealed the following: (1) a significant increase in CVI (linear trend; $F(1, 15) = 8.42; P < .01; \eta^2 = .36$) that peaked marginally during the massage (quadratic trend; $F(1, 15) = 3.13; P < .1; \eta^2 = .17$) for only the massage therapy group; (2) a significant increase in vagal tone (linear trend; $F(1, 15) = 5.62; P < .05; \eta^2 = .27$) that peaked during the massage (quadratic trend; $F(1, 15) = 4.54; P < .05; \eta^2 = .23$) for only the massage therapy group; (3) a significant increase in gastric motility (linear trend; $F(1, 15) = 10.66; P < .01, \eta^2 = .42$) for only the massage therapy group; and (4) a significant decrease in tachygastria (linear trend; $F(1, 15) = 9.87; P < .01; \eta^2 = .39$) for only the massage therapy group.
Correlation Analyses

Correlation analyses revealed that relative weight gain was significantly related to changes in vagal tone during the massage ($r(16) = .69, P < .01$) and changes in gastric motility after the massage ($r(16) = .55, P < .01$). This finding suggests that neonates exhibiting the greatest increase in vagal activity during the massage and the greatest increase in gastric motility immediately after the massage on the first day of treatment gained the most weight during the 5-day treatment period.

DISCUSSION

Consistent with previous studies, preterm neonates receiving massage therapy gained 27% more weight than controls even though they did not consume more calories than controls.1-10 Consistent with the model proposed by Field,10 vagal activity peaked during massage therapy and remained significantly higher than baseline throughout the 15-minute poststimulation period. The consistent findings obtained using 2 independently derived estimates of vagal activity (CVI14 and vagal tone14,16) support the validity of these metrics as noninvasive estimates of vagal activity. The preterm neonates receiving massage therapy did not exhibit increased CSI activity during or after the massage therapy procedure. As expected, gastric motility increased and tachygastria decreased during the treatment and posttreatment periods.

To our knowledge, this is the first study to examine gastric motility in response to massage therapy in neonates. Measures of vagal and gastric motility were measured only during the first treatment day. Future research should assess vagal activity and gastric motility throughout the 5-day treatment period.

Even though all of the preterm neonates in this study were medically stable and exhibited comparable diagnoses and severity of illness profiles, we did not account for any systematic differences in the types of medications administered throughout the study. This could have potentially confounded our weight gain, vagal activity, and gastric motility findings, because preterm neonates are commonly given medications that affect weight gain (eg, diuretics, steroids) and cardiovascular, respiratory (eg, methylxanthines), and gastrointestinal (eg, antacids, prokinetic agents) function.

The moderate-pressure massage group exhibited significantly (21%) greater weight gain during the treatment period than the sham massage therapy group. Like the standard care control group, the sham massage therapy group did not exhibit a significant change in vagal activity or gastric motility during the treatment or posttreatment phases of the study. These moderate- versus light-pressure massage therapy findings suggest the involvement of pressure receptors and/or baroreceptors. Animal studies also indicate that pressure receptor stimulation activates the vagus, in turn releasing food absorption hormones13 and ornithine decarboxylase.11,12 Further, a recent study indicated that compared with light-pressure stimulation, moderate-pressure stimulation reduced heart rate and central nervous system arousal in adults,19 and a neonate massage study indicated more optimal growth (weight gain and length) and development (Brazelton Neonatal Behavior Assessment scores) after moderate- versus light-pressure massage during the first few months of life.20

Consistent with our model, the change in vagal activity elicited by massage therapy was significantly related to weight gain during the 5-day treatment period. This suggests that neonates who demonstrate increased vagal activity during massage are more likely to benefit from massage therapy. In fact, the 12 preterm neonates who demonstrated an increase rather than a decrease in vagal activity during the first massage gained 19% more weight than the 4 neonates who exhibited a decrease in vagal activity.

Taken together, these findings offer partial support for our hypothesized model indicating that moderate-pressure massage leads to greater weight gain through its effects on vagal activity and gastric motility. Further validation of this model will require assessing the effects of vagal activity and gastric motility on food absorption and digestive hormones during massage therapy while controlling for other potential mediating factors in a larger sample.

We thank the mothers and neonates who participated in this study and Julia Beutler, Larissa Feijo, Karla Gill, and Yanezy Vera for their help with participant recruitment and data collection. We also thank John Allen for his help with the ECG analysis software.

REFERENCES

BREASTFEEDING AND OVERWEIGHT: LONGITUDINAL ANALYSIS IN AN AUSTRALIAN BIRTH COHORT

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Objective To examine adiposity in relation to breastfeeding using longitudinal analysis in an Australian birth cohort.

Study design Repeated surveys from 16 weeks gestation to 8 years in a cohort (N = 2087) recruited through antenatal clinics. Overweight was defined by National Center for Health Statistics 95th percentiles for weight-for-length at 1 year and body mass index (BMI) at 3, 6, and 8 years. Overweight was examined using Generalized Estimating Equations with results summarized as OR. BMI Z scores were analyzed in mixed models.

Results At 1 year, infants breastfed >12 months were the leanest group (mean Z score -0.16, 95% CL -0.28, -0.04; not breastfed 0.16, 95% CL 0.02, 0.29; breastfed ≤4 months 0.31, 95% CL 0.22, 0.40; 5-8 months 0.17, 95% CL 0.06, 0.27; 9-12 months 0.11, 95% CL 0.01, 0.22). From 1 to 8 years, children breastfed ≤4 months had the greatest risk of overweight (OR 1.29, 95% CL 0.89, 1.97) and the highest prevalence of maternal obesity, smoking, and lower education.

Conclusions Infants breastfed >12 months were leaner at 1 year but not at 8 years. Breastfeeding ≤4 months was associated with greatest risk of overweight and adverse maternal lifestyle. Familial factors may modify associations between breastfeeding and adiposity beyond infancy. (J Pediatr 2005;147:56-61)

Although breastfeeding may be protective against overweight or obesity in childhood and adolescence, the evidence is not conclusive because of differences among reported studies. These include retrospective collection of data, inconsistent definitions of breastfeeding, variations in adjustment for confounders, differences in sample size, and different definitions of overweight or obesity. However, a recent meta-analysis reported a small protective effect of breastfeeding relative to no breastfeeding. Adjustment for confounding decreased the possible protective effect and, although the authors considered that further adjustment for residual confounding was unlikely to remove the effect, links between breastfeeding and obesity are associated with socioeconomic characteristics and maternal factors such as obesity and smoking during pregnancy. Consideration of such covariates is particularly important given the clear associations between maternal obesity or overweight and lower rates, or shorter duration, of breastfeeding and the role of maternal weight as a strong predictor of overweight in children.

However, most reports that have examined adiposity in relation to breastfeeding based on cross-sectional, or repeated cross-sectional, data have not used longitudinal analysis. We used data from the Western Australian Pregnancy Cohort (Raine) Study, a birth cohort in Perth, Western Australia, followed from 16 to 18 weeks of gestation to 8 years of age to examine associations between breastfeeding and measures of adiposity at the ages of 1, 3, 6 and 8 years. Prospective collection of all neonatal measurements and several maternal characteristics allowed longitudinal analysis with adjustment for a range of covariates.

<table>
<thead>
<tr>
<th>BMI</th>
<th>Body Mass Index</th>
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<tr>
<td>BW</td>
<td>Birth weight</td>
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<tr>
<td>SAS</td>
<td>Statistical Analysis Systems</td>
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<tr>
<td>CL</td>
<td>Confidence Limits</td>
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</table>

From the University of Western Australia, School of Medicine and Pharmacology, Royal Perth Hospital and Western Australian Institute for Medical Research, Perth, Australia; the University of Western Australia, School of Women’s and Infants’ Health; Women’s and Infants’ Research Foundation, Perth, Australia; the Telethon Institute for Child Health Research and Centre for Child Health Research, University of Western Australia, Perth, Australia; and the University of Western Australia, Faculty of Medicine and Dentistry, Perth, Australia.

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METHODS

Participants in the Western Australian Pregnancy Cohort Study were serially recruited between 16 and 20 weeks gestation from the public antenatal clinic at King Edward Memorial Hospital or from nearby private practices in Perth, Western Australia, between 1989 and 1992. The initial cohort comprised 2860 live births. All mothers gave written informed consent, and the study was approved by the institutional ethics committee.

Information collected by midwives included birth weight (BW) and length, mothers' pre-pregnancy weight, educational level, parity, age, smoking status during pregnancy, and whether breastfeeding started. Cutoff points of 25 kg/m² and 30 kg/m² were used, respectively, to define maternal overweight or obesity. During the child's first year, mothers were asked to record in a diary the age at which breastfeeding stopped. This formed the basis of an interview with a study nurse at the time of the 1-year survey when mothers were asked if they had ever breastfed and the duration of breastfeeding. The age at which breastfeeding stopped was again elicited at interview at the time of the survey of 3-year-olds. We use “breastfeeding” to refer to any breastfeeding and do not distinguish between exclusive and partial breastfeeding.

Children were surveyed at the ages of 1, 3, 6, and 8 years. Weight was measured to the nearest 100g using Wedderburn digital chair scales with children wearing only underclothes, and height to the nearest 0.1 cm with a Holtain stadiometer. Body mass index (BMI) was calculated as weight (kg)/height (m)².

Statistical Methods

The Statistical Package for the Social Sciences version 11.5 (SPSS, Chicago, Ill) or the Statistical Analysis Systems (SAS) software version 8.0 (SAS Institute, Cary, NC) was used for analyses. Using the SAS programs provided on the National Center for Health Statistics/Centers for Disease Control website, weight-for-length was calculated for 1-year-olds and BMI Z scores for 3-, 6-, and 8-year-olds. Overweight was defined according to the sex-specific 95th percentiles of the National Center for Health Statistics/Centers for Disease Control growth charts for weight-for-length in infants and for BMI in older children. Categories of breastfeeding were defined as: never breastfed, breastfed ≤4 months, breastfed 5 to 8 months, breastfed 9 to 12 months, and breastfed >12 months. These categories were used in mixed models (PROC MIXED in SAS) with Z score for BMI at 3, 6, and 8 years as the dependent variable. Initial models included adjustment for BW, gestational age, ethnicity (Caucasian or non-Caucasian), and sex. A second set of models added maternal BMI, smoking status during pregnancy (current smokers vs never- and ex-smokers), first child or other, and educational level (tertiary qualification, secondary school, trade qualification or apprenticeship). Generalized Estimating Equations with a logit link using PROC GENMOD in SAS modeled overweight from the ages of 1 to 8 years using the same sets of covariates as for PROC MIXED. Generalized Estimating Equations allow modeling of ordinal data while accounting for the correlation between observations repeated in the same person. Results were considered significant if \( P < .05 \). For pairwise comparisons between breastfeeding categories Bonferroni adjustments were used.

RESULTS

After exclusion of multiple pregnancies, congenital abnormalities, and children born before 37 weeks of gestation, the present analysis comprised 2087 infants at birth, 1710 children at 1 year, 1184 at 3 years, 1480 at 6 years, and 1430 at 8 years in whom weight and height (length) had been measured.

Mothers with tertiary education comprised 7% of non-attenders and 11% of attenders at 1 year (\( P < .001 \)), 7% and 12%, respectively, at 3 years (\( P < .001 \)), 17% and 11%, respectively, at 6 years (\( P < .001 \)), and 6% and 12%, respectively, at 8 years (\( P < .001 \)). Smoking during pregnancy was significantly more prevalent (\( P < .001 \) for each comparison) among mothers of children who did not attend the surveys at 1 year (38% vs 24% of attenders), 3 years (31% vs 24%), 6 years (35% vs 23%), or 8 years (33% vs 24%). Mothers who were overweight or obese before pregnancy comprised 20% of non-attenders and 17% of attenders at 1 year (\( P = .079 \)), 19% and 17%, respectively, at 3 years (\( P = .258 \)), 20% and 17%, respectively, at 6 years (\( P = .036 \)), and 20% and 16%, respectively, at 8 years (\( P = .009 \)).

Attendance at 1, 3, 6, or 8 years was not significantly associated with birth order, with first-born children comprising 50% of non-attenders at 1, 3, and 6 years and 52% at 8 years (\( P > .05 \) for all comparisons). Participants who were not breastfed comprised 11% of those who did not attend at 1 year and 12% of attenders (\( P = .237 \)). Respective proportions were 14% and 12% at 3 years (\( P = .043 \)); 16% and 12% at 6 years (\( P < .001 \)), and 17% and 11% at 8 years (\( P < .001 \)). In General Linear Models (GLM) adjusted for sex there were no statistically significant differences in weight or height in earlier surveys between those who did not attend the survey at 8 years, at 6 years, or at 3 years. Mean BW was significantly higher in those who attended at 1 year (3472 g, SEM 11 vs 3407 g, SEM 24; \( P = .012 \)) or 6 years (3475 g, SEM 12 vs 3425 g, SEM 18; \( P = .022 \)) but did not differ significantly between attenders and non-attenders at 3 or 8 years.

Breastfeeding data were not available for 80 children surveyed at 1 year, 92 at 3 years, 123 at 5 years, and 122 at 8 years. Comparison of these children with those for whom breastfeeding details were known, with adjustment for sex, showed no statistically significant differences in weight or height (length) at birth, 1, 3, 6, or 8 years. Maternal BMI did not differ significantly between these groups, nor was there a statistically significant difference in educational level. However, there was a significantly greater proportion of current smokers (37% vs 24%; \( P < .001 \)) among mothers for whom breastfeeding data were not recorded.
Associations Between Maternal Characteristics and Breastfeeding Practices

Full or partial breastfeeding was continued for at least 6 months in 46% of mothers and for more than 12 months in 17%. Duration of breastfeeding (Table I) was significantly longer in mothers with tertiary education. Smoking during pregnancy, maternal overweight or obesity, and having a first-born child were related to shorter duration of breastfeeding. Breastfeeding for not more than 4 months was associated with the greatest proportion of mothers with secondary education, those who smoked during pregnancy, were overweight or obese, or mothers for whom the child was first-born.

Risk of Overweight or Obesity and Breastfeeding

At 1 year, 113 children (6.7%) were overweight with 69 (5.9%) at 3 years, 91 (6.2%) at 6 years, and 115 (8.0%) at 8 years. Of overweight 1-year-olds who attended subsequent surveys, 24 of 71 (34%) remained overweight at 3 years, 24 of 87 (28%) at 6 years, and 26 of 89 (29%) at 8 years. Of overweight 3-year-olds, 26 of 56 (46%) remained overweight at 6 years and 27 of 54 (50%) at 8 years. Sixty-five of 81 overweight 6-year-olds (80%) were still overweight at the age of 8 years. In total, 232 of 1672 children (13.9%) with data for breastfeeding were classified as overweight in at least one survey between the ages of 1 and 8 years. Proportions did not differ significantly with category of breastfeeding (Table II).

At 1 year, Z score for weight-for-length was lower in the group breastfed for >12 months and differed significantly from all other categories of breastfeeding. Mean Z scores according to category of breastfeeding were: not breastfed 0.16 (95% confident limits [CL] 0.02, 0.29, P = .006); breastfed ≤4 months 0.31 (95% CL 0.22, 0.40, P < .001); breastfed 5 to 8 months 0.17 (95% CL 0.06, 0.27, P < .001); breastfed 9 to 12 months 0.11 (95% CL 0.01, 0.22, P < .001); breastfed >12 months −0.16 (95% CL −0.28, −0.04).

Figure shows Z scores in the 823 children who attended all surveys; there was no dose-response association with duration of breastfeeding. Z scores overall were highest in the group breastfed ≤4 months, whereas the group not breastfed showed the consistently lowest scores beyond infancy. Longitudinal analysis in mixed models with adjustment for BW, gestational age, ethnicity, and sex showed a statistically significant effect associated with the category of breastfeeding.
(P = .012) but no significant interaction between age and breastfeeding group (P = .295). After adjustment for maternal factors, there was no statistically significant effect of category of breastfeeding (P = .261) and no significant interaction between age and category of breastfeeding (P = .296). The least squares means for Z scores in this model were: not breastfed 0.17 (95% CL 0.04, 0.30), breastfed ≤4 months 0.25 (95% CL 0.17, 0.33), 5 to 8 months 0.16 (95% CL 0.06, 0.26), 9 to 12 months 0.27 (95% CL 0.17, 0.37), and >12 months 0.14 (95% CL 0.04, 0.24).

Using Generalized Estimating Equations (Table III) with the group not breastfed as the reference category, the probability of exceeding the 95th percentile between 1 and 8 years was not significantly associated with duration of breastfeeding, with or without adjustment for maternal factors. With “breastfeeding >12 months” as the reference category, however, the probability of exceeding the 95th percentile was significantly greater in the group breastfed ≤4 months. Although there was a trend in risk associated with breastfeeding from ≤4 months to >12 months, there was little difference in risk between the group not breastfed and those breastfed for >12 months so that a dose-response relationship was not seen overall.

**DISCUSSION**

Among 1-year-olds in this birth cohort study, which uses longitudinal analyses with data collected prospectively, children breastfed for >12 months were the leanest, whereas those breastfed ≤4 months had the highest mean Z scores for weight-for-length. From 1 to 8 years, BMI Z scores associated with duration of breastfeeding tended to converge and showed no statistically significant differences after adjustment for maternal factors.

Higher rates of overweight in infants breastfed for <3 months have been suggested previously. In our study, breastfeeding for ≤4 months was associated with maternal overweight or obesity, lower education, and smoking during pregnancy. In the United States, maternal BMI was the variable that most influenced overweight and obesity among 3- to 6-year-olds, whereas adjustment for maternal BMI attenuated the relationship between breastfeeding and overweight in adolescents. We found a shorter duration of breastfeeding among overweight or obese mothers, consistent with other reports. Lower rates and duration of breastfeeding also are associated with lower socioeconomic status, a factor related to overweight and obesity, and to adverse health behaviors. Familial factors, lifestyle, and socioeconomic status could underlie the observed relationships, as suggested by others.

Gilman et al reported that risk of overweight between the ages of 9 and 14 years in children in the United States was 20% lower in those breastfed for at least 7 months compared with those breastfed for ≤3 months. However, reported no reduction in risk of overweight related to breastfeeding among 3- to 6-year-olds in the United States, and no dose-response effect. In both these studies breastfeeding data were collected retrospectively and the study of Gillman et al used self-reported height and weight in adolescents.

Grummer-Strawn and Mei used US data from more than 150,000 children, more than 12,000 of whom had data linked to maternal pregnancy records. Participants were from low-income groups, only 6% were breastfed for >6 months, and 70% were not breastfed. No statistically significant associations were found, overall, between duration of breastfeeding and overweight among these 4-year-olds. However, in non-Hispanic whites a dose-response effect was seen, with a 51% reduction in risk of overweight in children breastfed for at least 12 months. The authors suggested that differences in lifestyle or in the use of formula feeding may have obscured such an association in other racial groups.

A recent systematic review that examined the association between breastfeeding and obesity in childhood identified 954 potentially relevant studies; nine were eligible for inclusion based on criteria such as sample size, the inclusion of adjustment for confounders, reporting of OR, and clear definition of obesity. The meta-analysis, comprised of almost 70,000 persons, found an adjusted OR of 0.78 (95% CL 0.71, 0.85) for breastfeeding relative to “not breastfed.” If our data are categorized as “breastfed” or “not breastfed,” the adjusted OR is 1.19 (95% CL 0.76, 1.86; P = .449), reflecting similarities between children not breastfed and those breastfed for >12 months.

The similarities between these groups are unexplained. We excluded multiple pregnancies, infants born before 37 weeks gestation, and those with congenital abnormalities. Infants not breastfed had BW and gestational age similar to those in other categories of breastfeeding. One possible explanation relates to the composition of breast milk. Among diabetic mothers, a greater volume of breast milk ingested by their offspring was associated with an increased risk of...
overweight at the age of 2 years, and breast milk from diabetic women has been reported to be higher in energy content. Maternal overweight and breastfeeding practices were associated in our cohort and, if breast milk composition were affected by insulin resistance in overweight mothers, failure to establish breastfeeding might favor leanness by avoiding exposure to hypercaloric breast milk.

Although characteristics of non-attenders may have led to bias, its possible direction is not clear. Attenders and non-attenders differed significantly in the proportion not breastfed and in maternal factors such as education, overweight, and smoking during pregnancy. Among attenders at the ages of 1 and 6 years, BW was significantly greater than in the non-attenders. Cross-sectional analysis of our data found that maternal BMI and smoking, as well as BW, predicted greater BMI in 8-year-olds. Higher BMI associated with maternal factors among non-attenders may have led to an underestimate of overweight in this cohort. However, lower BW among non-attenders would bias findings in the opposite direction, as would the higher proportion of infants not breastfed.

Although we found that measures of adiposity associated with duration of breastfeeding tended to converge with increasing age, overweight at 12 months may influence later body mass, given the tracking of BMI from childhood through adult life. However, only about 30% of overweight 1-year-olds were still overweight at 3, 6, or 8 years compared with 80% of overweight 6-year-olds who remained overweight at 8 years. Associations between size at 1 year and later adiposity require further analysis as our cohort ages.

Although there were differences between infants breastfed for ≤4 months and for >12 months, other well-established benefits provide strong arguments for continuing to promote breastfeeding. Correlations between overweight in children breastfed for ≤4 months and maternal characteristics are consistent with an effect of familial factors, including lifestyle, on adiposity in this population, as suggested in other studies.

Table III. OR estimates from Generalized Estimating Equations with exceeding the 95th percentile for weight-for-length at 1 year and BMI at 3, 6, and 8 years as the dependent variable

<table>
<thead>
<tr>
<th>OR</th>
<th>95% CL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference category not breastfed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not breastfed</td>
<td>1.00</td>
<td>1.96</td>
</tr>
<tr>
<td>≤4 months</td>
<td>1.29</td>
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</tr>
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<td>5–≤8 months</td>
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</tr>
<tr>
<td>9–≤12 months</td>
<td>0.86</td>
<td>0.53</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>0.89</td>
<td>0.54</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
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<tr>
<td>Reference category not breastfed</td>
<td></td>
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<tr>
<td>Not breastfed</td>
<td>1.00</td>
<td>0.89</td>
</tr>
<tr>
<td>≤4 months</td>
<td>1.29</td>
<td>0.50</td>
</tr>
<tr>
<td>5–≤8 months</td>
<td>0.81</td>
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<tr>
<td>9–≤12 months</td>
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</tr>
<tr>
<td>&gt;12 months</td>
<td>0.90</td>
<td>0.58</td>
</tr>
<tr>
<td>Model 1</td>
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<td></td>
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<tr>
<td>Reference category breastfed ≥12 m</td>
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<td></td>
</tr>
<tr>
<td>Not breastfed</td>
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<tr>
<td>≤4 months</td>
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<td>1.20</td>
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<td>5–≤8 months</td>
<td>1.49</td>
<td>0.94</td>
</tr>
<tr>
<td>9–≤12 months</td>
<td>1.36</td>
<td>0.84</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>1.00</td>
<td>1.00</td>
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</table>

Numbers in breastfeeding categories were: not breastfed 206 (13.1%); breastfed ≤4 months 513 (16.8%); breastfed 5–8 months 351 (13.4%); breastfed 9–12 months 308 (13.3%); breastfed >12 months 294 (10.5%).

1 Adjusted for BW, gestational age, ethnicity, and sex.
2 Additional adjustment for maternal BMI, maternal smoking during pregnancy, first child, and maternal education.
REFERENCES

METABOLIC, HORMONAL, OXIDATIVE, AND INFLAMMATORY FACTORS IN PEDIATRIC OBESITY-RELATED LIVER DISEASE

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Objective To examine the role of metabolic, hormonal, oxidative, and inflammatory factors in pediatric obesity-related liver disease.

Study design In 50 obese children (age 7 to 14 years) with (n = 20, group 1) or without (n = 30, group 2) hypertransaminasemia and ultrasonographic liver brightness, we studied insulin resistance (fasting glucose/insulin ratio [FGIR]) and serum levels of leptin, iron, transferrin, ferritin, C-reactive protein (CRP), white blood cell (WBC) count, tumor necrosis factor (TNF)-α, interleukin (IL)-6, C282Y and H63D mutations, and erythrocytic glutathione peroxidase (GPX) activity.

Results FGIR (6.7 ± 4.1 vs 9.2 ± 5.2; P = .02), serum ferritin (88.8 ± 36.0 vs 39.9 ± 24.0 ng/mL; P = .0001), serum CRP (5.4 ± 6.0 vs 1.1 ± 1.6 mg/dL; P = 0.004), and GPX (8.4 ± 0.9 vs 5.0 ± 0.5 U/g Hb; P = .05) were significantly higher and more frequently deranged in group 1 than in group 2. FGIR, ferritin, and CRP values were simultaneously deranged in 41% of the group 1 patients and in none of the group 2 patients (P = .098). Serum leptin, iron, and transferrin, WBC, TNF-α, IL-6, and C282Y and H63D mutations were similar in the 2 groups.

Conclusions Insulin resistance, oxidative stress, and low-grade systemic inflammatory status are implicated in pediatric obesity-related liver disease. These findings may be useful in planning pathophysiologically based therapeutic trials for hepatopathic obese children who are unable to follow hypocaloric diets. (J Pediatr 2005;147:62-6)

Liver involvement in obese individuals has become a leading cause of liver function test abnormalities.1,2 It is classified within the abnormalities of nonalcoholic fatty liver disease (NAFLD), a condition ranging from simple hepatic steatosis (a putatively common and benign disease with an indolent course) to progressive necroinflammatory and fibrotic damage of the liver.2,3 Although liver involvement is suggested by liver brightness on ultrasonography (US) and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, the true prevalence of NAFLD remains obscure, largely because of the variability of definition criteria, including the threshold of hypertransaminasemia itself.4,5

NAFLD is being increasingly recognized in children.6-16 The reported prevalence of hypertransaminasemia in obese children varies between 10%14 and 24% to 25%,10,12,13 and US liver brightness has been reported to vary between 22.5%14 and 77%.13

The reasons underlying liver involvement and disease progression in only a proportion of obese individuals remain unclear. In adults and in animal models there is evidence that increased fat deposition within the hepatocytes of obese individuals results from augmented hepatic delivery of free fatty acids.17,18 The latter is amplified by insulin resistance, which impairs suppression of lipolysis.19 Excessive fatty acid oxidation in the liver generates free radicals, which damage hepatocytes and induce fibrogenesis through

<table>
<thead>
<tr>
<th>ALT</th>
<th>Alanine aminotransferase</th>
<th>IL</th>
<th>Interleukin</th>
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<tbody>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
<td>NAFLD</td>
<td>Nonalcoholic fatty liver disease</td>
</tr>
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<td>CRP</td>
<td>C-reactive protein</td>
<td>NASH</td>
<td>Nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>FGIR</td>
<td>Fasting glucose-to-insulin ratio</td>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>FFA</td>
<td>Free fatty acid</td>
<td>US</td>
<td>Ultrasonography</td>
</tr>
<tr>
<td>GPX</td>
<td>Glutathione peroxidase</td>
<td>WBC</td>
<td>White blood cell</td>
</tr>
<tr>
<td>HFE</td>
<td>Hereditary familial hemochromatosis</td>
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Liver involvement in obese individuals has become a leading cause of liver function test abnormalities.1,2 It is classified within the abnormalities of nonalcoholic fatty liver disease (NAFLD), a condition ranging from simple hepatic steatosis (a putatively common and benign disease with an indolent course) to progressive necroinflammatory and fibrotic damage of the liver.2,3 Although liver involvement is suggested by liver brightness on ultrasonography (US) and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, the true prevalence of NAFLD remains obscure, largely because of the variability of definition criteria, including the threshold of hypertransaminasemia itself.4,5

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cytokine production. Two studies conducted in children that reported that the antioxidant vitamin E induced normalization of hypertransaminasemia but did not affect ultrasonographic liver brightness also support the concept that oxidative stress plays a pathogenetic role in obesity-related liver disease. Although insulin resistance is considered pivotal to the development of fatty liver, few data have been reported in the pediatric literature. Similarly, abnormal iron handling and leptin levels are also implicated in the pathogenesis of fatty liver, but data in childhood are conflicting and scarce.

Interleukin (IL)-6 produced by fat cells induces the synthesis of C-reactive protein (CRP) by the liver; thus, obesity is associated with low-grade systemic inflammation. It remains to be established whether the inflammatory involvement is more severe in obese adults or children affected by liver disease.

Here we examine globally, and also in the same series of obese children, the role of metabolic, hormonal, oxidative, and inflammatory factors in pediatric obesity-related liver dysfunction.

**METHODS**

In the first stage of this study, we retrospectively recorded the anthropometric measurements and the results of liver function tests and US examinations contained in the clinical records of 256 obese (body mass index > 95th percentile) Italian children who had been monitored for at least 1 year at the pediatric obesity clinics participating in our project.

To ensure a distinct separation between individuals with and individuals without obesity-related liver disease, the study protocol was designed to evaluate only prepubertal patients (age > 6 years) who presented the following inclusion criteria: stable or increased percent of overweight due to poor compliance to a prescribed slimming diet and exercise program (n = 119), US liver brightness coupled with a persistent increase of ALT and/or AST levels > 1.5 times above normal values for age persisting for more than 6 months (hepatopathic obese patients), and normal US liver findings coupled with persistently normal ALT and AST levels (obese controls). Exclusion criteria were normalization of liver function tests after decrease in the percent overweight during follow-up, fluctuating transaminase levels reaching normal or near-normal values in the last 2 biochemical evaluations, and known causes of liver abnormalities other than obesity. Fever and respiratory tract infection during the acute phase of the disease were considered temporary exclusion criteria.

Of the 119 children identified from our pool of 256 obese children, 101 consented to a complete reassessment of anthropometric parameters, liver function tests, and a new US liver examination. Only 50 of 101 children met the more stringent inclusion criteria for the study of metabolic, hormonal, oxidative, and inflammatory factors involved in the pathogenesis of liver disease. Of these 50, 20 were hepatopathic obese children with chronic elevation of AST and/or ALT and US liver brightness (group 1). The other 30, who had persistently normal serum AST and/or ALT levels in the absence of US liver brightness at study entry, were assigned to the obese control group (group 2). All 50 patients were prepubertal, with a mean age of 9.0 ± 2.4 years; 26 were girls. None had previously been treated with hepatotoxic drugs, had undergone surgery, had received either blood or blood products, or had a history of alcohol consumption. No patient had a history of short gut syndrome, small bowel intestinal bypass, Cushing's disease, or diabetes mellitus, which could have caused hepatic steatosis. All were asymptomatic. None had arterial hypertension. The liver was slightly enlarged but of normal consistency in 6 patients of group 1. None had splenomegaly or other stigmata of portal hypertension.

In patients with liver involvement, causes of increased transaminase levels other than obesity (eg, muscular disease, viral hepatitis B and C, autoimmune hepatitis, α1-antitrypsin deficiency, cystic fibrosis, Wilson's disease, hemochromatosis, hereditary fructose intolerance, amino acid disorders, atypical celiac disease) were ruled out by appropriate tests.

Routine liver function tests in addition to ALT and AST (ie, alkaline phosphatase, γ-glutamyltransferase, bilirubin, total protein, protein electrophoresis) were also determined. Ultrasonography of the liver was carried out as described previously. White blood cell (WBC) count, serum CRP level, lipid levels, glucose level, glycosylated hemoglobin level, fasting insulin and glucose levels, iron status (iron levels, percent of transferrin saturation), and ferritin level were determined by standard methods.

Samples of fresh sera and plasma for determining dosage of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and leptin were collected from all subjects. Blood spots were also collected on filter paper for polymerase chain reaction analysis. Lysed red blood cells were obtained from all subjects for a glutathione peroxidase (GPX) assay.

**Experimental Methods**

The fasting glucose-to-insulin ratio (FGIR) was to measure insulin resistance, with insulin resistance diagnosed when values were < 7. Blood cells eluted from filter paper were lysed and DNA was purified for polymerase chain reaction–single-strand conformation polymorphism analysis to detect the C282Y and H63D mutations causative of hereditary familial hemochromatosis (HFE), as described elsewhere. Serum concentrations of TNF-α and IL-6 were determined by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn) in accordance with the manufacturer’s instructions. A spectrophotometric reading was performed on microplates using 450-nm filters. The enzymatic activity of GPX was evaluated by an indirect colorimetric method (Bioxytech GPx-340; Oxis Research, Portland, Ore). Each sample was washed in 0.9% NaCl solution and lysed in sterilized bi-distilled frozen water. The ensuing oxidation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) to NADP+ was photometrically measured by spectrophotometry (model DU 640; Beckman, Brea, Calif) at 340 nm for 180 minutes; data are expressed as U/g hemoglobin.
Ultrasonographic liver cholesterol (mg/dL; AST:ALT (ratio) 0.56
AST (U/L; normal, ALT (U/L; normal, ±

Mandato et al The Journal of Pediatrics

Statistical Analysis

Age (years) 10.9 ± 3.2
BMI 27.1 ± 1.3
ALT (U/L; normal, < 40) 85.1 ± 40.9
AST (U/L; normal, < 40) 41.2 ± 18.9
AST:ALT (ratio) 0.56 ± 0.41
Cholesterol (mg/dL; normal, < 170) 153.9 ± 7.6
Triglycerides (mg/dL; normal, 50-200) 108.1 ± 12.1
Ultrasoundographic liver brightness (n) 20/20

Table I. Demographic data, anthropometric measurements, and aminotransferase values in the 2 groups of obese subjects at study entry

<table>
<thead>
<tr>
<th>Group 1 (hepatopathic obese patients)</th>
<th>Group 2 (obese controls)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F) (n)</td>
<td>8/12</td>
<td>16/14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.9 ± 3.2</td>
<td>9.3 ± 2.7</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1 ± 1.3</td>
<td>27.4 ± 1.3</td>
</tr>
<tr>
<td>ALT (U/L; normal, &lt; 40)</td>
<td>85.1 ± 40.9</td>
<td>23.2 ± 6.7</td>
</tr>
<tr>
<td>AST (U/L; normal, &lt; 40)</td>
<td>41.2 ± 18.9</td>
<td>24.8 ± 5.3</td>
</tr>
<tr>
<td>AST:ALT (ratio)</td>
<td>0.56 ± 0.41</td>
<td>1.05 ± 0.3</td>
</tr>
<tr>
<td>Cholesterol (mg/dL; normal, &lt; 170)</td>
<td>153.9 ± 7.6</td>
<td>162.9 ± 8.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL; normal, 50-200)</td>
<td>108.1 ± 12.1</td>
<td>101.9 ± 19.5</td>
</tr>
<tr>
<td>Ultrasoundographic liver brightness (n)</td>
<td>20/20</td>
<td>0/30</td>
</tr>
</tbody>
</table>

BMI, Body mass index; NS, not significant.
Mean values are reported as mean ± standard deviation.
In the hepatopathic obese patients, liver function tests other than ALT and AST were within normal limits except GGT, which was slightly increased in 3 individuals.

Informed consent was obtained from the family of each subject included in the study. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki approved in 1975 and revised in 1983, and was approved by the local ethics committee.

Statistical Analysis

Differences between means were evaluated using the unpaired Student t-test. Fisher’s exact test was used to calculate the probability value for the relationship between 2 dichotomous variables (eg, patient gender). Correlation between continuous variables was evaluated by the Pearson test. The statistical significance level selected for all tests was P < .05.

RESULTS

Table I gives demographic and anthropometric measurements, as well as the results of serum lipid and liver function tests, of groups 1 and 2 at study entry. All parameters, except ALT and AST values and AST:ALT ratios, were similar in the 2 groups. In group 1, ALT levels were high in all patients; both ALT and AST were elevated in 7 patients, but in only 2 of these was AST greater than ALT.

As shown in Table II, FGIR ratios were 6.7 ± 4.1 in group 1 and 9.2 ± 5.2 in group 2 (P = .02). Values were deranged in 78% of the patients in group 1 and in and 22% of those in group 2 (P = .0036). Interestingly, FGIR values were inversely correlated with ferritin levels (r = −.6; P = .04).

DISCUSSION

Gradual weight loss and regular exercise are considered the first-line treatment for obesity-related liver disease in children and adults. However, these are often difficult to achieve, and it is not known whether this approach is beneficial in advanced disease. Innovative therapies that can modify the pathogenic mechanisms of liver damage are thus particularly urgent in obese children, whose longer life expectancy (compared with adults) makes them more prone to additional hepatotoxic noxae.

Insulin resistance is not uncommon in obese preadolescents and adolescents. It plays a major role in the pathogenesis of NAFLD in adults and in animal models. Kawasaki et al reported a high correlation between hyperinsulinemia and hypertransaminasemia in a group of obese prepubertal Japanese children. More recently, Schwimmer et al reported that impaired insulin sensitivity was nearly universal in a group of American adolescents with biopsy-proven NAFLD. Our study corroborates their findings by showing that insulin resistance is approximately 4 times more frequent already in prepubertal children affected by obesity-related liver disease compared with age-matched controls. This finding is not trivial given the beneficial effects of antihyperglycemic agents on hepatic insulin sensitivity and on liver enzyme levels obtained in a pilot study in adult nonalcoholic steatohepatitis (NASH).

Data on the role of iron and HFE mutations as cofactors implicated in the pathogenesis and progression of NAFLD in adults are conflicting. It is now well established that despite increased ferritin levels, serum iron indices (ie, iron levels and percent transferrin saturation) and hepatic iron are rarely abnormal in adult patients with NAFLD. In our pediatric series we observed the same

Serum leptin, iron, transferrin, and transferrin saturation levels were similar in the 2 groups. Serum ferritin was 88.8 ± 36 in group 1 and 39.9 ± 24 ng/mL in group 2 (P < .0001). Values were > 100 ng/mL in 46.6% of the group 1 patients and in 4.5% of the group 2 patients (P = .0038).

Molecular analysis of the C282Y and H63D mutations of the HFE gene revealed no significant differences between the 2 groups.

CRP was significantly higher in group 1 (P = .004), and values were deranged in 64% of the group 1 patients versus 23% of the group 2 patients (P = .02). WBC, TNF-α, and IL-6 serum levels were similar in the 2 groups. TNF-α was correlated with IL-6 (r = .7; P = .005). CRP was positively correlated with IL-6 (r = .61, P = .001) and ferritin (r = .6; P = .04) values and negatively correlated with FGIR (r = −.8, P = .03). Nonetheless, IL-6 and TNF-α did not correlate with ferritin. GPX activity tended to be higher in group 1 (P = .05).

Clusters of biochemical abnormalities in the same individual were observed only in group 1. FGIR, ferritin, and CRP values were simultaneously abnormal in 41% of the group 1 patients and in none of the group 2 patients (P = .098).
pattern of normal iron indices and increased ferritin observed in adults.

No association was found between the HFE gene mutations H63D and C282Y and obesity-related liver dysfunction. The high prevalence of heterozygosity for the H63D mutation in patients and controls was consistent with that reported for the Italian normal population.32,33 Because the ferritin levels of our population correlated with CRP values, elevated ferritin should be considered an acute-phase reactant rather than a consequence of increased iron stores. Determining whether iron is indeed involved in the liver injury in our children would require liver biopsy.

Regarding the interplay between iron status and insulin sensitivity, we found a significant correlation between ferritin levels and insulin resistance. The pathophysigenetic significance of this association (ie, insulin resistance-associated iron overload) remains unclear.19

High CRP values and WBC counts, which are markers of a low-grade systemic inflammatory status, have been reported in both obese adults and obese children.26,34 Their correlation with liver damage has not yet been studied in detail. Our study confirms that obese children have a moderately increased inflammatory status, as shown by slightly elevated CRP values than in normal individuals. Interestingly, the increase in CRP values was much more pronounced in children with liver involvement. As expected, CRP levels also were significantly correlated with serum levels of proinflammatory IL-6. The latter was also significantly correlated with TNF-α.

In adult studies, inflammation has also been implicated in insulin resistance and in the pathogenesis of type 2 diabetes mellitus.35 In our study we found a positive relationship between elevated CRP concentrations and insulin resistance, which demonstrates this association already in children.

Among the molecules involved as a second hit in NAFLD, attention has focused on leptin, a peptidic hormone prevalently derived from adipocytes. However, the available data are conflicting, probably because of the lack of appropriate controls.25,36 In our study we were unable to find differences in leptin levels between the group 1 and group 2 patients. This finding is in agreement with recent findings obtained in adult NASH patients and well-matched controls.5,37,38

In contrast to other pediatric series of NAFLD, our study has a prevalence of girls. Although this prevalence is not statistically significant, it would be interesting to evaluate in a larger group of patients whether the preponderance of girls affected the comparison of leptin values between groups.

Among other putative pathogenic factors that had not been extensively investigated in hepatopathic obese children, we assessed the antioxidant reserve by measuring GPX activity in red blood cells. Glutathione peroxidase detoxifies cells from peroxides and is one of the first lines of defense against free radicals. Because free radicals may form highly reactive radicals, GPX is critical in protecting cells against lipid peroxidation.39,40 In our study, GPX activity was greater in the group 1 patients than in the group 2, which probably indicates enzyme induction by toxic agents in the initial stages of liver disease.41,42 Further studies on other measures of oxidant injury or lipid peroxidation should help provide insight into the role of oxidative stress involvement in hepatopathic obese children.

In conclusion, our results show that insulin resistance and oxidative stress but not iron status are implicated in pediatric obesity-related liver disease. Moreover, our data—like those obtained in adult NASH37,38—are not consistent with a role for leptin in the pathogenesis of pediatric obesity-related liver disease.

Increased systemic inflammation of hepatopathic obese children versus obese controls and the relationship between both CRP and ferritin with insulin resistance reported here point to the existence of a complex interplay involving low-grade inflammation and insulin sensitivity that deserves further study. Taken together, these data may be useful in the planning of innovative therapeutic approaches to liver dysfunction in obese children who are unable to follow hypocaloric diets.

Keep in mind, however, that our study protocol included only patients who had both US liver brightness and a hypertransaminasemia level that unequivocally distinguished nonhepatopathic from hepatopathic obese subjects. Consequently, our patients might not be representative of the general pediatric obese population, in which there are borderline manifestations of obesity-related liver disease. In

### Table II. Metabolic, hormonal, inflammatory, and oxidative factors studied in the 2 groups of obese subjects

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (hepatopathic obese patients)</th>
<th>Group 2 (obese controls)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGIR (ratio; normal, ≤7)</td>
<td>6.7 ± 4.1</td>
<td>9.2 ± 5.2</td>
<td>.02</td>
</tr>
<tr>
<td>Serum leptin (ng/mL; normal, M, 3-5; F, 4-8)</td>
<td>16.5 ± 1.7</td>
<td>16.6 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Serum iron (µg/dL; normal, 16-24)</td>
<td>83.3 ± 33.0</td>
<td>73.5 ± 23.3</td>
<td>NS</td>
</tr>
<tr>
<td>Transferrin (g/L; normal, 0.95-3.85)</td>
<td>2.9 ± 0.4</td>
<td>2.8 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Transferrin saturation (normal, 30%-40%)</td>
<td>21.5 ± 2.0</td>
<td>22.1 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Ferritin (ng/mL; normal, 7-140)</td>
<td>88.8 ± 36.0</td>
<td>39.9 ± 24.0</td>
<td>.0001</td>
</tr>
<tr>
<td>% C282 Y heterozygotes</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>% H63 D heterozygotes</td>
<td>30.0</td>
<td>23.0</td>
<td>NS</td>
</tr>
<tr>
<td>Serum TNF-α (pg/mL)</td>
<td>21.0 ± 8.0</td>
<td>9.0 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Serum IL-6 (pg/mL)</td>
<td>2.9 ± 1.1</td>
<td>2.4 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/dL; normal, 0-0.5)</td>
<td>5.4 ± 6.0</td>
<td>1.1 ± 1.6</td>
<td>.004</td>
</tr>
<tr>
<td>GPX activity (U/g hemoglobin)</td>
<td>8.4 ± 0.9</td>
<td>5.0 ± 0.5</td>
<td>.05</td>
</tr>
</tbody>
</table>

NS, not significant.

Mean values are reported as mean ± standard deviation.
this context, it would be interesting to verify whether our results are applicable to patients with different degrees of liver involvement.

We are grateful to Mrs. Jean Gilder for her linguistic revision of this manuscript.

REFERENCES


36. Serin E, Ozer B, Gumurdulu Y, Kayaseleku F, Kul K, Boyacioglu S. Serum leptin level can be a negative marker of hepatocyte damage in non-alcoholic fatty liver. J Hepatol 2002;37:752-9.


Objective To determine whether risk factors for cardiovascular disease and diabetic nephropathy, as evidenced by abnormalities of ambulatory blood pressure (ABP), dyslipidemia, and microalbuminuria (MA), are present in adolescents with type 2 diabetes mellitus (T2DM).

Study design We enrolled 26 minority adolescents recently diagnosed with T2DM and 13 obese control subjects without diabetes mellitus. ABP monitoring was performed, and a 24-hour urine, a fasting lipid profile, blood urea nitrogen, creatinine, homocysteine, and hemoglobin A1c levels were obtained. The patients with T2DM underwent echocardiograms.

Results Forty percent of the patients with T2DM had MA ($\geq 30$ mg of microalbumin/day), compared with none of the control subjects ($P < .05$). There were no significant differences between patients with T2DM who had MA and patients with T2DM who didn’t have MA in demographics, characteristics, casual BP, echocardiographic findings, and hemoglobin A1c levels. Average daytime systolic BP was greater in patients with T2DM with MA than patients without MA (129 versus 121 mm Hg, $P = .03$) and compared with the control subjects (113 mm Hg, $P = .01$). Patients with MA had an average daytime systolic BP load that was higher than patients without MA (37.1 versus 5.1%, $P = .008$) and compared with the control subjects (2.6%, $P < .001$).

Conclusion As in adults, adolescents with T2DM exhibit abnormalities of ABP, dyslipidemia, and microalbuminuria. (J Pediatr 2005;147:67-73)
METHODS

Setting and Study Design

Patients who fulfilled the following criteria were recruited from the Pediatric Diabetes Center at the Children’s Hospital at Montefiore in the Bronx, NY: age 10 to 18 years, a diagnosis within the past 3 years of T2DM according to the standard American Diabetes Association criteria,13 and serum test results negative for antibodies to glutamic acid decarboxylase-65 or insulin autoantibodies. Patients were ineligible when they were metabolically unstable, as defined by the history of an episode of diabetic ketoacidosis within the previous 2 months. Patients with any genetic syndrome that would predispose them independently to either diabetes mellitus or to kidney disease were also excluded. Patients were eligible when they were taking antihypertensive medications. Our reasoning was that the inclusion of patients with potentially treated blood pressures would make the study groups more similar and therefore strengthen any statistical differences observed.

A control group was recruited that consisted of patients who, in the previous 6 months, had been referred because of risk factors to the Pediatric Diabetes Center for oral glucose tolerance testing, yet were found to have normal glucose tolerance. Risk factors included being overweight (ie, BMI for age and sex ≥85th percentile) and having any 2 of the following: a family history of T2DM in a first- or second-degree relative, being of a race/ethnicity at high risk for diabetes mellitus, or having acanthosis nigricans.13

Written informed consent was obtained from the parent or guardian of each subject. Subjects who were 13 to 18 years old also provided written informed consent. Written informed assent was obtained from children aged 10 to 13 years. The protocol was approved by the Montefiore Medical Center institutional review board.

Procedures

Subjects had a study visit that included a history and a physical examination. Family health history, smoking status, and medication and vitamin usage were assessed. A subject was considered to have a positive family history of hypertension when it was reported in a first-degree relative or a grandparent. Families identified the race/ethnicity of the subject. Standing height was measured by using a wall-mounted stadiometer. Body weight was obtained with the patient in his or her own light clothes without footwear. Waist and hip circumference was measured in a standard fashion.14 BMI was calculated by dividing the weight in kilograms by the square of the height in meters. The BMI Z score, a reflection of the number of SDs from the mean BMI on the basis of age and sex, was also determined.

The casual blood pressure of subjects with T2DM was measured in a standard fashion.14 BMI was calculated by dividing the weight in kilograms by the square of the height in meters. The BMI Z score, a reflection of the number of SDs from the mean BMI on the basis of age and sex, was also determined.

The baseline blood pressure of subjects with T2DM was noted from the blood pressure recording obtained in the standard fashion from the most recent Diabetes Clinic visit. Casual blood pressure was obtained from the blood pressure obtained in the standard fashion from the control subjects’ oral glucose tolerance test. All were diagnosed with casual hypertension when their casual blood pressure was ≥95th percentile blood pressure on the basis of the subject’s age, sex, and height according to the Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents.15

The subjects underwent a 24-hour ABP recording on an outpatient basis that was obtained with the Spacelabs 90217 ambulatory monitor (Spacelabs Medical, Issaquah, Wash), fitted and programmed as previously described.16 Awake, or daytime, and sleep, or nocturnal, periods were determined with a diary provided by the subjects.

Systolic or diastolic hypertension in the day or night was diagnosed when the average ambulatory BP for the period was >95th percentile for the subject’s sex and height according to normative values for ABP reported by Wuhl et al.17 Blood pressure load was defined as the percentage of readings for a given period that exceeded the 95th percentile for that individual. A BP load >40% was considered to be elevated.18 Percent dipping was calculated for both average systolic and diastolic BP with the following formula:

\[
\frac{[(\text{daytime BP} - \text{nocturnal BP})/\text{daytime BP}] \times 100}{\text{daytime BP} - \text{nocturnal BP}}
\]

Each subject was categorized as a “dipper” (decrease in average systolic and diastolic BP ≥10% during sleep) or a “non-dipper” (decrease <10%).19

All subjects collected a 24-hour urine sample for microalbumin and creatinine quantification. A sample was considered adequate and complete when it contained 15 to 25 mg of creatinine per kilogram (for their ideal body weight based on age, sex, and height). MA was diagnosed when the amount of urinary microalbumin was ≥30 mg per day on this single specimen.

Fasting blood was drawn for blood urea nitrogen, creatinine, hemoglobin A1c, homocysteine, low-density lipoprotein, high–density lipoprotein, triglyceride, and cholesterol levels. These tests were performed in the Montefiore Medical Center’s clinical laboratory. The lipid panel and hemoglobin A1c were interpreted according to the American Diabetes Association clinical practice recommendations.13 The remaining serum tests were compared to standardized normal values. The estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease (MDRD) formula.20 Glomerular hyperfiltration was diagnosed when the eGFR was >140 mL/min/1.73m².

Only the subjects with T2DM underwent an m-mode and 2-dimensional echocardiogram. Left ventricular mass (LVM) was calculated according to the formula of Deveraux:21

\[
\text{LVM (in grams)} = 0.8 \times [1.04 \times (\text{IVSd} + \text{LVIDd} + \text{PWd})^3 - \text{LVIDd}^3] + 0.6
\]

in which IVSd is interventricular septal thickness at end diastole, LVIDd is left ventricular internal dimension at end diastole, and PWd is posterior wall thickness at end diastole (all in centimeters). Left ventricular mass index (LVMI) was calculated by dividing the left ventricular mass by height in
meters\textsuperscript{2,7}. A value of 38.6 g/m\textsuperscript{2.7} is the 95th percentile found in healthy children with normal BP. Subjects with a greater value in this sample were categorized as having left ventricular hypertrophy.\textsuperscript{22}

### Statistical Analysis

Continuous data are presented as mean ± SD. Categorical values are presented as relative frequencies. The Mann-Whitney U test was used to compare continuous nonparametric values between the control and diabetic groups, and between the diabetic group with MA and the diabetic group without MA. Results of this comparison are reported as medians (25th percentile, 75th percentile). The Fisher exact test was used to determine the significance of associations between categorical dependent variables and group. SPSS software version 11.5 (SPSS, Chicago, Ill) was used for all statistical analyses.

### RESULTS

Of the 34 patients with T2DM contacted to participate in this study, 26 (76\%) were enrolled. Patients who declined to participate were similar to enrolled subjects regarding their sex distribution, age, duration of T2DM, BMI, and BMI Z score (data not shown). Participant characteristics are presented in Table I. They had a BMI (kg/m\textsuperscript{2}) ranging from the normal (18.5-24.9) to the extremely obese (>40). All participants were identified as a minority race/ethnicity. There were no significant differences between the subjects with T2DM and the control group in their age, sex distribution, family history of hypertension, race/ethnicity distribution, BMI, BMI Z score, or waist-hip ratio.

There were several significant differences between the findings in the group with T2DM and the control group. Forty percent of the subjects with T2DM had MA compared with none of the control group (P < .05). Also, 53.8\% of the group with T2DM had an elevated hemoglobin A\textsubscript{1c} level whereas none of the control group had this result (P < .01). In addition, 69.2\% of the subjects with T2DM were found to have dyslipidemia, which was significantly more than the 23.1\% found in the control group (P < .05). There was no significant difference between the prevalence of casual hypertension among the group with T2DM versus the control group (58\% versus 23\%), although this lack of significance may have been because of the small sample size. There were also no significant differences in the prevalence of hyperfiltration (84.6\% versus 69.2\%) and of systolic non-dipping (56\% versus 42\%) between the group with T2DM and the control group. None of the subjects had elevated homocysteine levels. Among all the subjects with T2DM, there was found to be a significant direct correlation between the eGFR and the amount of urinary albumin (r = 0.413, P = .05). The patients with T2DM who had MA had a significantly higher eGFR than the patients with T2DM who did not have MA (200 versus 165 mL/min/m\textsuperscript{2}, P = .003). Among the patients with T2DM, there were no significant correlations between the level of hemoglobin A\textsubscript{1c} and GFR (r = 0.075, P = .667) or between the level of hemoglobin A\textsubscript{1c} and MA (r = 0.207, P = .233).

Laboratory and ABP results are shown in Table II. Hemoglobin A\textsubscript{1c} and triglyceride levels were significantly higher in the patients with T2DM. Patients with T2DM also demonstrated several significantly higher ABP results, including average daytime systolic BP, average asleep systolic BP, average asleep diastolic BP, daytime systolic BP load, asleep systolic BP load, and asleep BP diastolic load. All these ABP differences in the 2 groups were present whereas casual BPs were not significantly different. The patients with T2DM had lower nocturnal declines of systolic and diastolic BP than subjects without T2DM, but these differences were not significant.

Table III shows the characteristics and results of the patients with T2DM who had MA compared with patients with T2DM who did not have MA and to the control group.

### Table I. Characteristics of the patients with diabetes mellitus and control subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All with diabetes mellitus (n = 26)</th>
<th>Control group (n = 13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>15.0 ± 1.9 (11.8-18.1)</td>
<td>14.1 ± 2.4 (11.1-18.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>14 (53.8%)</td>
<td>8 (61.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>8 (30.8%)</td>
<td>3 (23.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hispanic Latino</td>
<td>15 (57.7%)</td>
<td>8 (61.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>More than 1 race</td>
<td>1 (3.8%)</td>
<td>2 (15.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>2 (7.7%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Family History of hypertension</td>
<td>18 (69%)</td>
<td>9 (69%)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of T2DM, months</td>
<td>17.6 ± 11.4 (1-37)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>BMI, kg/m\textsuperscript{2}</td>
<td>35.3 ± 7.5 (22.0-51.7)</td>
<td>35.3 ± 5.8 (25.7-45.2)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>4.3 ± 2.4 (0.6-10.4)</td>
<td>4.2 ± 1.6 (1.8-7.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.92 ± 0.08 (0.70-1.07)</td>
<td>0.93 ± 0.12 (0.78-1.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Continuous variables are presented as Mean ± SD (minimum-maximum).
Categorical variables are presented as the number (percentage) of the whole group.
NS = Not significant; n/a = not applicable.
There were no significant differences in the 2 groups with T2DM in their hemoglobin A1c level, age, sex distribution, race/ethnicity, duration of T2DM, homocysteine level, BMI, or BMI Z score. Patients with T2DM who had MA had greater waist-to-hip ratios, indicating greater central obesity, than the patients with T2DM who did not have MA. Patients with MA also had significantly higher total cholesterol and low-density lipoprotein cholesterol levels than patients with T2DM who did not have MA.

The patients with T2DM who had MA had several ABP findings that were significantly greater than those of patients with T2DM who did not have MA and those of the control subjects, including average daytime systolic BP, average daytime diastolic BP, daytime systolic load, and daytime diastolic load. There were no significant differences in the groups’ casual BPs. The asleep average BPs and loads tended to be higher from the control subjects to patients with T2DM who did not have MA to patients with T2DM who had MA, but these findings did not achieve significance.

Twenty-four of 26 of the patients with T2DM underwent an echocardiogram. One echocardiogram yielded no data because of technical reasons. Five of the patients (22%) were found to have LVH. As shown in Table III, there were no significant differences in the prevalence of LVH or the degree of LVMI between the group with T2DM who had MA and the group with T2DM who did not have MA.

Three of the patients with T2DM were receiving antihypertensive medications. We analyzed all the results with the exclusion of the data of these 3 patients and found no additional significant differences. Only the difference in the waist-hip ratio between the patients with T2DM who had MA and patients with T2DM who did not have MA became insignificant. Because the findings were unaffected, statistically the data from these 3 subjects were retained in the analysis.

### DISCUSSION

This study examined risk factors for cardiovascular and renal disease in adolescents with T2DM and reveals that hypertension and incipient nephropathy are common even after a relatively short duration of T2DM. These adolescents probably had undiagnosed T2DM for >3 years, but still would have had it for less time than their adult counterparts, who may have the condition for decades. Although casual hypertension and glomerular hyperfiltration may be associated with obesity itself, it appears that ambulatory hypertension, dyslipidemia, and MA are attributable to the effects of T2DM.

Hyperfiltration is an early functional renal change that is thought to be the first manifestation of diabetic nephropathy. It is followed by the development of structural renal changes.

### Table II. Comparison of control subjects and patients with diabetes mellitus

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All with diabetes mellitus (n = 26)</th>
<th>Control group (n = 13)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>7.4 (6.0, 9.1)</td>
<td>5.5 (5.4, 5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>11.5 (9, 13)</td>
<td>12 (9.5, 13.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.6 (0.58, 0.7)</td>
<td>0.7 (0.55, 0.75)</td>
<td>NS</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>88.5 (77, 102)</td>
<td>90 (74, 108)</td>
<td>NS</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>43.5 (38, 50.5)</td>
<td>47 (45, 51)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>123 (78.5, 152.5)</td>
<td>79 (42.5, 110)</td>
<td>.01</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>161 (139, 174)</td>
<td>158 (129, 176)</td>
<td>NS</td>
</tr>
<tr>
<td>Homocysteine, umoles/L</td>
<td>6.6 (4.9, 8.1)</td>
<td>6.7 (5.1, 8)</td>
<td>NS</td>
</tr>
<tr>
<td>Casual SBP, mm Hg</td>
<td>130 (122.8, 139)</td>
<td>123 (109, 133)</td>
<td>NS</td>
</tr>
<tr>
<td>Casual DBP, mm Hg</td>
<td>68 (63.8, 74.2)</td>
<td>65 (58.5, 75.5)</td>
<td>NS</td>
</tr>
<tr>
<td>ABP findings†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average daytime SBP, mm Hg</td>
<td>123 (117, 129)</td>
<td>113 (107, 118)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Average daytime DBP, mm Hg</td>
<td>72 (66, 75)</td>
<td>68 (96, 110)</td>
<td>NS</td>
</tr>
<tr>
<td>Average asleep SBP, mm Hg</td>
<td>111 (105, 120)</td>
<td>99 (96, 110)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Average asleep DBP, mm Hg</td>
<td>61 (56, 64)</td>
<td>56 (55, 58)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Daytime systolic load, %</td>
<td>24 (4.2, 36.8)</td>
<td>2.6 (0, 8.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Daytime diastolic load, %</td>
<td>10 (3.1, 23.6)</td>
<td>9 (2.6, 13.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Asleep systolic load, %</td>
<td>16.7 (8.7, 62.6)</td>
<td>5 (0, 26.6)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Asleep diastolic load, %</td>
<td>22.2 (7.5, 36.4)</td>
<td>6.4 (1.0, 18.6)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Systolic dip, %</td>
<td>8.3 (3.9, 13.8)</td>
<td>11 (4.6, 16)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic dip, %</td>
<td>10.2 (7.6, 21.2)</td>
<td>15.8 (11.3, 21.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Shown are medians (interquartiles 25, 75).
*Mann-Whitney test.
†See text for definitions.
leading to MA, then proteinuria, then renal insufficiency, and ultimately to end-stage renal disease. Hyperfiltration is found in 30% to 40% of adults with newly diagnosed T2DM. It was present in most of this sample of adolescents with T2DM and also in most of the control subjects with obesity. However, differing from the control group, 40% of these patients with T2DM already had MA, indicating that they may already be progressing along the continuum to overt nephropathy. Of concern is that these adolescents have had known T2DM for <3 years, yet they have a greater prevalence of MA when compared with adults who have T2DM, who have been shown to have a cumulative incidence of MA of approximately 5% per year.

Some patients with diabetes mellitus never progress to chronic renal failure despite decades of hyperglycemia. It is unclear at this time what separates them from patients who do

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 13)</th>
<th>T2DM no MA (n = 15)</th>
<th>T2DM with MA (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>13.6 (11.9, 16.8)</td>
<td>15 (13.7, 16.6)</td>
<td>15.3 (12.6, 17.1)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male/Female 8 female (62%)</td>
<td>7 female (47%)</td>
<td>6 female (60%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Non-Hispanic Black 3 (23%)</td>
<td>5 (33%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td></td>
<td>Hispanic Latino 8 (62%)</td>
<td>10 (67%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td></td>
<td>More than 1 race/ethnicity 2 (15%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>Other 0 (0%)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Duration of T2DM, months</td>
<td>n/a</td>
<td>18 (6, 30)</td>
<td>17 (10.2, 27.8)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>35.1 (31.2, 40.2)</td>
<td>34.7 (26, 40.8)</td>
<td>37 (33.6, 43)</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>3.9 (3.1, 5.7)</td>
<td>3.5 (1.9, 5.3)</td>
<td>4.5 (3.8, 7.0)</td>
</tr>
<tr>
<td>Waist-h-ratio</td>
<td>0.91 (0.83, 1.02)</td>
<td>0.90 (0.86, 0.94)</td>
<td>0.98 (0.90, 1.05)</td>
</tr>
<tr>
<td>Laboratory studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A₁c, %</td>
<td>5.5 (5.4, 5.8)</td>
<td>6.5 (5.9, 9.0)</td>
<td>8.0 (6.6, 10.3)</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>12 (9.5, 13.5)</td>
<td>12 (9, 13)</td>
<td>10.5 (8, 12)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.7 (0.55, 0.75)</td>
<td>0.7 (0.6, 0.7)</td>
<td>0.55 (0.4, 0.6)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>90 (74, 108)</td>
<td>81 (69, 149)</td>
<td>97 (90, 110)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>47 (45, 51)</td>
<td>42 (36, 54)</td>
<td>46 (38.8, 49.8)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>79 (42.5, 110)</td>
<td>100 (69, 149)</td>
<td>142.5 (109, 165)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>158 (129, 176)</td>
<td>148 (126, 170)</td>
<td>172.5 (158, 191)</td>
</tr>
<tr>
<td>Homocysteine, umoles/L</td>
<td>6.7 (5.1, 8)</td>
<td>7 (5.8, 9.9)</td>
<td>6.3 (4.6, 7)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>145 (134, 182)</td>
<td>165 (154, 182)</td>
<td>200 (152, 225)</td>
</tr>
<tr>
<td>Urinary MA, mg/day</td>
<td>10.5 (3.5, 12)</td>
<td>8 (3, 17)</td>
<td>98.5 (38, 118)</td>
</tr>
<tr>
<td>Casual SBP, mm Hg</td>
<td>123 (109, 133)</td>
<td>130 (124, 139)</td>
<td>123.5 (118, 148)</td>
</tr>
<tr>
<td>Casual DBP, mm Hg</td>
<td>65 (58.5, 75.5)</td>
<td>65 (61, 70)</td>
<td>72 (62, 76)</td>
</tr>
<tr>
<td>ABP findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average daytime SBP, mm Hg</td>
<td>113 (107, 118)</td>
<td>121 (114, 125)</td>
<td>129 (122, 137)</td>
</tr>
<tr>
<td>Average daytime DBP, mm Hg</td>
<td>68 (96, 110)</td>
<td>68 (64, 73)</td>
<td>76 (70, 80)</td>
</tr>
<tr>
<td>Average asleep SBP, mm Hg</td>
<td>99 (96, 110)</td>
<td>109 (104, 112)</td>
<td>120 (106, 130)</td>
</tr>
<tr>
<td>Average asleep DBP, mm Hg</td>
<td>56 (55, 58)</td>
<td>58 (55, 62)</td>
<td>63 (58, 73)</td>
</tr>
<tr>
<td>Daytime systolic load, %</td>
<td>2.6 (0, 8.2)</td>
<td>5.1 (2.8, 30)</td>
<td>37.1 (24.9, 67.8)</td>
</tr>
<tr>
<td>Daytime diastolic load, %</td>
<td>9 (2.6, 13.6)</td>
<td>8.3 (2.6, 21.2)</td>
<td>28.1 (11.5, 41.4)</td>
</tr>
<tr>
<td>Asleep systolic load, %</td>
<td>5 (0, 26.6)</td>
<td>15 (6.7, 19)</td>
<td>53.3 (10.2, 89.8)</td>
</tr>
<tr>
<td>Asleep diastolic load, %</td>
<td>6.4 (10, 18.6)</td>
<td>20 (0, 31.2)</td>
<td>28.6 (9.6, 78.7)</td>
</tr>
<tr>
<td>Systolic dip, %</td>
<td>11 (4.6, 16)</td>
<td>8.3 (4, 14)</td>
<td>10.8 (2.2, 13.3)</td>
</tr>
<tr>
<td>Diastolic dip, %</td>
<td>15.8 (11.3, 21.3)</td>
<td>14 (8.2, 20.5)</td>
<td>10.2 (6, 23.6)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>n/a</td>
<td>3/4 (21.4%)</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>n/a</td>
<td>31.6 (22.3, 35.6)</td>
<td>35 (26, 39.1)</td>
</tr>
</tbody>
</table>

Categorical variables are presented as the number (percentage) of the whole group.
Continuous variables are shown as medians (Interquartiles 25, 75).
*See text for definitions.
†P <.05, control group versus patients with T2DM with no MA.
‡P <.05, control group versus patients with T2DM with MA.
§P <.05, patients with T2DM with no MA versus patients with T2DM with MA.
progress, but dyslipidemia may be a factor. The persistent hyperinsulinemia seen in T2DM has been shown to cause chronic up-regulation of de novo lipogenesis, whereas the relative insulin deficiency at the tissue level results in decreased lipoprotein lipase activity and inadequate lipolysis. The resultant hyperlipidemia may accelerate atherosclerosis and cause intrarenal microvascular damage that contributes to the development of MA. Our data demonstrate that adolescents with T2DM of short duration and with MA show significantly higher low-density lipoprotein and cholesterol than those without MA. This finding is consistent with previously reported data in adults with T1DM and T2DM with MA.

Another factor that may predispose a patient with diabetes mellitus to progression to overt nephropathy is hypertension. Patients with T2DM are at increased risk for hypertension because the hyperinsulinemia causes sodium retention, fluid overload, and increased activity of the sympathetic nervous system. Hypertension is strongly correlated with MA in adult patients with diabetes mellitus, and both hypertension and MA are predictors of future cardiovascular and renal events. Treatment of the hypertension and MA has been shown in adults to postpone the development of or even ameliorate established nephropathy. Detection of hypertension is therefore vital in the care of a patient with diabetes mellitus. Increasingly, ABP monitoring is proving to be the most useful method for diagnosing hypertension in patients with diabetes mellitus.

Abnormal ABP profiles have been reported in adults with T1DM, adults with T2DM, and adolescents with T1DM, but never, to the best of our knowledge, in adolescents with T2DM. Adolescents with T1DM have been shown to have average daytime systolic, nighttime systolic, and nighttime diastolic BPs that are significantly higher than normal, published controls. Theochari et al also reported that adolescents with T1DM had significantly higher daytime systolic and diastolic BPs and greater systolic and diastolic BP loads when compared with age- and sex-matched control subjects. This sample of adolescents with T2DM has similar ABP findings, which were significantly higher than their non-diabetic counterparts with obesity. These differences in ambulatory blood pressure monitoring (ABPM) were found in the absence of significant differences in the casual BPs, demonstrating that the ABPM may be a more sensitive tool than office BP checks. There were no associations between the ABP findings and the echocardiographic data, probably because of limited power of the study to detect these differences.

Abnormalities of ABP have clearly been associated with MA in adolescents with T1DM. Lurbe et al observed 75 adolescents with T1DM for 2 years and found that an increase in the average systolic BP during sleep (109.9 ± 11.3 mm Hg to 114.9 ± 11.7 mm Hg, P = .01) preceded the development of MA. MA did not develop in subjects whose average systolic BP remained unchanged (106.0 ± 8.8 mm Hg to 106.4 ± 14.8 mm Hg). When the subjects with T2DM in this study were divided into those with and those without MA, significant differences appeared in the average daytime BP and daytime BP loads, with higher ABP values consistently associated with the finding of MA.

Nocturnal non-dipping has been repeatedly shown to be associated with a poorer renal prognosis in studies of adults with diabetes mellitus. Farmer et al studied 26 patients, with a mean age 54 years, who had either T1DM or T2DM. Those classified as nocturnal non-dippers had significantly greater declines in their creatinine clearance with time (−7.9 mL/min/year versus −2.9 mL/min/year, P < .05). The high prevalence of nocturnal non-dipping in the patients with diabetes mellitus (56%) and in the control group (42%) is a concern. Nocturnal differences trended toward higher average and load values for subjects with MA, but these findings were not statistically significant, probably because of the limitation in the study’s power to detect such a difference. The samples sizes of 13, 15, and 10 of the control, diabetes with MA, and diabetes without MA groups, respectively, had a power of 26%, 31%, and 20%, respectively, to detect a significant correlation coefficient of 0.4 between the ABP results and the amount of MA. Another possibility is that some members of both groups may be non-dippers for a reason other than obesity or diabetes mellitus. For example, Wilson et al demonstrated that approximately 30% of healthy, normotensive, non-obese African American adolescents are non-dippers.

This study complements what is known about renal and cardiovascular abnormalities in T2DM by adding data about adolescents who are minorities. Risk factors for the early development of cardiovascular and renal disease, including dyslipidemia, hyperfiltration, MA, and ambulatory hypertension, are clearly present in this population, suggesting that longitudinal studies with long-term follow-up are indicated. There is 1 report in the literature about the natural history of T2DM diagnosed in childhood. Of 79 children re-contacted as long as 15 years after the diagnosis of T2DM, 9% had died, 6.3% were receiving dialysis, and 38% of the pregnancies had been lost. Therapeutic interventions, such as diet and exercise modification, angiotension-converting enzyme inhibitors or angiotensin receptor blockers, and/or lipid-lowering agents should be studied. Also warranting further investigation are the high prevalence of hyperfiltration and non-dipping in the “healthy,” obese control group.

REFERENCES

THE RELATIONSHIP BETWEEN THE LOCATION OF PEDIATRIC INTENSIVE CARE UNIT FACILITIES AND CHILD DEATH FROM TRAUMA: A COUNTY-LEVEL ECOLOGIC STUDY

FOLAFOLUWA O. ODETOLA, MD, WILLIAM C. MILLER, MD, PHD, MATTHEW M. DAVIS, MD, MAPP, AND SUSAN L. BRATTON, MD, MPH

Objectives To describe the relationship between the location of Pediatric Intensive Care Unit (PICU) facilities and county-level child death from trauma in the contiguous USA.

Study design We conducted a cross-sectional ecologic study using county-level data on death due to trauma in children 0 to 14 years of age from 1996 to 1998. These data were linked to 1997 county-level data on availability of PICU facilities.

Results In 1997, PICU facilities were present in 9% of USA counties. There were 18,337 childhood deaths from trauma in the study period. The presence of PICU facilities in a county was associated with lower mortality from trauma (incidence rate ratio [IRR] = 0.72; 95% CI 0.67-0.78) compared to counties without PICU facilities. After controlling for residence in rural and low-income counties, and the presence of adult medicosurgical intensive care units, the presence of PICU facilities in a county remained associated with lower rates of death from trauma (IRR = 0.82; 95% CI 0.75-0.89).

Conclusion The presence of PICU facilities is related to lower mortality rates due to traumatic injuries at the county level. This finding may reflect the concentration of pediatric subspecialty care in counties with PICUs. This association merits further study with individual-level observations. (J Pediatr 2005;147:74-7)

Trauma-related injuries are a leading cause of death in U.S. children and a significant public health problem, with more than 1.5 million childhood injuries and approximately 500,000 hospitalizations annually,1 with an estimated societal cost of about $250,000 per incident.2 Care for these injuries is usually conducted in Pediatric Intensive Care Units (PICU) in counties where such units are available. Availability of intensive care units for the care of critically ill and injured children in the U.S.A. has increased over time.3,4

Prior studies have shown that in areas where specialized pediatric emergency and critical care services are not available, the outcome of pediatric critical illness and injury is adversely affected.5,6 A direct relationship between higher patient volume and lower risk-adjusted mortality rates has been described in the care of children requiring surgical, trauma, or critical care.7-10 Although considerable variation exists in the processes of care among PICUs,11,12 the admission of a critically ill or injured child to a non-tertiary care PICU has been associated with higher odds of death when compared with care in a tertiary care PICU, adjusting for severity of illness.5 Likewise, studies of critically injured children treated in designated pediatric trauma centers have reported better outcomes than for children treated in general trauma centers.6,13,14

The relationship between the location of PICU facilities and population outcomes for pediatric trauma has not been well described. Knowledge of this relationship will help inform health care policymakers and hospital management teams regarding the future establishment and distribution of PICU facilities in the U.S.A. This study was conducted to assess the relationship between the location of PICU facilities and county-level child death from trauma in the U.S.A.

ICD-9 International Classification of Diseases, 9th revision
IQR Inter-Quartile Range
IRR Incidence Rate Ratio
PICU Pediatric Intensive Care Unit

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10.1016/j.jpeds.2005.02.012
Table I. Characteristics of counties by availability of PICU facilities

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PICU present (n = 271)</th>
<th>PICU absent (n = 2839)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Urban location</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>Median Income (1990 US)</td>
<td>$39,813 ($35,056-$45,190)</td>
<td>$33,046 ($29,363-$38,375)</td>
</tr>
<tr>
<td>Children in poverty (/10,000 children 0-14 years)</td>
<td>218 (157-289)</td>
<td>230 (162-313)</td>
</tr>
<tr>
<td>Population (0-14 years)</td>
<td>156,740 (53,994-387,937)</td>
<td>13,787 (6,555-30,130)</td>
</tr>
<tr>
<td>Median mortality rate (/10,000 children 0-14 years)</td>
<td>1.02 (0.64-1.39)</td>
<td>1.22 (0.43-2.17)</td>
</tr>
</tbody>
</table>

### METHODS

The study outcome was child death defined as death of a child 0-14 years attributed to injuries, as defined by diagnosis codes. Counties in the U.S.A. were the units of analysis. Counties in the states of Hawaii and Alaska were excluded to preserve geographic continuity.

### Data Sources

**Hospital facility data.** Data from the 1997 American Hospital Association annual survey on hospital facility availability were used to ascertain the presence of PICU facilities and adult medicosurgical intensive care units at the county level. The survey does not contain information regarding pediatric trauma systems designation or adult trauma systems that might also care for children.

**Mortality data.** We used data from the National Center for Health Statistics compressed mortality file. The file summarizes all deaths in the U.S.A., stratified by age group, race, sex, and 4-digit International Classification of Diseases, 9th revision (ICD-9) code, aggregated by county of residence, which may or may not have been the county where the death occurred.

We restricted the data to the leading causes of death in children 0-14 years of age, collapsing across age, race, and sex categories for the 3-year period 1996–1998. Thereafter we analyzed data on all deaths caused by trauma in children 0-14 years at the county level. Deaths from suicide or homicide were excluded. Denominator population data for all children 0-14 years, obtained from the U.S.A. census, were also included in the mortality file. Mortality rates were calculated as a ratio of death counts in children 0-14 years in each county per total population of children 0-14 years residing there. These rates were expressed per 10,000 children 0-14 years in the counties. The ICD-9 codes used to ascertain a diagnosis of traumatic injury are listed in the appendix (available online at www.us.elsevierhealth.com/jpeds).

**Poverty data.** We selected poverty as a county-level control variable, because lower socioeconomic status and poverty have been linked to increased risk of child death. We obtained the number of children 0-17 years that were living below the poverty level as identified in the 1990 U.S.A. census.

**County of residence.** Delayed transfer of critically ill or injured patients from rural areas to tertiary care facilities, which are often located in urban areas, could negatively impact outcome. A higher mortality rate from pediatric trauma has also been reported in rural versus urban areas. The county of residence was dichotomized into rural versus urban counties on the basis of the 10-level rural-urban continuum codes provided by the U.S.A. Department of Agriculture.

### Statistical analysis.

Data were aggregated at the county level and linked using the Federal Information Processing System county codes. All count data were standardized to the county population of children 0-14 years. For descriptive statistics, median values and their interquartile range (IQR) were reported. Mortality rates per 10,000 children 0-14 years were reported at the county level and compared between counties on the basis of availability of PICU facilities, using the Mann-Whitney test.

Thereafter we used negative binomial regression analysis to perform bivariate comparisons of mortality rates between counties with PICU facilities and those without and to subsequently construct multivariate models adjusting for county of residence, poverty, and the presence of adult medicosurgical intensive care units at the county level, adding one variable at a time. Negative binomial regression models account for distributions with the mode at zero and probability masses that decline as the count increases, as in phenomena with low expected rates such as child death. Incidence rate ratios (IRR) with corresponding 95% confidence intervals were calculated to estimate the difference in mortality rates between counties with PICU facilities and those without such facilities. Analyses were conducted using Stata 7 for Windows (Stata Corporation, College Station, Texas).

### RESULTS

Of 3110 U.S.A. counties in 1997, only 271 (9%) had PICU facilities, located predominantly (99%) in urban counties (Table I). Assessing county characteristics, the median household income across all U.S.A. counties was $33,670 (IQR: $29,583-$39,205). Counties with PICU facilities had a higher median household income of $39,813 ($35,056-$45,190) compared with counties without PICU facilities, which had a median household income of $33,046 ($29,363-$38,375). The median population of children aged 0-14 years in U.S.A. counties was 15,746 (6991-38,587), and counties with PICU facilities had a larger population of children, with a median of 156,760 (53,994-387,937) compared with counties without PICU facilities with a median of 13,787 (6555-30,130). The counties without PICU facilities had a larger proportion of children living in poverty per 10,000
children 0-14 years in the county (Table I). Adult medicosurgical intensive care units were present in 1675 (54%) of the U.S. counties.

Among children 0-14 years of age, there were 96,413 deaths from the 10 leading causes of death between 1996 and 1998 (Table II). Of these, 18,337 (19.0%) deaths were from trauma. The median mortality rate from trauma at the county level was 1.17 deaths per 10,000 population of children 0-14 years (IQR: 0.47-2.08).

In regression analyses (Table III), residence in a county with PICU facilities was associated with significantly lower rates of death from trauma (IRR = 0.72; 95% CI 0.67-0.78) compared to counties without PICU facilities. Controlling for residence in rural versus urban counties, the proportion of children living in poverty in each county, and the county-level availability of adult medicosurgical intensive care units, the presence of PICU facilities in a county remained associated with significantly lower mortality rates from trauma (IRR = 0.72; 95% CI 0.67-0.78) when compared with counties without such facilities.

### DISCUSSION

As PICU facilities expand in size and number, it is essential to understand how their location may impact patterns of care and death for children. Death from trauma, which accounted for one fifth of all pediatric deaths in the U.S. in the 3-year sample studied, was significantly lower in counties with PICU facilities.

Rapid stabilization and definitive care of trauma victims have been associated with improved outcomes. Proximity and rapid transport to a hospital where such care can be provided is critical and may result in major reduction of mortality rates in trauma patients. We have described lower rates of death from trauma in counties with PICU facilities compared with counties without such facilities, which argues for the importance of proximity to care in the presence of pediatric trauma and critical care specialists with high levels of expertise and technical skills. Of note, we could not control for the availability of trauma surgeons, nor were we able to control for the availability of pediatric trauma facilities or designated adult trauma facilities that treat children. These 2 factors may be positively associated with the presence of PICU facilities and may have affected our findings. We controlled for the presence of adult medicosurgical intensive care units at the county level to account for any confounding by these units because children might be treated for traumatic injuries at such facilities.

Another possible explanation for our findings regarding death from trauma could be that the organization of Emergency Medical Services for Children, the emergency transport system established for prehospital stabilization and transport of ill or injured children, is better coordinated in counties with PICU facilities because of familiarity with and more frequent use of the services. This might enable coordinated and rapid delivery of prehospital care for childhood trauma that could be vital to ultimate survival. In counties with PICU facilities, several factors other than the availability of PICU facilities could be related to the finding of lower county-level rates of death from trauma. This might include prehospital care, the organization of critical care services including appropriate centralization of care, and improved access to critical care services through well-coordinated transport programs. On the other hand, an approach to improving pediatric trauma outcomes in rural areas might include the use of telemedicine to facilitate access to pediatric critical care services, with rapid and appropriate triage of critically ill and injured children resident in rural and underserved areas.

We found a significant preponderance of PICU facilities in counties that were urban, which would be expected to have higher median household incomes and higher population densities. These factors may affect the per capita trauma-related mortality rate among children 0-14 years in the county and were therefore controlled for in multivariate regression analyses. The fact that adjustment for rural-urban status and proportion of children living in poverty did not substantively change our findings indicates the comparatively strong effect of the presence of PICU services at the county level.

### Table II. Mortality attributed to the 10 leading causes of child death in the United States 1996–1998

<table>
<thead>
<tr>
<th>Causes of child death</th>
<th>Number of deaths</th>
<th>% of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions of perinatal origin</td>
<td>39,284</td>
<td>41.0</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>21,729</td>
<td>22.5</td>
</tr>
<tr>
<td>Trauma/Accidents</td>
<td>18,337</td>
<td>19.0</td>
</tr>
<tr>
<td>Homicide</td>
<td>3573</td>
<td>4.0</td>
</tr>
<tr>
<td>Heart disease</td>
<td>3447</td>
<td>3.5</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>3223</td>
<td>3.0</td>
</tr>
<tr>
<td>Malignancies</td>
<td>2780</td>
<td>3.0</td>
</tr>
<tr>
<td>Pneumonia/Influenza</td>
<td>2236</td>
<td>2.0</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1193</td>
<td>1.0</td>
</tr>
<tr>
<td>Benign neoplasms</td>
<td>611</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>96,413</td>
<td>100.0</td>
</tr>
</tbody>
</table>

### Table III. Negative binomial regression models of child trauma mortality

<table>
<thead>
<tr>
<th>Death due to trauma/accidents</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) PICU in county</td>
<td>0.72 (0.67-0.78)</td>
</tr>
<tr>
<td>(2) Rural-urban county</td>
<td>0.75 (0.70-0.80)</td>
</tr>
<tr>
<td>(3) Child poverty</td>
<td>0.78 (0.72-0.84)</td>
</tr>
<tr>
<td>(4) Adult ICU</td>
<td>0.82 (0.75-0.89)</td>
</tr>
</tbody>
</table>

Model 1 compares IRR for counties with PICUs versus counties without PICUs.
Model 2 adds to Model 1 a variable indicating rural-urban county status.
Model 3 adds to Model 2 a variable indicating the proportion of children in the county living in poverty.
Model 4 adds to Model 3 a variable indicating the presence of adult medicosurgical ICUs at the county level.

The final model compares incidence death rates for counties with PICUs versus counties without PICUs, adjusting for county rural-urban status, proportion of children in the county living in poverty, and the county-level availability of adult medicosurgical ICU facilities.
Our analyses have certain limitations common to ecologic studies. One is that the validity of the inferences made will depend on the ability to control for differences in confounders at the county level, including individual patient variables. To address this concern, we controlled for certain county-level variables related to child death, including poverty and rural status of the county, while recognizing our inability to control for other known and unknown potential confounders that could affect the validity of our conclusions. The American Hospital Association (AHA) data used for the availability of PICU facilities might be incomplete, leading to incorrect estimates of the county-level availability of PICU facilities. Also, the organizational characteristics of the PICUs are unknown. While describing the availability of the PICU facilities, the ability to access such services, and the efficiency of resource use within the PICUs could not be ascertained within the context of this study. An additional limitation is that the causes of death were ascertained from death certificates and are susceptible to inaccuracies of detection and attribution that may have biased our findings. Also, because of data limitations, this study could not address the attributable mortality rate from the individual causes of trauma in children and could therefore not compare mortality rates from these causes of trauma between counties with and without PICU facilities.

Ecologic studies are not grounds for drawing causal inferences. Further investigation with studies that include patient physiological data and adjustment for severity of illness, as well as facility and provider information are warranted. There also should be further study regarding transfer of pediatric trauma patients to facilities with higher pediatric capacity.

REFERENCES

A POLYMORPHISM IN PLASMA PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE IS INVOLVED IN RESISTANCE TO IMMUNOGLOBULIN TREATMENT IN KAWASAKI DISEASE

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Objective To investigate whether reduced levels of plasma platelet-activating factor acetylhydrolase (PAF-AH) as a result of a genetic polymorphism are involved in the pathogenesis of Kawasaki disease (KD).

Study design The frequency of a V279F polymorphism (G/T transversion) in the PAF-AH gene was quantified in 76 Japanese children with KD and 112 healthy Japanese adults using the allele-specific polymerase chain reaction (PCR). Associations between genotype, clinical features, and resistance to intravenous immunoglobulin (IVIG) were investigated in the patients with KD. Plasma PAF-AH activity was measured by using [3H]-acetyl-PAF.

Results There were no significant differences in genotype frequency between patients and controls (P = .51). Compared with the GG (normal genotype) group, significantly more patients in the GT (heterozygous) + TT (homozygous deficient) group required additional IVIG (52% vs 14%, P = .001). The duration of fever and maximum serum C-reactive protein (CRP) levels also were significantly increased in the GT+TT group (P = .012 and .036, respectively), whereas plasma PAF-AH activity was significantly lower (P < .0001).

Conclusion We conclude that the V279F polymorphism in the plasma PAF-AH gene and consequent enzymatic deficiency is one of the factors for IVIG nonresponse in Japanese patients with acute KD. (J Pediatr 2005;147:78-83)

Kawasaki disease (KD) is an acute systemic vasculitis of childhood and its etiology remains unknown.1,2 Susceptibility to KD may be genetically influenced because the incidence of KD is high among Asian and Asian-American populations.3 The standard therapy for KD is intravenous immunoglobulin (IVIG), which reduces both the duration of fever and the prevalence of coronary artery lesions (CAL).4 However, 10% to 15% of patients have persistent fever despite IVIG therapy.5,6

Platelet-activating factor (PAF) is one of the most potent inflammatory mediators; it stimulates the release of arachidonic acid, prostaglandins, and leukotrienes, and it induces interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) gene expression in certain cells.7-9 Plasma PAF acetylhydrolase (PAF-AH) is a recently identified extracellular phospholipase A2 that tightly regulates both the synthesis and degradation of PAF to avoid inappropriately high levels.10-14 The V279F polymorphism (G/T transversion, at position 994 in exon 9) in the plasma PAF-AH gene is associated with a decreased level of plasma PAF-AH activity.15,16 A significantly higher prevalence of the mutant allele has been found in several disease states.17-20

Serum from patients with acute KD contains elevated levels of eicosanoids and cytokines (IL-1, IL-2, IL-6, IL-8, and TNF-α).21-25 This may be because of reduced plasma PAF-AH activity allowing accumulation of PAF, which would cause an increase in serum levels of these inflammatory mediators. Nevertheless, there have been no reports of any association between PAF-AH gene polymorphism and KD, or of any involvement of PAF or PAF-AH in the pathogenesis of KD. The purpose of our study was to test the

CAL Coronary artery lesion
CRP C-reactive protein
IL Interleukin
IVIG Intravenous immunoglobulin
KD Kawasaki disease

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In Resistance To Immunoglobulin Treatment In Kawasaki Disease

A Polymorphism In Plasma Platelet-Activating Factor Acetylhydrolase Is Involved

In an analysis of plasma PAF-AH genotype

In the study population

factor for IVIG nonresponse.

gene may give rise to the clinical features of KD or be a risk hypothesis that the V279F polymorphism in the PAF-AH gene may give rise to the clinical features of KD or be a risk factor for IVIG nonresponse.

Figure 1. Allele specific PCR assay. Genotypes were designated as GG (normal), GT (heterozygous), and TT (homozygous deficient). Antisense primer B indicates the G allele at position 994, and C indicates T. M, marker.

METHODS

Study Population

The study protocol was reviewed and approved by the Ethical Commission of Wakayama Medical University Hospital (Wakayama, Japan).

A total of 76 Japanese patients with KD (44 boys and 32 girls, ranging in age from 1 month to 11 years and 4 months [median, 28.8 months]) were studied after written informed consent had been obtained from their parents. All patients were seen at our hospital between September 1988 and December 2003, fulfilled the diagnostic criteria for KD, and received both IVIG (total dose, 2 g/kg) and aspirin (30 mg/kg/day) within 7 days of the onset of symptoms. Although all patients received a total of 2 g/kg of IVIG, the administration schedule differed depending on the time of treatment. The first 35 patients (19 boys and 16 girls, seen between September 1988 and August 1999) received 400 mg/kg for 5 consecutive days; the 41 patients (25 boys and 16 girls) seen after September 1999 received 1 g/kg for 2 consecutive days.

We defined a clinical IVIG-nonresponder as a patient who showed no resolution of fever (to less than 37.5°C) within 24 hours of completing IVIG therapy. These nonresponders were treated with additional IVIG at the same daily dosage (400 mg/kg or 1 g/kg). All patients were treated without knowledge of their PAF-AH genotype. Unrelated healthy Japanese adult volunteers (n = 112, age range, 21 to 55 years) with no history of KD or ischemic heart disease also were studied as controls to determine the population frequency of the gene polymorphism.

Analysis of Plasma PAF-AH Genotype

Genomic DNA was extracted and purified from peripheral whole-blood leukocytes using a GenTLE DNA isolation kit (Takara, Ohtsu, Japan). The plasma PAF-AH genotype was determined using the allele-specific polymerase chain reaction (PCR) as described previously. The genotype was determined by two independent amplifications. The sequences of the sense primer (sense primer A) and two antisense primers (antisense primer B and C) were as follows: sense primer A: 5'-CTATAGATATCAGCTT-3'; antisense primer B: 5'-TCACGAGTCCTGAATAA-3'; antisense primer C: 5'-TCACGAGTCCTGAATAAA-3'.

PCR was performed in 30 μL volumes which included DNA (100 ng), 10x PCR buffer containing 15 mmol/L MgCl2 (3 μL), 2 mmol/L of deoxyribonucleotide triphosphate (dNTP) (3 μL), 40 pmol of paired primer, and 1.25 U Ampli Taq Gold DNA polymerase (0.25 μL; Applied Biosystems, Branchberg, NJ). Amplifications were performed as follows: first, one cycle for 10 minutes at 94°C; second, five cycles for 1 minute at 94°C, 1 minute at 56°C followed by 1 minute at 72°C; third, 30 cycles for 30 seconds at 94°C, 30 seconds at 52°C followed by 30 seconds at 72°C; and fourth, one cycle for 5 minutes at 72°C. The size of the PCR products was 108 base pairs (bp). The products were analyzed by electrophoresis on a 3% agarose gel stained with ethidium bromide.

The PCR products amplified by sense primer A and antisense primer B are equivalent to a partial exon 9 product containing the normal sequence (G allele at position 994), and those by sense primer A and antisense primer C are equivalent to a partial exon 9 product containing the mutation (T allele at position 994). Genotypes were designated as GG (normal), GT (heterozygous), and TT (homozygous deficient) (Figure 1).

PAF-AH Activity Assay

Plasma PAF-AH activity was determined as described by Miwa et al.

Statistical Analysis

All values are presented as the median (range). Statistical analysis was performed using StatView J-5.0 software (SAS Institute, Cary, NC). Associations between categorical variables were examined by Fisher’s exact test. Continuous variables for the two genotype groups were compared using the Mann–Whitney U test. Differences at a two-tailed P value of <.05 were considered statistically significant.

Table I. Frequencies of plasma PAF-AH genotypes in controls and patients with KD

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No.</th>
<th>GG</th>
<th>GT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>112</td>
<td>78 (70)</td>
<td>33 (29)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Patients with KD</td>
<td>76</td>
<td>57 (75)</td>
<td>18 (24)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Genotype frequencies are expressed as number of subjects (percentage).

GG, normal genotype; GT, heterozygous for V279F polymorphism; TT, homozygous for V279F polymorphism.
RESULTS

The frequencies of the GG (normal) and GT (heterozygous) + TT (homozygous) genotypes were 70% and 30%, respectively, among the healthy controls, and 75% and 25%, respectively, among the patients with KD (Table I). These differences between the groups were not significant (Fisher’s exact test, P = .51). Furthermore, the genotype frequencies for the healthy controls were similar to those previously reported in Japanese population studies (GG, 76.8%; GT+TT, 23.2%); TT, 31%).20

The clinical characteristics of patients with KD with the GG and GT+TT genotypes are listed in Table II. The two groups showed no significant differences in the median age at onset, sex ratio, and number of days between onset of symptoms and the start of IVIG. The median duration of fever was significantly longer (Mann-Whitney U test, P = .012) and the start of fever was significantly greater (Mann-Whitney U test, P = .009) in patients with the GT+TT genotype than in those with the GG genotype. The median total IVIG dose was significantly greater (Mann-Whitney U test, P = .009) and the total IVIG dose was significantly different between patients with the GT+TT genotype and those with the GG genotype in each of the dosage groups (data not shown) and the combined group (Tables II and IV). As shown in Table III, the frequency of patients requiring additional IVIG also was statistically significantly different in each of the dosage groups and the combined group. It suggests that the outcome of this study was not influenced by the IVIG dosage regimen.

DISCUSSION

The V279F polymorphism in the plasma PAF-AH gene was demonstrated to be associated with IVIG-nonresponse, prolongation of fever, and an increased serum CRP level in patients with KD, but it was not associated with the development of KD. Because plasma PAF-AH activity is determined by the V279F polymorphism,16 decreased activity of the enzyme as a result of an underlying genetic propensity may be an important factor that predisposes toward IVIG-nonresponse or the pathogenesis of KD.

Miwa et al15 found a higher prevalence of PAF-AH deficiency in Japanese children with severe asthma than in healthy children. Stafforini et al18 reported that the prevalence of the V279F polymorphism was significantly higher in Japanese patients with asthma than in healthy control subjects. These findings suggest that PAF activates inflammatory cells and causes microvascular leakage, bronchoconstriction, and airway hyperresponsiveness. Xu et al found no difference in
genotype frequencies between healthy controls and Japanese children with either nephrotic syndrome or hemolytic uremic syndrome, but they did show that the V279F polymorphism is associated with relapse of nephrotic syndrome and the severity of renal damage in hemolytic uremic syndrome. Lack of PAF-AH activity because of this polymorphism also has been shown to be an independent risk factor for ischemic heart disease. According to these findings, PAF-AH may be important in protecting tissues by degrading PAF and oxidized phospholipids to biologically inactive molecules.

In the present study, plasma PAF-AH activity also is reduced in KD patients with the V279F polymorphism. The degree of change in PAF-AH activity because of this polymorphism was similar to those reported in other diseases. Lack of PAF-AH activity because of this polymorphism also has been shown to be an independent risk factor for ischemic heart disease. According to these findings, PAF-AH may be important in protecting tissues by degrading PAF and oxidized phospholipids to biologically inactive molecules.

In the present study, plasma PAF-AH activity also is reduced in KD patients with the V279F polymorphism. The degree of change in PAF-AH activity because of this polymorphism was similar to those reported in other diseases. Lack of PAF-AH catalytic activity may allow PAF and oxidized phospholipids to recruit, which in turn activates the production of IL-1, IL-6, TNF-α, and other inflammatory mediators. Thus, circulating levels of inflammatory cytokines may increase to a greater extent in patients with KD with the V279F substitution than in those with the normal genotype.

The mechanism of action of IVIG in KD is unknown. Possible explanations include immunologic blockade of Fc receptor, increasing the production of antibodies against the specific etiologic agent, or down-regulation of cytokine production. The binding of gamma globulin to Fc gamma receptors may result in the down-regulation of cytokine production. It therefore appears that cytokine down-regulation may be the major role of IVIG therapy in the acute phase of KD. However, a subgroup of patients with KD are IVIG-nonresponders. The mechanism underlying this failure to respond to IVIG also is unknown, but it may be linked to the persistence of circulating cytokines. In this study, the IVIG-nonresponse rate was significantly higher among patients with the mutant allele than among those with the normal genotype. Therefore, IVIG may not prevent all PAF-mediated acute inflammatory responses. Several pathways may be involved in the inflammatory response to KD, and, although IVIG suppresses the major inflammatory pathways, such as the Fc receptor-mediated pathway, other pathways may not be suppressed in some patients. If one of these other pathways is regulated by plasma PAF-AH activity, IVIG may be unable to suppress it sufficiently in patients with a mutant allele. In addition, the excessive levels of PAF-mediated inflammatory cytokines seen in patients with a mutant allele may be responsible for the significant increase in the duration of fever and serum CRP levels found during the present study. The involvement of PAF in these inflammatory mechanisms is supported by observations in animal models. The intravenous administration of recombinant PAF-AH reduced neutrophil infiltration in

### Table IV. Laboratory values for patients with KD according to plasma PAF-AH genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>GG (n = 57)</th>
<th>GT+TT (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum serum sodium (mEq/L)</td>
<td>134 (120-140)</td>
<td>133 (130-138)</td>
<td>.059</td>
</tr>
<tr>
<td>Minimum serum albumin (g/dL)</td>
<td>3.1 (2.4-4.4)</td>
<td>3.0 (2.3-3.9)</td>
<td>.27</td>
</tr>
<tr>
<td>Maximum serum CRP (mg/dL)</td>
<td>10.4 (1.3-25)</td>
<td>13.5 (1.8-26)</td>
<td>.036 *</td>
</tr>
<tr>
<td>Maximum WBC count (10⁹/μL)</td>
<td>1.51 (0.86-3.97)</td>
<td>1.51 (0.69-3.03)</td>
<td>.44</td>
</tr>
<tr>
<td>Maximum neutrophil count (10⁹/μL)</td>
<td>0.94 (0.44-3.33)</td>
<td>0.95 (0.40-2.77)</td>
<td>.27</td>
</tr>
<tr>
<td>Minimum platelet count (10⁹/μL)</td>
<td>29.3 (2.0-68.5)</td>
<td>30.3 (17.1-63.1)</td>
<td>.94</td>
</tr>
<tr>
<td>Plasma PAF acetylhydrolase activity (nmol/min/50 μL)</td>
<td>1.6 (0.9-2.7)</td>
<td>0.8 (0.0-1.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Values are median (range). P values for categorical variables are based on Fisher’s exact test. P values for continuous variables are based on the Mann-Whitney U test.

CRP, C-reactive protein; WBC, white blood cell.

*P < .05.

**Figure 2.** Plasma PAF acetylhydrolase activity in patients with KD grouped according to the presence (GT+TT) or absence (GG) of the V279F polymorphism (G/T transversion) in the plasma PAF-AH gene. In the GT+TT group, closed circles indicate GT samples; an open circle indicates TT sample.**
myocardial ischemia-reperfusion injury in rabbits and increasing PAF-AH activity by administering dexamethasone prevented the development of necrotizing enterocolitis produced by intravascular injection of PAF in newborn rats. These studies support the possibility that degradation of PAF and oxidized phospholipids with recombinant PAF-AH administration may have therapeutic benefit in IVIG-nonresponders.

Recently, several investigators have reported genetic polymorphisms associated with susceptibility to KD, such as changes leading to an increase in TNF-α, or the development of CAL, such as changes in the CD14 gene and monocyte chemotactrant protein 1 gene. This study demonstrated that genetic polymorphism can influence the outcome of KD therapy. Genetic analysis to identify polymorphism in the PAF-AH gene and consequent reduction in levels of the enzyme may thus help to clarify the mechanism of action of KD therapy.

According to recent reports, IVIG-nonresponse is the major risk factor for CAL. However, not all IVIG-nonresponders develop these lesions. Burns et al reported that 10% of IVIG-nonresponders developed CAL, but about 1% of IVIG-responders also developed CAL. Thus, the development of CAL may involve several factors besides IVIG-nonresponder status. In the present study, the V279F polymorphism in the plasma PAF-AH gene was associated with IVIG-nonresponse but not with the development of CAL. The incidence of our patients with CAL (19/76; 25%) was, however, higher than in other reports (<5%). This may be explained by the fact that our hospital is a regional referral center.

A limitation of this study was that it was not possible to perform direct measurements of PAF. However, we believe it reasonable to assume that PAF accumulation is brought about by lack of PAF-AH activity because the PAF concentration is tightly regulated by PAF-AH.

We conclude that the V279F polymorphism in the plasma PAF-AH gene and consequent enzymatic deficiency is an important factor for IVIG nonresponse in Japanese patients with acute KD.

REFERENCES


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Sample mailing label

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J. H. DOE, MD
531 MAIN ST
CENTER CITY, NY 10001-001

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Objective To examine whether and how institutional review boards (IRBs) are using their web-sites to provide guidance to investigators conducting pediatric research.

Study design We studied guidance on pediatric research from IRB web-sites at the 25 US medical schools, plus affiliated hospitals, research centers, and public health schools, and the top National Institutes of Health-funded (> $5 million) children’s hospitals with separate IRBs. We also included 1 IRB that was not otherwise eligible because other IRBs use its web-based research ethics training program. Our final study population was 39 IRB web-sites.

Results IRB web-sites generally provide basic information about pediatric research. However, few IRBs discuss important ethical issues on which the regulations are silent. Moreover, some IRBs provide incorrect advice about the regulations. More detailed IRB guidance may help pediatric investigators think through ethical issues and protect children in clinical research. Helpful approaches we identified include checklists and “points to consider,” concrete examples to illustrate regulatory requirements, and discussion of areas of controversy.

Conclusion Few IRBs present the kind of detailed guidance that investigators might need to ensure ethically designed protocols. IRBs should revise their web-sites to ensure that they provide accurate, comprehensive, and sufficiently detailed guidance. (J Pediatr 2005;147:84-9)
METHODS

Eligible Institutions

IRBs from the 25 US medical institutions that receive the most funding from the National Institutes of Health (NIH) were eligible for our study. These schools receive more than half of NIH funding, and therefore, their IRBs handle the largest number of protocols annually.27 For completeness, we also included hospitals, research centers, and public health schools affiliated with these medical institutions and the top NIH-funded children's hospitals (>5 million).28 We also included 1 medical school IRB from outside the top 25 NIH-funded institutions because we were aware that other IRBs use the web-based research ethics training program it developed. Altogether, we identified 45 eligible institutions (Appendix; available online at www.us.elsevierhealth.com/jpeds).

ACCESSING IRB GUIDANCE. We identified the IRB web-sites by following links on the institution's “Research” page or by using the main institution web-site's search engine, index, or site map. We used these key words in our search: “institutional review board,” “IRB,” “ethics committee,” “human research committee,” “committee on human research,” and “human subjects.” When these features failed to identify an IRB site, we navigated the institution web-pages using alternative administrative and program services links. We were unable to access IRB web-sites for 3 of the eligible institutions and found no reference to IRBs on the web-sites of 2 other eligible institutions. In addition, 2 eligible institutions were covered by 1 IRB web-site.

From October 2002 to January 2003, we downloaded IRB guidance and policies about research involving children from the web-sites. This information included formal guidelines, manuals, sample consent forms, fact sheets, frequently asked questions, and other discussions. We identified relevant guidance using indices, links, and search engines on the IRB web-site. We developed search criteria in consultation with University of California at San Francisco reference librarians and used these key words: “children,” “child,” “minor(s),” “infant,” “adolescent,” and “youth.” We searched each web-site again in April 2004 for any new materials since our last visit.

FOLLOW-UP. In March 2003, we contacted the top IRB official (e.g., administrator or director) or institutional official responsible for the IRB (e.g., associate dean for research, vice president of clinical trials) at each eligible institution, including those for which we had found no web-site or policies, to confirm that we had accurate and up-to-date policies. We were unable to follow-up with 1 of the institutions because we were unable to locate any links to the IRB web-site or appropriate contact information on the institution's web-site. Also, because 2 eligible institutions had an overlapping IRB, we only needed to contact the 1 IRB. In all, we contacted 43 institutions. Thirty of the institutions we contacted responded to our request (response rate, 70%). Forty percent responded (17/43) that the information we gathered was complete, 14% (6/43) provided us with additional documents, 14% (6/43) chose not to participate in our follow-up, and 1 IRB responded that it was revising its policies. One IRB without a publicly accessible web-site sent us relevant guidance that was available on its internal web-site and that it plans to make publicly available. We have included this IRB guidance in our final sample. The other 4 IRBs that we contacted that either did not have a public web-site or had no relevant policies on their web-site did not supply us any relevant policies on follow-up. Our final study population was 39 IRB web-sites (Table I; Appendix).

CLASSIFICATION OF IRB GUIDANCE. We developed coding topics on the basis of issues explicitly addressed in the federal regulations or identified in the ethics literature as issues of concern for pediatric research. We revised these topics after consulting with our advisory board of 3 outside experts in pediatrics, research ethics, and behavioral science. Two research team members then independently coded the IRB guidance on the predetermined topics. To ensure consistency and reliability in our review, we calculated the agreement between reviewers' coding for 10 sample guidance documents until we reached at least 90% agreement. We added codes for topics that emerged through our review of the IRB guidance. Our research questions for each topic are set forth in Table II (available online at www.us.elsevierhealth.com/jpeds).

Next, we conducted a close reading of the IRB guidance for each topic and compared guidance from different IRB web-sites to identify guidance that followed or went beyond current practice for ethics and quality (helpful guidance) and guidance that misinterprets federal regulations (misleading guidance). We used a stepwise consensus procedure. The research team identified examples of helpful and misleading guidance through discussions and consensus. We provided copies of the examples to the advisory board, which then reviewed these examples in a conference call. Final inclusion as helpful or misleading guidance required agreement from a majority of the advisory board.

Although our sample size was extremely small, we compared children's hospitals with their own IRBs to all other IRBs using a Fisher exact test to determine whether there was any evidence to suggest that 1 group may be more likely to address our study topics.
RESULTS

Content of IRB Guidance: Regulatory Requirements

REGULATIONS AND RESEARCH RISK CATEGORIES. Most IRBs refer to the federal regulations and the research risk categories that pertain to pediatric research (Table III; available online at www.us elsevierhealth.com/peds). However, few explain the terms used in the regulations. For example, only 4 IRB web-sites (10%) provide examples of what constitutes minimal risk. One of these provides sample protocols and explains how they meet the minimal risk criteria.

ASSENT FROM CHILD. All IRB web-sites discuss the requirement for assent from children participating in research. Less than half of IRB web-sites ask specific questions about plans for soliciting assent, although the extent of questioning varies. For example, 1 web-site asks simply whether assent will be obtained, whereas another asks detailed questions, including who will obtain assent, what form the assent will take, and how comprehension will be assessed.

PARENTAL PERMISSION. Almost all IRB web-sites (38/39) specify the need for parental/guardian permission for a child’s participation in research.

WAIVER OF ASSENT AND PERMISSION. Approximately 2/3 of IRB web-sites mention that the child's assent, permission of the parent or guardian, or both may be waived under Subpart D and describe when it is permissible to do this. Fewer web-sites discuss the possibility of waiving assent or permission under the Common Rule’s waiver provisions.

IRB Content: Beyond Regulatory Requirements

OBTAINING ASSENT. Forty-one percent of IRB web-sites (16/39) have sample pediatric assent forms and templates that differ from sample adult consent forms. These pediatric forms use shorter, simpler words, a straightforward sentence structure, white space between paragraphs, and pictures to present information. In contrast, 41% (16/39) of IRBs simply add a signature line for the minor to the adult consent form, although 1 of these recommends adding a 1 paragraph explanation of the study “at the reading level of the youngest child” before the signature. One template explicitly states that the formal requirements of informed consent do not apply to assent and that less information is required. In contrast, 2 IRBs specify that the required assent script for children younger than 7 years should include all the elements of informed consent. Only 1 IRB addresses the need to get consent from children when they reach adulthood if their study participation continues.

Four IRB web-sites (10%) emphasize that investigators must tell children about the study even when written assent is not required because of the child’s age. One illustrates with an example of a nurse telling a child that she is going to draw blood with a needle stick that will hurt for a moment, without asking whether it is OK to do so. Another IRB specifies behavior in younger children—refusing to cooperate, crying—that should be interpreted as dissent.

One IRB web-site suggests ways to make the assent process more understandable to children, including using comic books to explain the project, arranging a meeting with previous participant families, and showing families the equipment used in the project. Another IRB provides tips from a child development expert for improving the assent process, including asking the child to demonstrate her understanding using a doll or other 3-dimensional materials.

PAYMENTS TO PARENTS. The discussion of payments to parents when their children participate in research varies considerably. Nine web-sites allow reimbursement to parents for time and expenses related to their children’s research participation (eg, child-care, travel, parking, and meals). Two permit payment of “incentives” or “inducements” to parents who enroll their children in research.

PAYMENTS TO CHILDREN. The guidance on payments to children participating in research ranges from generally discouraging, but not prohibiting, such payments (1 IRB) to strongly encouraging payments directly to children as the participants (2 IRBs). One of the latter states, “The children are the research subjects. They may undergo stress, discomfort or inconvenience as a result of participation in research studies, and there should be some effort made to compensate the children directly and personally.” Nine IRB web-sites also provide examples of acceptable reimbursement for minors. Two IRB web-sites advise against monetary payments and offer specific alternatives (eg, toys, gift certificates, books). Although 4 IRB web-sites recommend that younger children should receive smaller gifts or payments than adolescents or adults, none provides specific justification or a formula for determining an appropriate amount. One IRB classifies payments into 4 categories (reimbursement, compensation, tokens of appreciation, and incentives) and requires investigators to describe payments by category and to whom they are made. It discourages incentive payments in pediatric research. No web-site suggests soliciting parental preferences regarding payments to children.

RECRUITMENT. Few web-sites discuss special considerations concerning recruiting minors for research. One recommends that investigators get permission from the parents/guardian of a child already participating in a study before recruiting the child’s siblings, playmates, or both. Another asks investigators to minimize “the coercion implicit in requests to participate from parents, teachers, or other adult authorities” and “the fear of ridicule, social pressure, or peer pressure to participate.”

CONFIDENTIALITY. Three IRB web-sites (8%) address the confidentiality of research information for third parties (other
than parents) by providing sample language for the assent form. Nine IRB web-sites discuss 3 issues relating to confidentiality of children’s for their parents, with 2 IRBs addressing more than 1 issue. Five IRBs (13%) mention that adolescents may want to keep some information confidential, and 1 IRB specifically asks how the investigator will address this issue. Two IRBs (5%) mention the need for consistency between what is said in the assent and parental permission documents. Four IRBs (10%) address confidentiality of minors’ pregnancy tests.

**Genetic Research.** The guidance on genetic research in children or storage of children’s biological materials varies considerably. One web-site notes that such research has different implications for adults and children and includes “points to consider” for such studies. The second advises against involving children in predictive genetic studies so that they can make decisions for themselves as adults. Two discuss the child’s right to control use of stored materials when she reaches maturity, whereas another states it is the parent’s responsibility to inform the child about stored specimens. Finally, 1 IRB restricts disclosure of research-related genetic test results unless there is a specific intervention with improved efficacy when started before age 18. (Table III; available online at www.us.elsevierhealth.com/jpeds.)

**Children’s Hospital IRBs versus Other IRBs.** We compared the discussion of study topics by the 4 children’s hospital IRB web-sites to the other IRB web-sites to determine whether they were more likely to discuss these topics. All the children’s hospital web-sites discussed research payment to children and parents, whereas only 29% and 17%, respectively, of other IRB web-sites overall did (Fisher exact test P = .0048 and $P = .0003$, respectively). Otherwise, the children’s hospital IRBs appeared no more likely to have policies addressing our study topics than other IRBs.

**Helpful Practices**

We identified several helpful practices. For example, 4 IRB web-sites provide a list of “points to consider” about research with children and the mechanisms for protecting them, which may help investigators work through the pertinent regulatory framework and ethical considerations. The points to consider include: 1) the justification for conducting the research with children; 2) similar research that has been conducted in adults or older children; 3) minimizing the risks to children; 4) the role the parent will have during the research; 5) the experience the research team has in working with children; and 6) the effect the children’s previous experiences will have on their research experience. Some web-sites ask investigators to focus on particular areas of ethical concern, such as minimizing potential undue pressure during recruitment, determining appropriate compensation, and deciding whether to share information with parents. Other IRB web-sites use concrete examples to illustrate what is required by the regulations or local policies, such as child-specific assent forms, ways to enhance the assent process such as using pictures or demonstrations, and acceptable compensation for children and parents. Some IRBs also explain the reasons for their policies on controversial topics, such as compensation and predictive genetic testing on children on their web-sites, which may increase investigator understanding and acceptance of those policies.

**Policies that Misinterpret the Regulations**

We found some instances in which IRB web-sites misinterpret the federal regulations. One IRB incorrectly characterizes the category of “research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the disorder or condition.” The IRB adds the qualification “in which the risk is minor relative to the potential improvement in knowledge to be applied to general understanding” (emphasis supplied). However, under 45 C.F.R. 46.406, the correct qualifier is “a minor increase over minimal risk.” The incorrect phrase may allow a higher level of risk than is actually permitted by the regulations.

Another IRB’s assent policy informs investigators that they may waive assent if in the investigator’s “opinion this child cannot give informed assent…. This policy mistakenly suggests that the child’s assent needs to be informed. However, the rationale for assent rather than consent is that the child’s approval is needed even when the child is unable to appreciate the benefits and risks of the study.

**Discussion**

To ensure the ethical conduct of research involving children, the 2004 IOM committee on pediatric clinical research recommends that IRBs provide specific guidance to investigators about pediatric research and use web-sites to do so. Our study systematically assessed whether IRBs are currently providing such guidance.

We found that most IRB web-sites provide basic information about pediatric research. However, there are missed opportunities to help investigators understand difficult and confusing regulatory issues, such as “minimal risk” and “minor increase over minimal risk.” Moreover, a few IRBs provide incorrect advice about the federal regulations. Few IRBs discuss important ethical issues on which the regulations are silent.

Because investigators rely on IRB information, IRBs should ensure that their information is comprehensive, up-to-date, and accurate. At a minimum, IRB web-sites should address the basic regulatory requirements for pediatric research. However, as the IOM report suggests, IRB web-sites should also provide detailed guidance on how they interpret the regulatory requirements and highlight issues that pediatric investigators should consider. Furthermore, IRBs might use their web-sites to alert investigators to ethical controversies, such as payment to children or parents, and explain the reasons for their policies. Investigators must comply with local IRB policy. However, investigators who
understand the IRB's thinking on complicated issues may be better prepared to protect human participants. Moreover, such understanding may help investigators understand the rationale for IRB decisions when IRBs at different sites in a multi-site project disagree. Finally, such explanations may stimulate further discussion and analysis of unresolved issues.

We identified helpful approaches on some IRB websites that should be used more widely. Checklists and “points to consider,” which are widely used in quality improvement programs, can standardize procedures and eliminate unacceptable variation,44,45; both the National Bioethics Advisory Commission and IOM have recommended their use in human subject protection programs.46,47 Concrete examples may help investigators better understand abstract and difficult concepts in the federal regulations such as “minimal risk” and “assent.”46 IRB guidance can also draw attention to controversial ethical issues, such as payments to children and parents, genetic research, and research on stored samples, that are not explicitly discussed in Subpart D.

Some IRBs may question why they should devote their limited time and resources developing detailed web guidance. Arguably, many of these issues can be addressed through IRB review of individual protocols. However, protocol-by-protocol education is inefficient. Detailed guidance and checklists may increase the likelihood that crucial ethical issues will be carefully addressed in protocols.4 Comprehensive web guidance may also help investigators better prepare protocols and minimize re-submissions.4 Moreover, education is an essential component of an integrated human participant protection program.47 Preparing a protocol for the IRB focuses investigator attention on ethical issues and presents a “teachable moment.”46,48 Investigators are likely to consult IRB web-sites before submitting their protocols. Thus, IRBs have an opportunity to help investigators browsing the IRB web-site to think through ethical issues that arise in their research. Web-sites are particularly well-suited for this purpose because information can be layered to avoid overwhelming users, while making additional information available to those who want it.49-51 IRBs can also link to other websites or adapt existing resources to their own purposes. Our data and the IOM report give examples of such resources.4

Pediatric researchers should encourage their IRBs to adopt more specific guidance. Development of such guidance is important to training new investigators and facilitating appropriate pediatric research. Moreover, pediatric researchers can help IRBs develop guidance that is responsive to their needs. They can help identify the issues on which guidance is urgently needed and use their research experiences to suggest ways of making guidance more concrete.

Our study had several limitations. We only evaluated IRB guidance on publicly available IRB web-sites or those made available to us. IRBs may provide guidance directly to individual investigators, although such guidance would be less accessible to other investigators. In addition, information may have changed since we last visited the IRB web-sites. Finally, our sample may not be representative of all IRBs. However, the institutions in our sample carry out the most research, train future research leaders, and are likely to devote more resources to their IRBs than other institutions.

The authors thank our advisory board, Thomas J. Coates, PhD, Alan Fleischman, MD, and Marjorie Speers, PhD, for their helpful advice and feedback on this project, and Philip Rosenthal, MD, and Alexander Kon, MD, for their useful comments on earlier versions of this paper.

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6. 21 C.F.R. 601.27(a) (2003).
38. 45 C.F.R. § 46.405 (2003).
40. 45 C.F.R. § 46.102 (i) (2003).
42. 45 C.F.R. § 46.408 (2003).

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Deletion 22q11 (del22q11) is among the most common genetic syndromes, with an estimated prevalence of 1 per 2000 in the general population. It has been the subject of thousands of clinical and laboratory research papers and case reports. These studies have produced many important genetic and clinical discoveries and have also led to several misunderstandings about del22q11, generating confusion among parents as well as healthcare professionals.

Del22q11 is among the most clinically variable syndromes, with more than 180 features associated with the deletion. Table I provides a modified list of structural and functional anomalies that have been reported to occur in the syndrome. Although the phenotype is very expansive, covering nearly every biological and functional system, most clinicians associate the syndrome with conotruncal congenital heart disease (CHD), anatomic and/or neuromuscular abnormalities of the palate, typical facial appearance, and learning and psychiatric problems.2 However, physical manifestations have been reported that involve every organ system, and a well-defined behavioral and psychiatric profile has been described.3-5 Studies have shown that this variability is independent of genotype.4 A 3-Mb deletion is present in the large majority of cases, with a smaller 1.5-Mb deletion in <10% cases and some unique smaller deletions in a small number of cases. Phenotypic expression has not been shown to be related to the deletion size to date. Furthermore, there are many published examples of affected kindreds that demonstrate that the clinical presentation can be widely different even within a single family.5,6

The initial diagnosis of velocardiofacial syndrome (VCFS) in affected individuals is dependent on a number of factors, including the specific phenotypes expressed in the individual case, the type of specialist who is first alerted to the anomalies, and the patient's age. The analogy of the blind men and the elephant has been used to illustrate the specialty-dependent nature of how this disorder is viewed, and it also is reflected in how and at what point an affected child comes to diagnosis. A newborn will be diagnosed when he or she presents with a notable major malformation or medical complication, such as a CHD, hypocalcemia, and occasionally overt cleft palate. Children will often be labeled as having “DiGeorge syndrome” when they present with conotruncal heart anomalies in association with hypocalcemia, even when other anomalies are present. It is worth noting that most physicians equate the diagnosis of DiGeorge syndrome with del22q11. This is not true, as the findings that comprise DiGeorge sequence—hypoarathyroidism, absent thymus, and conotruncal CHD—are etiologically heterogeneous and have been associated with a number of causes, including a variety of cytogenetic rearrangements (eg, del10p, del17p) in infants of diabetic mothers, in Zellweger syndrome, and in peroxisomal disorders.

An older child may present with a history of findings that should have led to a diagnosis. For example, a child with a repaired CHD or resolved idiopathic neonatal hypocalcemia may manifest speech problems due to velopharyngeal insufficiency, developmental delay or learning problems, or even the typical facial appearance. These are consistent with the label of VCFS (or Shprintzen syndrome). At an even later age, the diagnosis is most often made in mildly affected individuals after the birth of a more classically affected child. Such older individuals will often have a history of school-related problems, hypernasal speech, or psychiatric disease. This is why most clinicians routinely test both parents when a child is first diagnosed.

Although each presentation is very different, it is important to remember that they represent points along the continuum of the same genetic disorder, and therefore require the same genetic counseling and medical management. However, this fundamental point can be lost among the confusing nomenclature that predates the discovery of the chromosome 22q11 deletion as the cause of this disorder.
Table I. Findings associated with deletions of chromosome 22q11.2 (modified from Shprintzen\(^1\) and Shprintzen et al\(^2\))

<table>
<thead>
<tr>
<th>Craniofacial/oral findings</th>
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<tbody>
<tr>
<td>1. Overt, submucous, or occult submucous cleft palate</td>
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<tr>
<td>2. Retrognathia (retruded lower jaw)</td>
<td></td>
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<tr>
<td>3. Platybasia (flat skull base)</td>
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<tr>
<td>4. Asymmetric crying facies in infancy</td>
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<tr>
<td>5. Structurally asymmetric face</td>
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<tr>
<td>6. Functionally asymmetric face</td>
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<td>7. Vertical maxillary excess (long face)</td>
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<td>8. Straight facial profile</td>
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<td>9. Congenitally missing teeth (one or several)</td>
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<td>10. Small teeth</td>
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<td>11. Enamel hypoplasia (primary dentition)</td>
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<td>12. Hypotonic, flaccid facies</td>
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<td>13. Downturned oral commissures</td>
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<td>14. Cleft lip (uncommon)</td>
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<td>15. Microcephaly</td>
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<td>16. Small posterior cranial fossa</td>
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<tr>
<th>Eye findings</th>
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<tr>
<td>17. Tortuous retinal vessels</td>
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<td>18. Suborbital congestion (&quot;allergic shiners&quot;)</td>
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<tr>
<td>19. Strabismus</td>
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<tr>
<td>20. Narrow palpebral fissures</td>
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<tr>
<td>21. Posterior embryotoxon</td>
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<td>22. Small optic disk</td>
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<td>23. Prominent corneal nerves</td>
<td></td>
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<td>24. Cataract</td>
<td></td>
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<td>25. Iris nodules</td>
<td></td>
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<tr>
<td>26. Iris coloboma (uncommon)</td>
<td></td>
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<tr>
<td>27. Retinal coloboma (uncommon)</td>
<td></td>
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<tr>
<td>28. Small eyes</td>
<td></td>
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<tr>
<td>29. Mild orbital hypertelorism</td>
<td></td>
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<tr>
<td>30. Mild vertical orbital dystopia</td>
<td></td>
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<tr>
<td>31. Puffy upper eyelids</td>
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<table>
<thead>
<tr>
<th>Ear/hearing findings</th>
<th></th>
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<tbody>
<tr>
<td>32. Overfolded helix</td>
<td></td>
</tr>
<tr>
<td>33. Attached lobules</td>
<td></td>
</tr>
<tr>
<td>34. Protuberant, cup-shaped ears</td>
<td></td>
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<tr>
<td>35. Small ears</td>
<td></td>
</tr>
<tr>
<td>36. Mildly asymmetric ears</td>
<td></td>
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<tr>
<td>37. Frequent otitis media</td>
<td></td>
</tr>
<tr>
<td>38. Mild conductive hearing loss</td>
<td></td>
</tr>
<tr>
<td>39. Sensorineural hearing loss (often unilateral)</td>
<td></td>
</tr>
<tr>
<td>40. Ear tags or pits (uncommon)</td>
<td></td>
</tr>
<tr>
<td>41. Narrow external ear canals</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nasal findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>42. Prominent nasal bridge</td>
<td></td>
</tr>
<tr>
<td>43. Bulbous nasal tip</td>
<td></td>
</tr>
<tr>
<td>44. Mildly separated nasal domes (nasal tip appears bifid)</td>
<td></td>
</tr>
<tr>
<td>45. Pinched alar base, narrow nostrils</td>
<td></td>
</tr>
<tr>
<td>46. Narrow nasal passages</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac and thoracic vascular findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>47. Ventricular septal defect</td>
<td></td>
</tr>
<tr>
<td>48. Atrial septal defect</td>
<td></td>
</tr>
</tbody>
</table>

Continued
### Table I. Continued

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>Malrotation of bowel</td>
</tr>
<tr>
<td>100</td>
<td>Diastasis recti</td>
</tr>
<tr>
<td>101</td>
<td>Diaphragmatic hernia (uncommon)</td>
</tr>
<tr>
<td>102</td>
<td>Hirschsprung's megacolon (rare)</td>
</tr>
<tr>
<td><strong>Limb findings</strong></td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>Small hands and feet</td>
</tr>
<tr>
<td>104</td>
<td>Tapered digits</td>
</tr>
<tr>
<td>105</td>
<td>Short nails</td>
</tr>
<tr>
<td>106</td>
<td>Rough, red, scaly skin on hands and feet</td>
</tr>
<tr>
<td>107</td>
<td>Morphea</td>
</tr>
<tr>
<td>108</td>
<td>Contractures</td>
</tr>
<tr>
<td>109</td>
<td>Triphalangeal thumbs</td>
</tr>
<tr>
<td>110</td>
<td>Polydactyly, both preaxial and postaxial (uncommon)</td>
</tr>
<tr>
<td>111</td>
<td>Soft tissue syndactyly</td>
</tr>
<tr>
<td><strong>Problems in infancy</strong></td>
<td></td>
</tr>
<tr>
<td>112</td>
<td>Feeding difficulty, failure to thrive</td>
</tr>
<tr>
<td>113</td>
<td>Nasal vomiting</td>
</tr>
<tr>
<td>114</td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>115</td>
<td>Irritability</td>
</tr>
<tr>
<td>116</td>
<td>Chronic constipation (not Hirschsprung's megacolon)</td>
</tr>
<tr>
<td><strong>Genitourinary</strong></td>
<td></td>
</tr>
<tr>
<td>117</td>
<td>Hypospadias</td>
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<tr>
<td>118</td>
<td>Cryptorchidism</td>
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<tr>
<td>119</td>
<td>Vesicoureteral reflux</td>
</tr>
<tr>
<td><strong>Speech/language</strong></td>
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<tr>
<td>120</td>
<td>Severe hypernasality</td>
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<tr>
<td>121</td>
<td>Severe articulation impairment (glottal stops)</td>
</tr>
<tr>
<td>122</td>
<td>Language impairment (usually mild delay)</td>
</tr>
<tr>
<td>123</td>
<td>Velopharyngeal insufficiency (usually severe)</td>
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<td>124</td>
<td>High-pitched voice</td>
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<tr>
<td>125</td>
<td>Hoarseness</td>
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<tr>
<td><strong>Cognitive/learning</strong></td>
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<tr>
<td>126</td>
<td>Learning disabilities (math conceptualization, reading comprehension)</td>
</tr>
<tr>
<td>127</td>
<td>Concrete thinking, difficulty with abstraction</td>
</tr>
<tr>
<td>128</td>
<td>Drop in IQ score in school years (test artifact)</td>
</tr>
<tr>
<td>129</td>
<td>Borderline normal intellect</td>
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<tr>
<td>130</td>
<td>Occasional mild mental retardation</td>
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<tr>
<td>131</td>
<td>Attention deficit hyperactivity disorder</td>
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<tr>
<td><strong>Miscellaneous anomalies</strong></td>
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<tr>
<td>132</td>
<td>Spontaneous oxygen desaturation without apnea</td>
</tr>
<tr>
<td>133</td>
<td>Thrombocytopenia, Bernard-Soulier disease</td>
</tr>
<tr>
<td>134</td>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>135</td>
<td>Poor body temperature regulation</td>
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<tr>
<td><strong>Psychiatric/psychological</strong></td>
<td></td>
</tr>
<tr>
<td>136</td>
<td>Bipolar affective disorder</td>
</tr>
<tr>
<td>137</td>
<td>Manic-depressive illness and psychosis</td>
</tr>
<tr>
<td>138</td>
<td>Rapid or ultrarapid cycling of mood disorder</td>
</tr>
<tr>
<td>139</td>
<td>Mood disorder</td>
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<tr>
<td>140</td>
<td>Depression</td>
</tr>
<tr>
<td>141</td>
<td>Hypomania</td>
</tr>
<tr>
<td>142</td>
<td>Schizoaffective disorder</td>
</tr>
<tr>
<td>143</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>144</td>
<td>Impulsiveness</td>
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<tr>
<td>145</td>
<td>Flat affect</td>
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### Table I. Continued

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<th>Number</th>
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<td>146</td>
<td>Dysthymia</td>
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<td>Cyclothymia</td>
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<tr>
<td>148</td>
<td>Social immaturity</td>
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<tr>
<td>149</td>
<td>Obsessive compulsive disorder</td>
</tr>
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<td>150</td>
<td>Generalized anxiety disorder</td>
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<tr>
<td>151</td>
<td>Phobias</td>
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<tr>
<td>152</td>
<td>Severe startle response</td>
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<tr>
<td><strong>Immunologic</strong></td>
<td></td>
</tr>
<tr>
<td>153</td>
<td>Frequent upper respiratory infections</td>
</tr>
<tr>
<td>154</td>
<td>Frequent lower airway disease (pneumonia, bronchitis)</td>
</tr>
<tr>
<td>155</td>
<td>Reduced T-cell populations</td>
</tr>
<tr>
<td>156</td>
<td>Reduced thymic hormone</td>
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<tr>
<td><strong>Endocrine</strong></td>
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</tr>
<tr>
<td>157</td>
<td>Hypocalcemia</td>
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<tr>
<td>158</td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td>159</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>160</td>
<td>Mild growth deficiency, relative small stature</td>
</tr>
<tr>
<td>161</td>
<td>Absent/hypoplastic thymus</td>
</tr>
<tr>
<td>162</td>
<td>Small pituitary gland (rare)</td>
</tr>
<tr>
<td><strong>Skeletal/muscle/orthopedic</strong></td>
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</tr>
<tr>
<td>163</td>
<td>Scoliosis</td>
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<tr>
<td>164</td>
<td>Spina bifida occulta</td>
</tr>
<tr>
<td>165</td>
<td>Hemivertebrae</td>
</tr>
<tr>
<td>166</td>
<td>Butterfly vertebrae</td>
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<tr>
<td>167</td>
<td>Fused vertebrae (usually cervical)</td>
</tr>
<tr>
<td>168</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>169</td>
<td>Sprengel's anomaly, scapular deformation</td>
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<td>170</td>
<td>Talipes equinovarus</td>
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<td>171</td>
<td>Small skeletal muscles</td>
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<tr>
<td>172</td>
<td>Joint dislocations</td>
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<tr>
<td>173</td>
<td>Chronic leg pains</td>
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<td>174</td>
<td>Flat foot arches</td>
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<tr>
<td>175</td>
<td>Hyperextensible/flax joints</td>
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<tr>
<td>176</td>
<td>Rib fusion</td>
</tr>
<tr>
<td>177</td>
<td>Extra ribs</td>
</tr>
<tr>
<td>178</td>
<td>Tethered cord</td>
</tr>
<tr>
<td>179</td>
<td>Syrinx</td>
</tr>
<tr>
<td><strong>Skin/integument</strong></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>Abundant scalp hair</td>
</tr>
<tr>
<td>181</td>
<td>Thin-appearing skin (venous patterns easily visible)</td>
</tr>
<tr>
<td><strong>Secondary sequences/associations</strong></td>
<td></td>
</tr>
<tr>
<td>182</td>
<td>Robin sequence</td>
</tr>
<tr>
<td>183</td>
<td>DiGeorge sequence</td>
</tr>
<tr>
<td>184</td>
<td>Potter sequence</td>
</tr>
<tr>
<td>185</td>
<td>CHARGE association</td>
</tr>
<tr>
<td>186</td>
<td>Holoprosencephaly (single case)</td>
</tr>
</tbody>
</table>
Defining The Clinical Spectrum Of Deletion 22q11.2

Del22q11: A BRIEF HISTORY

When one considers how common del22q11 is, should not be surprising that it was independently described at different times in widespread parts of the world. Consequently, several names have been attached to the condition, which has given the impression that there are several different disorders associated with deletions of 22q11. But these are not distinct disorders; rather, they reflect the fact that different specialists would care for the various manifestations seen with del22q11.

Most likely, the first description of del22q11 in the medical literature was by Sedlačková in 1955,10 followed by additional publications.16 Sedlačková, a phoniatrist in Prague, described a condition resulting in the combination of hypernasal speech with decreased facial animation. Sedlačková attributed the hypernasal speech to congenital shortening of the soft palate and a disorder of innervation that also affected the facial musculature. In reviewing her early publications, it is clear that not all of Sedlačková’s reported cases had VCFS, but many, if not most, did.

In 1968, Robert Strong, a pediatric cardiologist, described a family in which the mother and her 3 living children were affected. Three other children died in infancy and probably were affected as well. A review of the photographs published by Strong clearly demonstrates that all of the cases he reported had VCFS. Soon after that, Angelo DiGeorge, a pediatric endocrinologist at St. Christopher’s Hospital in Philadelphia, described 3 children with a lethal association of aortic arch anomalies.12 He attributed these findings to anomalous development of the third and fourth branchial arches, the embryonic structures that gave rise to the anomalous organs. In subsequent cases, DiGeorge noted an association of aortic arch anomalies.12

In 1969, Cayler13,14 described a series of cases with conotruncal heart anomalies and asymmetric crying facies. The patient photographs provided in Cayler’s initial paper are not necessarily consistent with the facial phenotype of VCFS, but a subsequent paper provided photographs of several cases with classical VCFS facial phenotypes, along with other cases that clearly did not have VCFS.15

Conotruncal anomaly face syndrome (CTAF) was the term applied to a disorder described in Japan by Kinouchi et al.27 Affected children manifest a typical CHD and a facial appearance that can now be recognized as similar to that seen in VCFS.

In 1978, Shprintzen8 described 12 individuals who had the association of CHD, hypernasal speech with palatal anomalies, characteristic facial appearance, and learning disabilities. A dozen other clinical features were described, and 1 case of mother–to–daughter transmission was reported, as was a case with Robin sequence. Shprintzen8 coined the term “velocardiofacial syndrome.” It was Cohen17 who designated the disorder as Shprintzen syndrome, an eponym subsequently applied by Smith in his third edition of Recognizable Patterns of Human Malformation.18 It was subsequently recognized by the team of researchers who delineated VCFS that DiGeorge sequence occurred as a secondary developmental disorder to VCFS, much like Robin sequence.19

The first report of an interstitial microdeletion at 22q11.2 in VCFS came from Scambler et al,20 followed by a similar report from Driscoll et al.21 In both reports, the subjects had variable clinical manifestations, including the presence of findings consistent with DiGeorge sequence. It is worthwhile to point out that the initial reports described an ~80% accuracy rate for fluorescence in situ hybridization (FISH) testing for del22q11, but we now know that FISH testing is essentially 100% accurate. If a patient tests negative for the deletion by FISH, then it is safe to assume that he or she does not have VCFS. However, as stated earlier, there are other causes of the DiGeorge phenotype, including other cytogenetic abnormalities (eg, 10q13 deletion) and nongenetic causes.

CATCH22

Several other conditions, including CTAF and Cayler syndrome (asymmetric crying facies and conotruncal CHD, reviewed by Lin et al22) were recognized as also being caused by deletions of 22q11.23,24 In an effort to unify the rapidly expanding number of conditions that were being found to be caused by chromosome 22q11 deletions, Wilson et al25 proposed the acronym CATCH22 (for conotruncal heart defect, abnormal face, T-cell deficiency, clefting, and hypocalcemia, all due to chromosome 22 abnormality). However, this term was rejected by clinical geneticists (as summarized by Burn26) because of the negative connotation associated with the term “catch-22” from Joseph Heller’s 1962 novel of the same name, in which the term “catch-22” means a no-win situation.27 Unfortunately, this term is still used by clinicians and investigators outside of genetics.

EXPANDING THE PHENOTYPE

Armed with knowledge of the clinical variability of del22q11 and an easy test to detect it, many investigators have sought to define the true phenotypic spectrum associated with del22q11. Hundreds of reports have documented new findings, ranging from polymicrogyria28 to juvenile rheumatoid arthritis.29 However, as the list of associated findings has grown to more than 180 (and continues to expand), the significance of the diagnosis has been lost. What this should mean is that there is literally no single finding that should exclude the diagnosis of del22q11. However, what it has come to mean is that anything is del22q11, which unfortunately has led to confusion and misunderstanding for patients and parents as well as healthcare providers regarding what is del22q11. This has inadvertently been exacerbated by several reports that have tried to expand the clinical spectrum of del22q11. Patients with 22q11 deletions have been reported with clinical findings that overlap with several known distinct genetic syndromes, including Noonan syndrome (NS)30,31 and autosomal dominant Opitz syndrome (ADOS),32 as well as both CHARGE and VATER associations.33
Table II. VATER, CHARGE, and del22q11 findings

<table>
<thead>
<tr>
<th>VA(C)TER</th>
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<tr>
<td>Vertebral anomaly</td>
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<tr>
<td>Anal anomalies</td>
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<td>Cardiac</td>
<td>(47–70)</td>
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<tr>
<td>TE fistula</td>
<td>(?)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Radial (106)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>or renal (154)</td>
<td>anomaly</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CHARGE</td>
<td></td>
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<tr>
<td>Coloboma</td>
<td>(26, 27)</td>
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<tr>
<td>Heart</td>
<td>(47–70)</td>
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<tr>
<td>Choanal atresia/</td>
<td>stenosis</td>
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<tr>
<td>Retarded growth</td>
<td>(159)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GU anomaly</td>
<td>(152–154)</td>
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<tr>
<td>Ear</td>
<td>(34–39)</td>
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</table>

The numbers correspond to their place in the table of findings associated with del22q11.2 in Shprintzen.38

It is now known that NS is caused by mutations in the PTP22 gene.34 However, it is also known that the NS phenotype can be seen with several other disorders, including Turner syndrome and neurofibromatosis type I.35 Just as these patients have neurofibromatosis type I with NS-like findings, patients with del22q11 and NS-like findings have del22q11, and they should be counseled and managed accordingly.

The same is true for ADOS. Patients with chromosome 22q11 deletion who have hypertelorism, hypospadias, and other Opitz syndrome findings have del22q11 and are at risk for all of the associated complications. There is an added layer of confusion with ADOS, because this form of Opitz G syndrome was mapped to chromosome 22q. However, none of the families in that original study were deleted at 22q11.36

Therefore, patients with chromosome 22q11 deletion who have findings that overlap with NS or ADOS should not be labeled as having “ADOS due to del22q11.” This incorrectly suggests that these patients have something other than del22q11, which can keep families and physicians from recognizing that the correct medical management plan is that for del22q11 and has also created confusion in the medical literature.37

For CHARGE and VATER, the issues should be even less unclear. Until recently, CHARGE and VATER were referred to as associations, and as such are not actively made diagnoses, because there is no confirmatory testing. For CHARGE, this has now changed, because the underlying genetic cause of CHARGE, mutations in the CHD7 gene, were identified in some patients with clinical findings of CHARGE.38

For both CHARGE and VATER, all of the constituent findings have been described with del22q11 (Table II). Take, for example, a child with a CHD and tracheoesophageal fistula. Such a child should be subject to a complete genetic evaluation, including complete personal medical and family histories, a detailed dysmorphologic physical examination, and appropriate testing, such as a chromosome analysis. If at the end of this evaluation no diagnosis is found, then the multiple findings can then be attributed to VATER association, the recognition that certain malformations occur together more commonly than would be predicted by chance alone. However, just as with NS and ADOS, if a patient is diagnosed with VATER based on physical findings but is later found to have a 22q11 deletion, then the explanation is not that the patient has VATER due to del22q11, but rather that the original diagnosis was wrong and that the patient has del22q11 and should be managed as a patient with del22q11.

POTENTIAL CONSEQUENCES OF INDISCRIMINANT TESTING

As noted earlier, numerous studies have demonstrated that del22q11 is both clinically variable and common. Although these studies have been very valuable in describing the clinical impact of del22q11, they also have had the untoward effect of leaving clinicians with the belief that any patient with a CHD should undergo FISH testing for the deletion. Such indiscriminant testing is a waste of resources, because not every type of CHD is associated with del22q11. For example, Ebstein’s anomaly and transposition of the great vessels are not typically seen in del22q11. One other concern is that a negative del22q11 test will be equated with ruling out the genetic disorder, as is illustrated by the following brief case report. (Due to privacy laws, elements of this case have been changed to ensure confidentiality.)

A 2-year-old boy was referred to genetics for evaluation. He had been tested by the cardiologists in the newborn period for a 22q11 deletion because of tetralogy of Fallot. He was found to be negative, and his parents were told that the tetralogy of Fallot was nonsyndromic. However, the boy manifested a broad forehead and prominent jaw, and had been hospitalized previously for jaundice due to suspected hepatitis. Based on these findings, a diagnosis was made of Alagille syndrome. This was confirmed by Jagged1 mutation analysis.

Most clinicians recognize that del22q11 testing is ordered very liberally for some indications, such as CHD, velopharyngeal insufficiency, and developmental delay. However, testing is still not performed in many instances where it may be indicated. For example, in certain conditions the physical manifestations suggestive of del22q11 may be masked by the associated secondary deformations. For example, developmental renal anomalies are a recognized finding in del22q11; however, a newborn with severe oligohydramnios due to renal hypoplasia will manifest the facies and physical sequelae of Potter’s sequence, so del22q11 testing may not be considered. Similarly, infants with del22q11 and Pierre–Robin sequence, a neural tube defect, or holoprosencephaly may also be missed. Careful evaluation of such infants is warranted.

Another group of patients in whom testing is warranted but not often performed is those with a known genetic syndrome, such as Marfan or Down syndrome, who also have conotruncal CHD, which is not typical for that condition. Deletions of 22q11 have been reported in such patients.
CONCLUSION

Over the last 30+ years, many names have been attributed to various clinical presentations of deletions of 22q11.2. As we have reviewed in this article, there is a single syndrome caused by deletions at 22q11.2, and this syndrome is caused only by deletions at 22q11.2. However, many clinicians remain confused as to which clinical disorders are and are not associated with del22q11.2.

There are 2 common misconceptions about the outcome of 22q11.2 deletions. One of these is that patients who have the identical deletion may have different syndromes. Thus, it is not uncommon to find both clinicians and molecular geneticists discussing the differences between VCFS, DiGeorge syndrome, CTAFS, Cayler syndrome, and other disorders that have been associated with deletions of 22q11. However, the various terms applied to patients with 22q11.2 deletions merely represent nosologic differences, not different diagnoses. The reason for this is best illustrated by the noted dysmorphologist M. Michael Cohen, Jr. in his excellent book, *The Child With Multiple Birth Defects: “Geneticists are more likely to share their toothbrushes than their terminology.”*

All of these different terms actually refer to the same disorder. Moreover, the phenotype develops over time, and so the clinical presentation may change dramatically over time. For example, what appears to be a primarily endocrine disorder in infancy may later present as a behavioral disorder at age 10 years with little or no endocrine pathology. Although it is unlikely that clinicians will abandon their favorite terminology, the realization that all of the labels refer to a single disease is of significant importance for physicians as well as researchers, and especially for parents.

A second misconception is that it is possible to have this syndrome without having the deletion. There is no convincing evidence to date to support this is true. The studies that reported an approximate 80% positive deletion rate were flawed by failing to control clinical diagnoses and accepting samples from multiple sources without verifying diagnostic validity or reliability. These studies were done at a time when our understanding of the entire clinical picture of deletion 22q11.2 was evolving. Today we would recognize that those patients who tested negative in those early studies in fact do not have this condition and thus are not at risk for the same medical and developmental/behavioral complications of the disorder.

REFERENCES

Hyaline Membrane Disease of Newborn Premature Lungs: A New Approach


In 1955, the cause of the highly lethal hyaline membrane disease in preterm infants was not understood. Lynch and Mellor reported the use of selective staining techniques to identify the components of the hyaline membranes in pathologic samples. They refuted a theory current at the time that aspiration of amniotic fluid caused the respiratory failure and the histopathologic findings. They found that the hyaline membranes stained similarly to the epithelium of the terminal bronchioles and alveolar ducts and concluded that hyaline membranes were concentrated secretions of the epithelium. They were puzzled about the fact that hyaline membranes were not present at birth but only after breathing, and they found hyaline membranes in the contralateral lung of a preterm with diaphragmatic hernia but not in the hypoplastic lung. Their assumption was that the membranes caused the disease. We know now that hyaline membranes are not secretory products of the epithelium but the denatured aggregates of injured epithelial cells, interstitial, and plasma components. Hyaline membranes are not present at birth because the preterm lung is generally not injured until it is ventilated and exposed to oxygen. The hypoplastic lung of the infant with diaphragmatic hernia did not have hyaline membranes, probably because that lung was never ventilated. We know that hyaline membranes are the result of epithelial injury and not the cause of hyaline membrane disease.
NEW TECHNIQUE FOR AIRWAY CORRECTION IN NEONATES WITH SEVERE PIERRE ROBIN SEQUENCE
ARLEN DENNY, MD, AND CHRISTIAN AMM, MD

To avoid tracheostomy in 11 neonates with severe Pierre Robin sequence, we used a technique of progressive elongation of the mandible (distraction osteogenesis) to correct tongue ptosis, increase pharyngeal airway, and correct micrognathia. All 11 patients were extubated within 3 to 6 days after beginning distraction. At 1 month 54.5% were oral feeders and at 1 year, 100%. Sleep studies were obtained on 7 patients and were normal 1 week to 1 month after operation. Growth was observed to be above the 50th percentile in all patients with no comorbidities. A 5-year clinical follow-up showed the operated mandible to maintain a normal shape and produce an undisturbed tooth eruption sequence. We conclude that distraction osteogenesis to increase the length of the short mandible is an effective alternative to tracheostomy in carefully selected patients. (J Pediatr 2005;147:97-101)

The Pierre Robin sequence, as classically described, consists of micrognathia (small retruded mandible), glossoptosis (tongue retroposition into the pharyngeal airway), possible cleft palate, upper airway obstruction, feeding difficulties, and growth retardation.1 In severe or refractory cases, a tracheostomy has been advocated to manage the airway in the neonatal period,2 and to allow for feeding. Tracheostomy carries a significant lifelong burden. Average age at decannulation is 3.1 years, and long-term sequelae of tracheal stenosis or tracheomalacia may be present in up to 50% to 75% of cases.3 In many centers, infants with tracheostomy also have a gastrostomy for feeding, with its attendant morbidity and death.

We have previously demonstrated the effectiveness of distraction osteogenesis, by elongating the mandible and displacing the tongue musculature insertions, allowing decannulation of tracheostomy-dependent pediatric patients with Pierre Robin sequence. Cross-sectional analysis of the airway showed a 67% mean improvement in airway cross-sectional area.4 Since 1998 we have applied this technique to selected neonates with severe Pierre Robin sequence as an alternative to tracheostomy and reported preliminary success in obtaining airway correction.5 This study reports 5-year outcomes regarding initial and late control of airway obstruction, feeding results, growth, and the maintenance of correction of mandibular deficiency after physiological growth.

METHODS

This was an uncontrolled clinical pilot study with 5-year follow-up. Between 1998 and 2003, the Neonatal Airway Management Team at Children’s Hospital of Wisconsin evaluated all neonates with Pierre Robin sequence suffering severe upper airway obstruction. The team consisted of a pediatric intensivist, a pediatric otolaryngologist, a pediatric anesthetist, and a craniofacial plastic surgeon. Radiologic evaluation, nasopharyngoscopy, bronchoscopy, and resting oxygen saturation monitoring were obtained on all patients to evaluate the entire respiratory tract and rule out other sites of obstruction.

The study included neonatal patients either seen primarily at the Children’s Hospital of Wisconsin or referred from other institutions for airway management. Traditional management failed in all these patients, including prone positioning, tongue-lip adhesion, and nasopharyngeal airway intubation.

Patients were selected for mandibular distraction if their upper airway obstruction met the following criteria: tongue posture caused by a small mandible as a primary source of obstruction, as evidenced on radiologic evaluation and nasopharyngoscopy, no other sites of airway obstruction (tracheomalacia, laryngomalacia, etc), and severe refractory obstruction otherwise requiring a neonatal tracheostomy for airway control. Patients with airway obstruction resulting from causes compounding tongue ptosis (circular pharyngeal collapse) or with obstruction at another level were not included in the study.
Fifteen neonates in whom traditional measures failed (positioning or tongue-lip adhesion) and who would have undergone neonatal tracheostomy were studied. Four patients were refused distraction. Three of these were found to have severe tracheomalacia, bronchomalacia, and laryngomalacia. The fourth infant was diagnosed with Caffey’s syndrome (idiopathic cortical hyperostosis) and was found to have a type 4 (circular) collapse of the entire oropharyngeal airway, including the lateral pharyngeal walls. The tongue base was not the only source of obstruction. These four infants were successfully treated by tracheostomy. The neonates selected for distraction were then followed up prospectively, with preoperative and postoperative sleep studies obtained when possible. Equipment necessary for sleep study in neonates was not available until after treatment of the first 5 patients. Length and weight data were collected. The craniofacial surgeon and the craniofacial orthodontist followed the growth and shape of the mandible, as well as dental development over the period of the study.

### RESULTS

Eleven patients (5 males and 6 females) were included in the study. The initial 5 patients were included in a preliminary communication reporting success in management of the initial airway obstruction. All patients had intermittent resting oxygen saturation levels less than 70% before operation. Further deterioration was noted during feeding in some patients. Five patients required intubation before operation to maintain ventilation (patients 3, 4, 6, 10, and 11). Age at operation was 3 days to 45 days (mean 18.54 days, median 7 days) (Table). One neonate (patient 2) had severe growth retardation when initially evaluated and underwent nasogastic feeding support until he weighed 3 kg.

All of the younger patients (3, 4, 8, 9, 10, 1, 2) were initially evaluated at our institution and referred for distraction when a tracheostomy was indicated for airway/feeding management, whereas the older patients (5, 6, 7, 11) were usually referred from other institutions. One patient had previously had a tongue-lip adhesion that failed (patient number 1).

Mandibular distractors were placed during operation with the patient under general anesthesia, and a surgical separation was created in the ramus of the mandible (Figure 1). All procedures were completed in less than 2 hours, with less than 30 mL of blood loss. The patients were kept intubated, and distraction was initiated on postoperative day 1 at a rate of 2 mm/d, then switched to a rate of 1 mm/d after 6 mm of distraction.

All patients were extubated within 3 to 6 days of distractor activation. A good clinical indicator of successful distraction was correction of the tongue from the initial vertical to a physiologically normal horizontal posture on

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Sex</th>
<th>Age at operation</th>
<th>Diagnosis</th>
<th>Polysomnography</th>
<th>Weight charts</th>
<th>Height charts</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>36 days</td>
<td>Isolated PR</td>
<td>NA</td>
<td>90-95th</td>
<td>50th</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>45 days</td>
<td>Stickler’s</td>
<td>Normal 1 mo after operation</td>
<td>80th</td>
<td>80th</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>7 days</td>
<td>Unidentified</td>
<td>NA*</td>
<td>75th</td>
<td>75th</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>7 days</td>
<td>Isolated PR</td>
<td>NA</td>
<td>60th</td>
<td>50th</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>14 days</td>
<td>Isolated PR</td>
<td>Severe abnormal before operation/normal I week after</td>
<td>50th</td>
<td>75th</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
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<td>Severe abnormal before operation/normal</td>
<td>&lt;3rd</td>
<td>&lt;3rd</td>
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<tr>
<td>7</td>
<td>M</td>
<td>19 days</td>
<td>? VCFS</td>
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<td>25th</td>
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<tr>
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<td>50th</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
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<td>50th</td>
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<tr>
<td>10</td>
<td>F</td>
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<td>11</td>
<td>M</td>
<td>28</td>
<td>Stickler’s</td>
<td>Severe abnormal before operation/normal</td>
<td>†</td>
<td>†</td>
</tr>
</tbody>
</table>

*Intubated before operation.
†Insufficient follow-up.

Eleven patients were found to have upper airway obstruction caused by tongue ptosis (Sher type 1 and 2) and underwent distraction osteogenesis to lengthen the mandible. An external-type distractor was used (Hoffman external distractor, Howmedica, Allendale, NJ, or Leibinger Multi-guide, Stryker Leibinger, Kalamazoo, MI). Patients selected for treatment by distraction represented 8% of all patients seen with a diagnosis of Pierre Robin sequence at Children’s Hospital of Wisconsin during the study period.
physical examination. This was observed early and progressively in the distraction process (Figure 2). Nasoendoscopy was performed with the patients under sedation to confirm the relief of tongue base obstruction before the patients were extubated. None of the patients needed any form of supplemental oxygenation beyond 14 days after operation. None of the distracted patients have needed any additional airway support, treatment or surgery.

Six patients (54.5%) were immediately started on oral feeding with no problems at the time of extubation, four required gavage feeds for less than 45 days (36.3%), and one patient (9%) (number 8) required a percutaneous endoscopic gastrostomy. Her oral feeding progressively improved, and she was feeding 100% orally at 1 year of age.

Six patients (patients 5 through 11) had preoperative polysomnography results that were interpreted as severely impaired. Postoperative polysomnography evaluation results were obtained on 7 patients (patients 2, and 5 through 11) 1 week to 1 month after distraction and were normal in all 7 patients.

Growth charts of our patients show that 10 patients are above the 50th percentile for length and weight. The remaining patient has severe growth retardation associated with severe cardiac malformations and probable VeloCardioFacial syndrome. Notably, no airway issues were noted on that patient during follow-up, and a normal sleep study result was obtained 1 week and 2 months after distraction (Table). This trend of average or above-average weight gain continues in the 4 patients with the longest follow-up (3 to 5 years).

Ten of the 11 study patients had incomplete cleft palates. All patients had uneventful repair of their cleft palate by 12 months of age and were extubated immediately after palatoplasty, with no airway issues noted, indicating adequate airway at the time of palate repair. Timing and outcome of cleft palate repair were unaltered by distraction. Figures 3 (available online at www.us.elsevierhealth.com/jpeds.) and 4 show selected patients.

Our first 2 patients are particularly illustrative: Patient 1 had been previously treated with a tongue-lip adhesion with no resolution of her symptoms. She was admitted with worsening airway symptoms 2 weeks after initial tongue-lip adhesion and failure to thrive. Her symptoms quickly improved and her growth accelerated shortly after operation. The oldest patient in this group, patient 2, was being treated at home with prone positioning. He was admitted to the hospital because of failure to thrive with worsening airway obstruction and loud respiration in spite of prone positioning. Polysomnography was performed, and the results were found to be severely abnormal. This infant had prompt resolution of his airway symptoms, with catch-up growth shortly after mandibular distraction.

DISCUSSION

Until recently, surgical techniques to increase the size and projection of the mandible were unavailable. The treatment of last resort for this neonatal emergency, when unresolved by prone positioning, nasopharyngeal intubation, or tongue-lip adhesions was tracheostomy. Perinatal tracheostomy has been deemed the definitive corrective procedure by many authors (12% to 40% in various studies).2

Tracheostomy in infancy carries a significant burden. The mortality rate from the tracheostomy alone independent of the underlying diagnosis is as high as 5%.3 The average age at decannulation in our institution is 3.1 years. Other centers report successful decannulation in only 5 of 15 patients with Pierre Robin sequence. Up to 60% of patients successfully

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**Figure 1.** Description of surgical technique to lengthen mandible by distraction osteogenesis. After distractor removal, mandible is indistinguishable from normal.

**Figure 2.** Above: Resting tongue position with neonate fully relaxed before operation. Both nasal and oral airways obstructed. Note vertical tongue posture with most of tongue above palatal shelves. Below: Resting tongue position with same patient fully relaxed after 2 weeks of distraction. Note horizontal posture of tongue. Nasal and oral airways are patent. P, Palatal shelves; T, tongue; CP, cleft palate.
decannulated will have chronic sequelae of recurrent granulomas, tracheomalacia, or tracheal stenosis.

Distraction osteogenesis is a technique that was first introduced for lengthening the long bones of the body. The technique involves cutting the bone, waiting a short time for a callus to form ("lag period"), then progressively advancing the segments of bone controlled on a rigid frame at 1 mm/d, up to 2 mm/d in the neonate. A consolidation phase follows.

Figure 4. Patient 2. A, Before surgery. B, At time of distractor removal, patient is sedated on mask ventilation with no airway problems. C, Normal dentition at age 54 months. D, Profile view of same patient at age 54 months. Note minimal scarring.
and allows the intervening distracted soft callus to ossify (Figure 1). This entire process is complete in less than 8 weeks in neonatal patients.

The principles of distraction osteogenesis have only recently been applied to the craniofacial skeleton. A growing body of experimental data and increasing experience have increased its applications.

We have progressively expanded this technique, first to successfully decannulate older children with Pierre Robin sequence and other patients with micrognathia that were tracheostomy dependent. After documenting successful treatment in younger children, we applied it to neonatal patients in an effort to prevent tracheostomy. This article is the first to report on long-term outcomes of these patients.

Possible complications from this technique include bony malunion, malalignment, and infection. Malunion and non-union have been very rarely observed in the craniofacial region, even more rarely in children. Infection and malalignment are avoided by careful surgical technique. Complications are infrequently observed in the craniofacial region, probably because of profuse vascularity. No complications occurred in this series.

A multidisciplinary team and significant expertise in pediatric distraction is essential for a successful outcome. Patient selection is also critical. An extensive workup is done to identify the patients who will benefit from this procedure. The entire upper aerodigestive tract is evaluated for other sites of obstruction. The pattern of closure of the nasopharynx is also examined, and the tongue has to be seen clearly either directly pushing against the posterior pharyngeal wall or indirectly by pushing the palate superiorly and posteriorly against the posterior pharyngeal wall, as the sole site of airway obstruction. After evaluation, the pediatric intensivist, pediatric otolaryngologist, pediatric anesthesit, and pediatric craniofacial surgeon make a team decision regarding treatment for each patient.

Several series reporting long-term follow-up of patients treated before the availability of distraction osteogenesis show these patients to display sequelae of growth retardation. It is likely that these are due to chronic intermittent upper airway obstruction in infancy, especially at night. Many of the patients with Pierre Robin sequence treated without distraction have abnormal sleep study results that persist through adolescence and adulthood. In our neonatal patients, distraction osteogenesis of the mandible corrected the clinically obvious airway obstruction. Remarkably, even subclinical obstruction that might appear only on polysomnography was not found, even as early as 1 week after operation. We have documented the persistence of these normal sleep study results up to 2 years after distraction.

In this series, all patients have been extubated after only 3 to 6 days of distraction, and tracheostomy has been uniformly avoided. Of these patients, 54.5% were immediately started on oral feeding with no problems, and 36.3% were unable to feed orally in spite of documented correction of the airway abnormality and required gavage feeds for 45 days or less. One patient required a long-term percutaneous endoscopic gastrostomy placement. These observations may be related to underlying abnormal functioning of the pharyngeal musculature that could be syndrome-specific.

One of the most striking observations after relief of airway obstruction and labored breathing is the early accelerated body growth. Long-term follow-up of our patients also shows normal growth that is maintained at the higher percentiles of growth charts without any special dietary interventions. This compares favorably to large studies of patients managed by traditional methods (tongue-lip adhesion) published in the literature before the availability of neonatal mandibular distraction.

The size and shape of the distracted mandible has been maintained. The mandible has been monitored by the team orthodontist and was observed to be growing appropriately in all patients, with up to 5 years of follow-up. It is unknown whether longer-term studies will reveal an inherent growth abnormality of the mandible, especially in specific syndromes (such as Stickler’s). Nonetheless, the distracted mandible is indistinguishable from normal by radiologic evaluation and clinical examination. On the basis of this and other series, the indications for traditional corrective surgery techniques, such as tongue/lip adhesion, subperiosteal tongue release, and tracheostomy, are being redefined.

We thank Dr Robert Kliegman, Chief of Pediatrics, Children’s Hospital of Wisconsin for his assistance in preparing this manuscript. We also wish to acknowledge the contributions and support of Dr Tom Rice, Chief of Pediatric Intensive Care, Dr Dick Behrens, Pediatric Anesthesia, and Dr David Beste, Pediatric Otolaryngology, Neonatal Obstructed Airway Team—Children’s Hospital of Wisconsin.

REFERENCES

We report on 2 children with Fabry disease who had radiologic evidence of microvascular central nervous system involvement despite the clinical absence of renal, cardiac, or cerebral manifestations. This suggests that treatment with enzyme replacement therapy may be necessary early in the disease to avoid irreversible complications. (J Pediatr 2005;147:102-5)

Fabry disease is a rare X-linked recessive disease caused by deficient activity of the lysosomal hydrolase α-galactosidase A (α-Gal A), which leads to accumulation of α-galactosyl-terminal lipids, particularly globotriaosylceramide in lysosomes, resulting in severe renal, cardiac, and cerebrovascular involvement. Males with the classical phenotype, who have virtually no detectable α-Gal A activity, develop end-stage renal disease at a mean age of 39 years and have a median lifespan of approximately 50 years. Carrier women can also have a wide range of disease manifestations ranging from no symptoms to symptoms as severe as those of classically affected males. Diagnosis of Fabry disease is often delayed, especially in the absence of a family history, because early symptoms can be subtle or nonspecific.

Until enzyme replacement therapy (ERT) became available in 2001, treatment for Fabry disease consisted of symptom-based treatment that did not address the underlying cause of the disease. With the availability of this disease-specific therapy, prompt diagnosis has assumed new importance so that treatment can begin before irreversible organ damage occurs, although the ability of ERT to treat parenchymal central nervous system (CNS) damage remains controversial.

Cerebrovascular manifestations in patients with the classical form of the disease include early stroke, transient ischemic attacks, white matter lesions, hemiparesis, vertigo or dizziness, and complications of vascular disease (such as diplopia, dysarthria, nystagmus, tinnitus, hemiataxia, memory loss, and hearing loss). A longitudinal study of cerebrovascular involvement in 50 patients who had a total of 129 magnetic resonance imaging (MRI) scans demonstrated increasing cerebral vasculopathy with age. The effects of progressive vasculopathy is seen in pediatric patients with Fabry disease, leading to transient ischemic attacks in patients as young as 12 years.

Progressive neuroradiologic findings in Fabry disease include dolichoectasia (vascular elongation with fusiform dilation) and extensive periventricular white matter signal hyperintensity associated with deep small vessel infarcts or lacunae in the basal ganglia. Classical periventricular white matter lesions can be found on T2 weighted images or fluid attenuated inversion recovery (FLAIR). Dolichoectasia is a common finding in the posterior circulation of these individuals, especially in the vertebrobasilar system. None of these findings is specific for Fabry disease. However, 2 recent reports describe pulvinar hyperintensity as a pathognomonic MRI sign of Fabry disease in some adults, with increasing frequency with age. These hyperintense images, attributed to tissue mineralization (calcification), can also be seen in computed tomography scans of the corresponding areas.

Here we describe brain MRI abnormalities found in two boys with Fabry disease who had no clinical evidence of cerebral involvement. The findings are similar to those seen in microvascular disease caused by chronic hypertension or atherosclerosis in adults, although the specific changes in the posterior circulation seen in adults with Fabry disease were not observed.
PATIENT 1

An 11-year-old white male who had complaints of acroparesthesias in the hands and feet beginning at age 7, anhidrosis, and frequent loose bowel movements was tested for Fabry disease after diagnosis in his maternal grandfather. Decreased activity of \( \alpha \)-Gal A confirmed the suspicion of Fabry disease, and sequence analysis revealed an R227Q mutation in the \( \alpha \)-Gal A gene. Baseline audiologic examination, electrocardiography, and echocardiography results were unremarkable. The ophthalmologic examination showed whorled corneal opacities in both eyes. Creatinine clearance was 147 mL/min (2.45 mL/s), and no proteinuria was found. The patient currently receives gabapentin 400 mg/day for pain management and agalsidase beta infusions (Fabrazyme, Genzyme Corporation, Cambridge, Mass) (1.0 mg/kg) every 2 weeks.

In axial T2 images there is minimally increased signal in both the basal ganglia and the subcortical white matter of both hemispheres (Figure 1). These areas are punctuate in shape and similar to the ones observed in adult microvascular disease. Minimal prominence of the cerebral sulci is also observed but without clear evidence of atrophy. A similarly increased signal in the periventricular white matter is also observed in the axial FLAIR sequence (Figure 2). No hyperintensities were observed in the pulvinar of this patient, as should be expected for patients in this age group.

PATIENT 2

An 8-year-old, white, symptom-free male was tested for Fabry disease after the diagnosis of his maternal grandfather. Decreased activity of \( \alpha \) Gal A confirmed the suspicion of Fabry disease, and sequence analysis revealed a 196-basepair deletion in the gene for \( \alpha \)-Gal A. Cardiac and renal evaluations in this patient are unremarkable, and creatinine clearance was estimated at 140.3 mL/min (2.34 mL/s).
T1 sagittal cuts of the brain show minimal prominence of the Virchow-Robin spaces (Figure 3). On the axial T2 sequences, multiple punctate areas in the subcortical white matter of both hemispheres showed a minimal increase in the signal, similar to the changes observed in patient 1, although they seem to be less prominent.

DISCUSSION

Although the pathologic condition of Fabry disease begins at birth or before birth, laboratory evaluations of children with this condition usually reveal no apparent abnormalities, and symptoms often do not manifest until 10 years of age or later. Here we report on 2 children with Fabry disease (a symptomatic 11-year-old and a symptom-free 8-year-old) who, in spite of having no clinical evidence of CNS, renal or cardiac involvement, showed early microvascular cerebral involvement demonstrated by MRI. These observations underscore the progressive nature of this disease and that it progresses silently well before clinical symptoms of organ damage are evident. These MRI findings, together with the reported occurrence of transient ischemic attacks in a 12-year-old patient with Fabry disease, suggest that the accumulation of substrates in the blood vessels of the CNS can produce serious consequences even at an early age. A report by Giacommini et al addresses the case of a previously symptom-free 19-year-old woman who presented with neurologic deficits secondary to basal ganglia and pontine infarction. The diagnosis of Fabry disease was made after cardiac, arterial and hematologic investigations did not identify the cause of the stroke, and the diagnosis was suggested only after a histologic evaluation. A similar argument may be applied to other organs. It is possible that delaying treatment may compromise the overall effectiveness of enzyme replacement therapy. Although it has been shown that intravenous enzymes cannot cross the blood brain barrier, the parenchymal consequences derived from vascular disease and endothelial deposition may be preventable with early intervention. Taking these facts into account, we suggest the use of MRI for baseline and follow-up of pediatric patients with Fabry disease to identify potential abnormalities that could benefit from enzyme replacement therapy.

REFERENCES


Hurler syndrome is a lysosomal storage disease resulting in fatal cardiac or neurologic sequelae unless alpha-iduronidase production is reconstituted with hematopoietic stem cell transplantation. We report on a 4-year, 6-month-old boy with mixed donor chimerism and low enzyme levels but a normal neurodevelopmental trajectory. (J Pediatr 2005;147:106-8)

Children with Hurler syndrome lack the lysosomal enzyme alpha-L-iduronidase. This results in glycosaminoglycan (GAG) accumulation with progressive mental retardation and death.1,2 Recombinant alpha-L-iduronidase appears to ameliorate some of the systemic effects in Hurler syndrome, but hematopoietic stem cell transplantation remains the only means of preventing the neurologic deterioration.3

Children with Hurler syndrome have normal intelligence at birth, but on average their IQ declines by 2 standard deviations within the first 2 years of life (30-point decrease in IQ).4 The negative correlation between age and IQ has been found to be significant ($r = -0.82$, $P \leq .0003$).2 Good neuropsychological outcomes after bone marrow transplantation (BMT) are dependent on multiple factors including age at transplantation (<24 months), mental developmental indexes >70 before transplantation, adequate engraftment (as measured by full donor chimerism), and posttransplantation iduronidase activity.4-6 We report the case of a patient with Hurler syndrome in whom a good neurologic outcome was achieved in spite of poor sustained engraftment and very low serum alpha-L-iduronidase activity after BMT.

CASE REPORT

At 9 months of age, the patient presented with coarse facies and a lumbar gibbus. He had dysostosis multiplex and a positive mucopolysaccharide (MPS) screen result. Hurler syndrome was confirmed by the absence of alpha-L-iduronidase activity in peripheral blood leukocytes. He had a homozygous mutation of his IDUA gene, W402X, common to those with a severe Hurler phenotype.

At 15 months of age, the patients underwent BMT from a male matched related donor. Conditioning regimen included cyclophosphamide (50 mg/kg × 4 doses), busulfan (based on targeted AUC 18mg/kg divided every 6 hours over 4 days), and low-dose total body irradiation (300 cGy). The patient was transplanted with $5.6 \times 10^8$ nucleated cells/kg. He had no unexpected transplant-related toxicity and specifically no central nervous system complications.

After BMT, his musculoskeletal abnormalities persisted but were stable, his facial features softened, and airway obstruction resolved. An echocardiogram obtained 2 years after transplantation showed resolution of both his atrial septal defect and mild valvular regurgitation.

Initially he fully engrafted. He was followed by chimerisms on whole blood and alpha-L-iduronidase levels on unfraccionated peripheral leukocytes. He expressed normal levels of alpha-L-iduronidase after transplantation but failed to sustain these beyond 4 months after BMT. The patient has remained at very low levels of activity (Table).

<table>
<thead>
<tr>
<th>BMT</th>
<th>Bone marrow transplantation</th>
<th>CNS</th>
<th>Central nervous system</th>
</tr>
</thead>
</table>

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Based on clinical evaluation and developmental achievements, it was felt that his pretransplantation development was normal. He sat at 6½ months, stood at 7 months, had single words at 10 months, and walked at 13 months. Two years after BMT (age 3 years, 3 months), a formal neuropsychological evaluation demonstrated development in the normal range. Full Scale intelligence testing revealed average intelligence (45th percentile). There was a minor discrepancy between his verbal (average range) and performance intelligence (low-average range). He had mild difficulties with visual spatial skills, primarily with block design. His language skills were normal on the Token Test for children.

His most-recent evaluation at age 4 years 5 months revealed dramatic improvements on the Peabody Developmental Motor Skills, with an age equivalent of 41 months. (This minor delay was attributed to his Hurler syndrome–induced flexion contractures of his fingers). He continued to do well in school and was communicating in both English and French. Repeat neuropsychological testing at that time revealed average full-scale intelligence with no discrepancy between his verbal and performance skills.

**DISCUSSION**

Hurler syndrome is a progressive disease that leads to coarse facial features, corneal clouding, hernias, hepatosplenomegaly, skeletal deformities, and progressive mental retardation. Death results from heart disease or respiratory failure in the first decade of life.

Cleary and Wraith showed that normal developmental milestones over the first year of life were achieved by all of their patients. However, neurodevelopment does not continue along a normal trajectory after the first year. Therefore our patient should have had evidence of neurologic deterioration if there were inadequate cerebral alpha-L-iduronidase activity.

The rationale for BMT lies in the provision of donor histiocytes that migrate to the central nervous system (CNS), differentiate into microglial cells, and provide an ongoing source of functional enzyme. We postulate that this occurred in our patient at sufficient levels to provide neuroprotection in spite of an inadequate peripheral enzyme activity.

Peters et al showed that iduronidase activity post BMT less than or equal to that of a heterozygous carrier donor (~50%) was associated with a poor neurologic outcome (Mental Development Index [MDI] ≤80). A statistically significant correlation was subsequently found between MDI at follow-up and peripheral enzyme activity in these patients (0.59, P = .02). Other studies have reported adequate developmental outcomes in children with less than 90% chimerism (although all had at least 50% chimerism). Our patient’s outcome suggests that even very low levels of peripheral enzyme activity level can be associated with normal development.

Data regarding the presence of alpha-iduronidase activity in the CNS after BMT is indirectly derived from cerebrospinal fluid and neuroimaging studies. Takahashi et al used magnetic resonance spectroscopy to measure central levels of GAGs before and after BMT in a patient with Hurler syndrome. After BMT, peripheral enzyme activity was greater than 50% of normal (13 nmol/mg/protein/h with normal 28 ± 7) but never achieved complete engraftment. At the patient’s 2-year follow-up, in spite of low enzyme activity, the levels of central GAGs were stable, routine neuroimaging results were normal, and the child had a 28-point increase in IQ. This is the first neuroimaging evidence that peripheral enzyme activity may be limited in predicting CNS enzyme activity. Our case adds support to this notion.

Limitations of this report include that it may be too early to predict our patient’s ultimate neurologic outcome, although if enzyme activity in the CNS were inadequate, he should have shown cognitive decline by age 4. Although delayed or minimal cognitive problems are seen in attenuated forms of MPS1, such as Hurler-Scheie syndrome, our patient presented with significant symptoms before 1 year of age, and his IDUA mutations are associated with a severe MPS1 phenotype. Thus we are confident he has Hurler syndrome.

Our case illustrates that normal peripheral blood alpha-L-iduronidase levels may not be required to sustain normal neuropsychological development in patients with Hurler syndrome after BMT. If techniques can be developed to identify prospectively those patients who are destined to have a good neurologic outcome in spite of low peripheral blood alpha-L-iduronidase levels (for example by functional neuroimaging or other central nervous system biochemical markers), we may avoid the morbidity and mortality of a second BMT.

**REFERENCES**


Vitamin D deficiency [serum 25-hydroxyvitamin D <25 nmol/L (<10 ng/mL)] was identified in 92% of rachitic Arab children and 97% of their mothers compared with 22% of nonrachitic children and 52% of their mothers. There was a positive correlation between maternal and child vitamin D levels. We conclude that mothers of rachitic children should be investigated and treated for vitamin D deficiency (J Pediatr 2005;147:109-11)

Vitamin D stores in women are low, and vitamin D deficiency rickets is common in Arab countries. The high prevalence of rickets is attributed to limited sunshine exposure and poor dietary vitamin D supplementation, especially in breast-feeding infants.1-3 In such high-risk populations, maternal vitamin D deficiency due to sunshine avoidance and low dietary vitamin D intake is also implicated in the pathogenesis of rickets.4,5 In spite of these associations, however, we are not aware of any comparative studies of vitamin D status of mothers of rachitic and nonrachitic children.

We have studied the vitamin D status and relevant sociocultural risk factors of rachitic and nonrachitic children and the vitamin D status of their mothers to test the hypothesis that mothers of rachitic children would have lower serum concentrations of 25-hydroxyvitamin D (25-OHD) and higher prevalence of vitamin D deficiency compared with controls. Although the definitions of hypovitaminosis D and vitamin D deficiency are still controversial,6 we used serum 25-OHD concentrations <25 nmol/L (<10 ng/mL), clinically consistent with osteomalacia and rickets, to indicate vitamin D deficiency.6

METHODS

Thirty-eight Arab children referred to the Pediatric Clinics of the United Arab Emirates (UAE) University’s 2 teaching hospitals in the Al Ain Medical District (AMD) and diagnosed with vitamin D deficiency rickets between January 1999 and January 2002 were included in this study. The AMD has a population of 300,000.

Each child was assessed by at least one of the authors, and a questionnaire on demographic, social and dietary characteristics was completed by interviewing the mother. Usual dress mode while outdoors was used to assess the body surface area exposed to sunshine, using an appropriate chart of body surface area adapted from Lund and Browder.7

Biochemical tests performed in each child and consenting mother included serum concentrations of calcium, inorganic phosphorus, and alkaline phosphatase by autoanalyzer, 25-OHD by high performance liquid chromatography, and intact parathyroid hormone (PTH) by radioimmunoassay kits (Nichols Institute, San Juan Capistrano, Calif). Details of these methods have been reported previously.8,9 The study was approved by the Research Ethics Committee of the institutions.

Fifty nonrachitic Arab children and their mothers previously studied in the same community served as controls.9 The control group was a convenience sample of children admitted to one of the Teaching Hospitals during the period February to September 2000 with conditions other than rickets. The results of relevant clinical characteristics and
vitamin D status of rachitic and nonrachitic children and the vitamin D status of their mothers were compared using nonparametric statistical tests.

**RESULTS**

The sex distributions, median age at study, and body surface exposure while outdoors were similar among the children. However, compared with controls, rachitic children had more prolonged breast-feeding ($P < .004$), less exposure to sunshine ($P < .001$), and lower rates of vitamin D supplementation ($P < .001$) (Table I).

Serum 25-OHD concentrations were significantly lower in rachitic children and their mothers than in controls ($P < .001$). Results of serum PTH levels were available only in rachitic children and their mothers and showed a trend toward negative correlation with serum 25-OHD concentrations.

**DISCUSSION**

Thirty-eight cases of rickets in almost 3 years in a population of 300,000 suggest that vitamin D deficiency rickets is common in this as in other Arab communities. We assume that the numbers are much higher because some pediatricians treated rachitic children without referral for this study. Excluding these cases, our rate remains higher than in Western countries. Compared with controls, rachitic children have higher risk factors for vitamin D deficiency such as less sunshine exposure and vitamin D supplementation and high rate of prolonged breast-feeding. Another study from Kuwait also found limited sunshine exposure in rachitic children. Thus rachitic children may represent the tip of the iceberg in a population at risk of vitamin D deficiency. We therefore recommend vitamin D supplementation and more sunshine exposure for all infants to eliminate vitamin D deficiency.

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**Table I. Comparison of characteristics of Arab children studied**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rachitic (n = 38)</th>
<th>Nonrachitic (n = 50)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M)</td>
<td>19 (50%)</td>
<td>30 (60%)</td>
<td>.35</td>
</tr>
<tr>
<td>Age (mo.)</td>
<td>13.5</td>
<td>13.0</td>
<td>.18</td>
</tr>
<tr>
<td>No. still breast-feeding (%)</td>
<td>35 (92%)</td>
<td>29 (58%)</td>
<td>.004</td>
</tr>
<tr>
<td>No. received vitamin D supplementation (%)</td>
<td>3 (8%)</td>
<td>19 (38%)</td>
<td>.001</td>
</tr>
<tr>
<td>Sunshine exposure (min/d)</td>
<td>0 (0-60)</td>
<td>45 (0-120)</td>
<td>.001</td>
</tr>
<tr>
<td>% Body surface area exposed</td>
<td>32 (0-74)</td>
<td>32 (0-50)</td>
<td>.33</td>
</tr>
</tbody>
</table>

Results presented as number (percent) or median (range).

**Table II. Biochemical tests (median and quartiles)**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Rachitic (n = 38)</th>
<th>Nonrachitic (n = 50)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum 25-OHD Concentrations (nmol/L)</td>
<td>8.0 (3.8, 15.3)</td>
<td>43.8 (25, 64.3)</td>
<td>.001</td>
</tr>
<tr>
<td>No. (%) 25-OHD Concentrations (&lt;25 nmol/L)</td>
<td>35 (92)</td>
<td>11 (22)</td>
<td>.001</td>
</tr>
<tr>
<td>Serum Ca (mmol/L)</td>
<td>2.22 (1.88, 2.35)</td>
<td>2.40 (2.25, 2.50)</td>
<td>.001</td>
</tr>
<tr>
<td>Serum P (mmol/L)</td>
<td>0.97 (0.77, 1.13)</td>
<td>1.45 (1.35, 1.61)</td>
<td>.001</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (IU/L)</td>
<td>834 (641, 1164)</td>
<td>156 (129, 219)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Conversion to metric units: Serum 25-hydroxyvitamin D (25-OHD), 1 nmol/L = 0.4 ng/mL; Calcium (Ca), 1 mmol/L = 4 mg/dL; Phosphorus (P) 1 mmol/L = 3.1 mg/dL.
preventing rickets in high-risk populations such as ours warrants future study.

Arab women and mothers of rachitic children in other high-risk populations have very low serum 25-OHD concentrations. If we regard serum 25-OHD concentrations of 50 to 80 nmol/L (20 to 37 ng/mL) as the adult lower normal range on the basis of recent studies, none of the mothers of rachitic children and only 2 of the control mothers would be considered to have normal vitamin D status. Worse still, nearly all mothers of rachitic children and half of controls had serum 25-OHD concentrations <25 nmol/L (<10 ng/mL). In contrast, in a large American study, only 12% of black women and less than 1% of white women had such very low serum 25-OHD levels.

In view of the positive correlation between maternal and child vitamin D status, this study suggests that vitamin D deficiency may be a maternal and childhood public health problem. In addition, the results support our hypothesis that mothers of rachitic children are at higher risk of vitamin D deficiency. Therefore, a diagnosis of rickets should strongly suggest the possibility of maternal vitamin D deficiency. This finding could be applicable in other populations at high risk for vitamin D deficiency and warrants confirmation.

A limitation of this study is that the study periods for the rachitic children and controls were different. The controls were studied during warmer months while rachitic children and their mothers were enrolled year round. This could theoretically result in higher 25-OHD concentrations in the controls and therefore partly explain some of the differences between the 2 groups. In support of our conclusions, however, we have not observed significant seasonal differences in serum 25-OHD concentrations in the UAE because of abundant sunshine experienced year round (unpublished observations).

Recently, some authors have suggested that evaluation of maternal vitamin D status should be performed as a second-line investigation of rickets. However, on the basis of the results of this study, we suggest that evaluation of maternal vitamin D status and appropriate therapeutic interventions should be part of the routine management of children with rickets in populations at high risk of vitamin D deficiency.

Interestingly, 3 of the mothers of rachitic children required treatment for osteomalacia. The diagnosis in these mothers would have been missed or delayed had they not participated in this study, and this suggests that maternal osteomalacia is underdiagnosed. Clearly, elimination of vitamin D deficiency in women, especially in mothers of rachitic children, requires an early recognition and a maternal vitamin D supplementation program unless more sunshine exposure can be encouraged. A comprehensive strategy that ensures adequate maternal and childhood vitamin D stores could have a significant public health impact on the health of mothers and children.

We thank Dr Mohamed Hayek for collecting blood samples from some of the mothers of the children in the study and Dr Reginald Tsang for valuable comments on the manuscript.

REFERENCES

KOILONYCHIA, DOME-SHAPED EPIPHyses, AND VERTEBRAL PLATYSYNDYLLIA

VICTORIA NGUYEN, BA, ROBERT L. BUKA, MD, JD, BRANDIE ROBERTS, MD, MARILYN JONES, MD, AND SHEILA FALCON FRIEDLANDER, MD

A 2.5-year-old girl presented with koilonychia since birth and was subsequently found to have dome-shaped femoral epiphyses and platyspondylia with anterior central tongues on a skeletal survey. (J Pediatr 2005;147:112-4)

CASE REPORT

A 2.5-year-old girl presented with “strange-looking” nails. The abnormality was noted at birth and involved all digits. Her nails displayed minimal growth and were intermittently tender to touch. The patient, born in Iraq, was a non-consanguineous product of a normal, spontaneous, term delivery. Her developmental milestones were appropriate. She had 5 normal siblings, and there was no family or geographic history of abnormal nails in her native Iraqi village. Examination revealed a well-developed, well-nourished girl whose height, weight, and head circumference were appropriate for her age. Teeth, hand, and foot structure and crease patterns were normal. Skin examination showed no pigment changes. Nails were spoon-shaped with thin and broken distal ends of the nail plate (Figure 1). All fingernails and toenails (Figure 2) were equally affected, with no radial preference. No triangular lunulae were detected, and the child had no pain on passive range of motion or on palpation. Patellae were present bilaterally. Hair appeared normal clinically and on hair mount. A radiographic skeletal survey was obtained for clues to the diagnosis. This scan revealed normal bone age and mineralization patterns. Incidentally, thoracic and lumbar platyspondylia (flatness of the vertebral bodies) (Figure 3) and dome-shaped femoral heads (proximal epiphyses) (Figure 4) were appreciable. Additionally, there were anterior central tongues of each vertebral body. The pedicles and disk spaces were normal, femoral condyles were symmetric bilaterally, and finger length was within normal limits. Although the patellae were not ossified at the time of evaluation, there was no indication that the patellae were actually not present on plain-film radiography. A complete blood count and iron panel to rule out anemia and hemochromatosis and chemistry panel and urinalysis to rule out renal involvement were within normal limits.

DISCUSSION

The differential diagnosis for this child’s findings included nail-patella syndrome (NPS), an autosomal dominant condition characterized by a clinical tetrad: nail changes (98%), absent or hypoplastic patellae (84%), elbow abnormalities, and iliac horns (68%).1 Nail changes are the most constant feature of NPS and characteristically present at birth. They include softening, spooning, discoloration, central grooving, splitting and cracking, narrowing, and, less commonly, thickening.2 Radial fingernails are more severely affected, whereas toenails are often uninvolved. Triangular lunulae are present in 88%. Loss of creases over the distal interphalangeal joints of the fingers (96%) is a sensitive clinical sign for NPS. Patellae may be small (75%), irregularly shaped, or absent (9%). There may be prominent medial femoral condyles with hypoplastic lateral femoral condyles. Typical radiologic findings of elbow involvement include dysplasia of the radial head, prominence of the medial epicondyle, and hypoplasia of the lateral epicondyle and capitellum. Iliac horns are pathognomonic for NPS and can be visualized on third-trimester ultrasound scans or on x-ray film at birth or early childhood. Renal involvement occurs in 37.5%, and

NPS Nail-patella syndrome
PPAC Progressive pseudorheumatoid arthritis of childhood
SEMD Spondyloepimetaphyseal dysplasia
proteinuria may be present from birth and is usually the first sign of renal involvement. Additional NPS findings include pes planus, back pain, lumbar lordosis, glaucoma, Lester’s iris (bilateral darker pigmentation around the central iris), and vasomotor problems.1 Our patient had evidence of dysplastic nails, but lacked other findings of NPS. Although up to 12.5% of NPS cases can occur sporadically, her negative family history and lack of supportive clinical findings argue against the diagnosis of NPS. In addition, she had 2 prominent radiologic findings not associated with NPS: dome-shaped femoral heads and platyspondylia with anterior central tongues. An extensive review of the literature failed to identify any documented cases of such nail findings associated with platyspondylia or dysplastic femoral heads.

Another less likely genodermatosis to be considered is trichorhinophalangeal syndrome. This syndrome can involve koilonychia but also includes slowly growing scalp hair, a pear-shaped bulbous nose, and brachyphalangia (cone-shaped epiphyses of hands and feet). Type I subtype features growth retardation and brachydactyly with sparse eyebrows. Type II subtype is characterized by multiple cartilaginous exostoses, mental retardation, microcephaly, and bushy eyebrows. Type III is marked by short stature, brachydactyly, and pronounced cone-shaped epiphyses with normal eyebrows.5 Other than koilonychia, our patient had none of the above findings.

Our patient had no symptoms or signs to suggest the presence of other conditions associated with koilonychias, including iron deficiency anemia, hemochromatosis, Raynaud’s disease, systemic lupus erythematosus, and trauma.4 Koilonychia has been anecdotally described in Plummer Vinson syndrome, monilethrix, familial cases, high altitude, Witkop’s tooth-and-nail syndrome, hemodialysis, toxic chemical exposure, a syndrome of leukonychia totalis and multiple sebaceous cysts, nutritional deficiency, Kindler syndrome (hereditary bullous poikiloderma), spontaneous liver cell adenomas, and steatocystoma multiplex, none of which are associated with skeletal findings.

A few case reports have noted the association of platyspondylia with dysplastic (but not dome-shaped) femoral heads. Spondyloepiphyseal dysplasia congenita, an inherited chondrodysplasia, exhibits platyspondylia, absence of the femoral head, short stature, and os odontoideum (dens separated from axis body).5 Spondyloepimetaphyseal dysplasia (SEMD) is associated with platyspondylia and vertebral...
anterior tongues, femoral epiphyseal embedment in the metaphyses, dwarfism, and brachydactyly.\textsuperscript{6} Finally, progressive pseudorheumatoid arthritis of childhood (PPAC), associated with platyspondyia with erosion of end plates, enlarged femoral heads, irregular acetabulae, narrow joint spaces with flat epiphyses, and progressive restriction of movement in all joints.\textsuperscript{7} Anterior tongues on vertebral bodies, as seen in our patient, have only been described in SEMD and PPAC. However, spondyloepiphyseal dysplasia congenita, SEMD, and PPAC are not consistent with a patient such as ours, who has a normal stature and dome-shaped femoral heads.

We conclude that the triad of koilonychia, dome-shaped epiphyses, and vertebral platyspondyia as seen in our patient represents a new syndrome. The normal appearance of her 5 siblings might be considered supportive of a spontaneous mutation, but the possibility of an autosomal recessive disorder cannot be ruled out. Further insight into the pathogenesis of this disorder may come with prospective monitoring of our patient's status for the possibility of other evolving anomalies, identification of other affected patients, and future mutational analysis of afflicted individuals.

We thank Jerry Dwek, MD, Assistant Clinical Professor of Radiology, Children’s Hospital and Health Center, San Diego for his expertise.

REFERENCES

We describe 7 Polynesian babies with a unique severe form of holocarboxylase synthetase deficiency characterized by antenatal growth retardation, subependymal cysts, only partial response to biotin, and a poor outcome. (J Pediatr 2005;147:115-8)

The enzyme holocarboxylase synthetase (HCS) is, in the presence of biotin, responsible for the biotinylation and thus activation of the 4 carboxylase enzymes: propionyl-CoA carboxylase (PCC), 3-methylcrotonyl-CoA carboxylase (MCC), pyruvate carboxylase (PC) and acetyl CoA carboxylase (ACC). HCS deficiency is a rare recessive inborn error of metabolism resulting, classically, in lactic acidosis, a characteristic rash, developmental delay, or encephalopathy in early infancy. Untreated it is a fatal condition, although in the vast majority of cases administration of biotin 10 to 20 mg/d rapidly resolves the biochemical and clinical anomalies, and the long-term prognosis is excellent.1 This article reports 7 recent cases of severe, only partially biotin-responsive, HCS deficiency in the Samoan and Cook Island Maori populations.

METHODS

A high incidence of HCS deficiency in Samoan infants was suspected previously but not formally reported. Physicians and laboratories with an interest in metabolic diseases in newborns in Auckland, Melbourne, and Sydney were contacted regarding recent cases. Seven patients were identified, and their hospital records were reviewed. Patient 4 had been reported previously.2 The diagnosis was suspected on the basis of the clinical history and the characteristic urine organic acid profile. Confirmation of the diagnosis was by enzyme analysis of 2 of the 4 biotin-dependent carboxylase activities in fibroblasts grown in medium lacking biotin (with dialysed fetal calf serum) and in medium with 10 μmol/L biotin3,4 or by DNA analysis for the known L216R mutation in the HCS gene.2

RESULTS

All the patients presented on day 1 of life with a severe lactic acidosis (Table). There was no consanguinity, and the parents were Samoan, except for patient 2 who was from the Cook Islands. Patient 4 was born in Melbourne, whereas the other cases were born in New Zealand. All the babies were born at term, and the mean birth weight was 2758 g with a range from 2260 to 3080 g. All had neuroradiologic evidence of bilateral subependymal cysts. The 2 babies who did not receive biotin died in the first week of life. The others showed a good initial clinical and biochemical response to the vitamin. In spite of receiving high doses of biotin, 3 of the children had erythematous desquamating rashes and recurrent episodes of sepsis and metabolic decompensation. They subsequently died during one of these episodes. Patient 2 had fewer problems with rash and metabolic decompensation but
Table. Summary of the cases

<table>
<thead>
<tr>
<th>Case</th>
<th>BW</th>
<th>Age at presentation</th>
<th>Initial pH, base excess, Lactate (mmol/L)</th>
<th>Initial treatment</th>
<th>Ongoing treatment</th>
<th>Radiology</th>
<th>Development</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2650</td>
<td>18</td>
<td>6.9</td>
<td>Nil else</td>
<td>Died day 3</td>
<td>Day 2 US subependymal cysts</td>
<td>NA</td>
<td>Died day 3</td>
</tr>
</tbody>
</table>
| 2    | 2260| 24                  | 6.97                                     | Biotin 20 mg      | Slow improvement | Antenatal and day 2 US subependymal cysts.  
CT diffuse white matter changes | Moderate-severe delay age 18 months | Returned to Cook Islands age 18 months, lost to follow-up |
| 3    | 3080| 6                   | 7.08                                     | Biotin 10 mg      | Ongoing acidosis | Day 2 US subependymal cysts, dilated ventricles, Day 3 CT diffuse white matter changes | Hypotonia, floppy at 3 months | Metabolic decompensation.  
Died age 3 months |
| 4    | 2800| 12                  | 7.2                                      | Biotin 20 mg      | Moderate improvement | CT 1 month subependymal cysts, ventriculomegaly, diffuse white matter changes | Moderate severe delay at 3 years | Persistent skin rash, episodes of sepsis and metabolic decompensation,  
Died age 3 years |
| 5    | 2910| 24                  | 6.9                                      | Nil else          | Died day 3       | Antenatal and day 2 US dilated cerebral ventricles, subependymal cysts | NA         | Died day 3  |
| 6    | 2690| 24                  | 7.08                                     | Biotin 40 mg      | Good recovery over 48 hours | Day 2 US subependymal cysts, mild ventriculomegaly | 4 months-moderate developmental delay | Persistent skin rash, septicemia, metabolic decompensation.  
Died 4 months |
| 7    | 2920| 24                  | 6.9                                      | Biotin 20 then 40 mg | Good recovery over 72 hours | Antenatal and day 3 US-subependymal cysts | Mild developmental delay 1 year | Recurrent infections.  
Skin healthy but ongoing lactic acidosis and abnormal organic acids age 18 months |

*BW*, Birth weight in grams; *US*, ultrasound; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *NA*, not applicable.

*In addition to ventilation, inotropes, fluids, bicarbonate and antibiotics.
at 18 months of age had moderate developmental delay and was subsequently lost to follow-up. Patient 7, at age 18 months, had recurrent admissions to hospital with infections but in spite of a persistent mild lactic acidosis (2 to 4 mmol/L) and grossly abnormal urine organic acids has only mild developmental problems and relatively normal skin.

All patients had urine organic acid profiles consistent with HCS deficiency. They were all homozygous for the L216R mutation. Typically fibroblasts from patients with HCS deficiency show grossly decreased PC and PCC activities when cells are grown in low-biotin media yet normal activities when cells are grown with 10 μmol/L biotin. In contrast, the 4 patient cell lines tested (patients 1-4) showed only modest increase (10% to 28% of expected) in PC and PCC activities with 10 μmol/L biotin. These enzyme activities remained deficient (<40% of control) even when cells were grown in 100 μmol/L biotin (data not shown).

**DISCUSSION**

This is the largest previously unreported group of patients with HCS deficiency and with a phenotype that is different from the classical biotin responsive form of the condition. Three patients, other than case 4, were previously described with partial biotin responsiveness. These children, one of whom was Samoan and heterozygous for the L216R mutation, are also different because their clinical outcome was relatively good, in vitro studies demonstrated a reasonable response to low-biotin medium (biotin concentration 0.01 to 10 μmol/L), and they were heterozygous rather than homozygous for a known severe mutation.

Our cohort was notable for a persistent and often severe widespread erythematous desquamating rash, recurrent episodes of metabolic decompensation (often secondary to skin-acquired staphylococcal septicaemia), and they had poor long-term prognosis in spite of receiving high-dose oral biotin and carnitine.

Most biotin-responsive HCS-deficient patients have at least one allele containing a mutation in C-terminal putative biotin binding domain of the gene. These mutations lead to a Km variant (ie, the enzyme has a lower affinity for biotin) that is easily overcome with oral biotin 10 to 20 mg day. The L216R mutation, however, is located in the N terminal region of the gene. These patients are believed to have a relatively normal Km but greatly reduced Vmax. Homozygosity for L216R probably results in an enzyme Vmax close to the minimum required velocity for cellular function at basal levels.

Variably enlarged ventricles and most unusual subependymal cysts were present in all the patients in the antenatal or early neonatal period (Figure). This finding suggests an antenatal cause of the lesions. Similar cysts were previously described in 2 patients with HCS and in patients with PC deficiency. They have been referred to as periventricular leukomalacia, although our cases all demonstrate cysts in a characteristic subependymal location inferior to the frontal horns and bodies of the lateral ventricles. In contrast, periventricular leukomalacia occurs lateral and superior to the ventricles and affects the peritrigonal white matter. The cysts in these infants were at the site of the germinal matrix.

Samoan infants born at term in New Zealand have a relatively high mean birth weight compared with Europeans (3700 vs 3500 g). The mean birth weight of this cohort (2758 g) is lower than expected and strongly suggests an antenatal effect of HCS on birth weight. Babies that present acutely in the first few days of life (n = 10) typically weigh less than 3000 g, whereas those with a later infantile initial presentation (n = 5) have birth weights greater than 3500 g (summary of patients known to authors). Thus severe forms of HCS deficiency result in intrauterine growth retardation and clinical presentation in the first few days of life whereas less-severe forms of the condition result in normal birth weight and later presentation. HCS must therefore have an antenatal function that is important for fetal growth. The finding of subependymal cysts on antenatal ultrasound scans especially in

**Figure.** Cerebral ultrasound scan performed on case 6 at 15 days of age. Coronal (A) and left parasagittal (B) images via anterior fontanelle demonstrate multiple bilateral subependymal cysts (white arrows) which protrude into lateral ventricles (black arrows) from below.
the presence of intrauterine growth retardation should alert the clinician to the possibility of HCS deficiency.

We thank Dr Maisie Wong, Dr Rita Teele, and Dr Kevin Carpenter for their assistance in the care of these patients.

REFERENCES


Screening for phenylketonuria (PKU) began in the early to mid-60s and proved to be the “poster child” for newborn screening for metabolic disorders. It allowed for the introduction of dietary treatment before the appearance of symptoms and irreversible brain damage. The enormous success of PKU screening established the foundation on which an increasingly large number of metabolic, other genetic, and nongenetic disorders are being added. Thus the menu of newborn screening has expanded on a broad national and international scale.

However, a cloud hangs over newborn screening for metabolic disorders, the cloud of either early discharge from the nursery or the variable time of performing the test for children who are admitted into an intensive care unit. This problem has been recognized for a number of years and recommendations for addressing it have been made and implemented. Unfortunately, errors still occur and can be illustrated by three patients in whom the diagnosis of PKU was missed.

Two of these children not detected by newborn screening were premature and were admitted to a neonatal intensive care unit. In an effort to avoid the inadequate result that might follow a transfusion, the newborn screening specimen was drawn on admission at 2 hours of age and was never repeated, despite recommendations to do so when a sample is obtained earlier than 24 hours of age. The third case resulted from a volitional early discharge at 4 hours of age and a failure on the part of the hospital to have a follow-up plan for such infants. In the first two instances, the phenylalanine value in the screening specimen was comfortably within the normal range, and, on that basis alone, no inference about the need for a follow-up specimen could have been drawn. In the third case, the newborn value for phenylalanine was at the upper end of the normal range when drawn at 4 hours, and a physician alert to the danger that early discharge posed might have requested a repeat specimen. The physician involved had focused only on the fact that the test for PKU was in the normal range. In each instance cited, failure to repeat the phenylalanine study in good time resulted in children who were moderately to severely retarded, autistic in their behavioral characteristics and readily responsive to low phenylalanine diet when finally prescribed. All three instances represent completely preventable cases of mental retardation.

These cases are rendered even more ominous by an informal survey of our pediatric colleagues and their practice regarding the assessment of newborn screening results. It appears few of the excellent physicians whom we queried were aware of the nuances of newborn screening, or habitually looked at anything save for the result. Thus, because patients are still occasionally discharged before 6 to 12 hours of age (hours at which most if not all patients in California would have been diagnosed) the physicians would be in no position to assess the newborn screen and to repeat it in the limited number of circumstances in which this was necessary. The problem may be mitigated by the current practice of assessing not only absolute phenylalanine levels but also the phenylalanine to tyrosine ratio, which would likely have picked up some of the missed cases because of the elevation in this ratio. Nevertheless, a problem would still exist.

The severity of this problem is only heightened by the addition of new tests, as is now occurring with the introduction of expanded newborn screening using tandem mass spectrometry (MS/MS). Each analyte is likely to have a different postnatal temporal profile and curve, and each might have to be assessed independently according to the time after birth at which the specimen was obtained. Although it might be possible, at least in principle, to educate physicians about the vagaries of a single analyte, it will be impossible for any person to assess all of the analytes, especially if they fall within the normal published range. Unless this situation is addressed, there will be more cases of disorders missed on newborn screening.

What then must the newborn screening laboratory do to avoid this situation? We believe that there are several steps that may be necessary: (1) to the extent possible, the levels of analyte should be quantitated and not merely reported qualitatively; (2) the time at which the specimen collected must be clearly delineated; and (3) each newborn screening specimen will eventually have to be examined by a computerized algorithm that will highlight not only those analytes with clearly abnormal levels but also will flag those whose levels are near the

PKU Phenylketonuria
upper limits of normal, but which may have been performed at a suboptimal time. There are models for such algorithms, eg, prenatal marker screening, but ones for newborn screening are likely to evolve slowly and require knowledge and consensus that may not now exist. Moreover, some prominent large-volume laboratories now report results only as positive or negative and would have to make a profound change in their program. Until then, clinicians will have to be made vigilant in assessing the results of newborn screening, make judgments as best they can, and be aware that in the presence of suboptimal development that they cannot be sure that a screened-for disorder is not in fact at the basis for developmental problems. This is a plea for heightened awareness, not indiscriminate metabolic testing.
CONGENITAL LATEROCERVICAL COMPLEX MASSES: ARE THEY ALL LYMPHANGIOMAS?

In a 34-gestational-week female, a huge cervical cystic mass, already diagnosed at 27 weeks, was evacuated in utero just before cesarian section. However, a few minutes after birth, the baby developed respiratory distress and required tracheal intubation. The physical examination showed a soft, right inframandibular and cervical mass (Figure 1), with anterior and lateral distortion of the ramus of the mandible. At 2 weeks of age, ultrasonography, computed tomography, and magnetic resonance imaging revealed a giant, mixed mass with two densitometric different parts: a cystic superficial portion of $55 \times 45$ mm and a deep, microcystic-solid portion of $35 \times 25$ mm. The mass dislocated the trachea and the oropharynx and deformed the mandibular bone; no connection with the central nervous system was reported (Figure 2; available online at www.us.elsevierhealth.com/jpeds). The images suggested the diagnosis of a mixed macro-micro cystic hygroma of the neck and excluded the possibility of teratoma.

The mass was treated with repeated drainage of the macrocystic portion and injection of OK-432 (Picibanil; Chugai Pharmaceutical Co. Ltd, Tokyo, Japan), a sclerosing substance. At 5 months of age, the surgical mass was resected. Histology revealed the unsuspected diagnosis of heterotopic neuroglial tissue (Figure 3; available online at www.us.elsevierhealth.com/jpeds). During the following months, the right mandibular ramus remodelled, greatly improving the aesthetic result of the operation. At 12 months follow up, the girl is growing well, and at magnetic resonance imaging, the mass has not recurred.

Heterotopic neuroglial tissue masses are very rare, congenital benign tumors that cause dislocation of bones; on the other hand, lymphangiomas are more frequent, benign hamartomatous neoplasms that infiltrate soft tissues and bones without distorsion and dislocation of skeletal structures. In our case, the distortion of the mandibular bone could have guided us to the diagnosis of a heterotopic neuroglial tissue mass.
Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial


Context No current therapies exist to improve the outcome from neonatal encephalopathy. Experimental data have demonstrated benefit from cerebral hypothermia following hypoxia-ischemia.

Objective To determine the efficacy of selective head cooling with mild systemic hypothermia on survival free of severe disability at 18 months of age in newborn infants with moderate or severe hypoxic-ischemic encephalopathy.

Design Multi-center, international, unmasked, randomized controlled trial.

Setting Twenty-five perinatal centers in the United States, United Kingdom, New Zealand, and Canada.

Participants Term newborn infants of at least 36 weeks gestation (n=234) with clinical evidence of moderate to severe neonatal encephalopathy (based on modified Sarnat criteria) and/or seizures, and clinical evidence of perinatal hypoxia-ischemia (Apgar score of 5 or less at 10 minutes, continued resuscitation or respiratory support at 10 minutes, or severe acidosis within one hour of birth) and with moderately or severely abnormal background activity or seizures on amplitude integrated electroencephalography (aEEG).

Interventions Infants were randomly assigned within 6 hours of birth to either head cooling (cooling cap with water circulated at 8-12°C [Olympic Medical Cool Care System]) with concomitant mild systemic hypothermia (rectal temperature 34-35°C) for 72 hours, or to conventional care (rectal temperature 36.8-37.2°C).

Main Outcome Measures The primary outcome was death or severe disability at 18 months of age. Secondary outcomes consisted of potential adverse effects of cooling and complications of hypoxia-ischemia including death, arrhythmia, coagulopathy, hypotension, abnormal renal function, electrolyte disturbance, bone marrow depression, raised liver enzymes, and metabolic acidosis.

Results Baseline clinical and aEEG characteristics were similar in the two groups. In the 218 (93%) infants followed to 18 months, there was no significant difference in the primary outcome of death or severe disability in the infants treated with hypothermia (unadjusted: 55% vs 66%, P=0.10, OR 0.61 [95% CI 0.34-1.09]; adjusted [for baseline aEEG amplitude, presence of seizures, and age at randomization]: P=0.05, OR 0.57 [95% CI 0.32-1.01]), or on any secondary outcome measures.

Two predefined subgroup analyses based on pre-randomization background aEEG amplitude abnormalities demonstrated: a) no apparent effect of delayed cerebral hypothermia on outcome in infants with severe aEEG abnormalities (n=46: 79% vs 68%, P=0.51, OR 1.8 [95% CI 0.49-6.4]), and b) benefit in infants with intermediate (moderate) aEEG abnormalities (n=172: 48% vs 58%, P=0.021, OR 0.47 [95% CI 0.26-0.87]; adjusted P=0.009, OR 0.42 [95% CI 0.22-0.88]) and the number needed to treat was six infants (95% CI 3.27).

Conclusions Selective head cooling with mild systemic hypothermia is a feasible therapeutic maneuver without clear-cut evidence of benefit in selected infants with moderate or severe hypoxic-ischemic encephalopathy. It may, however, improve the outcome for encephalopathic newborn infants with intermediate (moderate) abnormality on aEEG background amplitude.

Comment This important, well-designed randomized controlled trial investigated the biologically plausible hypothesis that hypothermia will improve outcome in newborn infants who have sustained a peripartum hypoxic-ischemic insult and who are at significant risk of death and/or neurological sequelae. In the study overall there was no definite benefit of delayed selective head cooling with mild systemic hypothermia on adverse outcome at 18 months of age.

One rationale for using the aEEG was to select infants most likely to benefit from therapeutic hypothermia, although there was no pre-randomization stratification according to aEEG...
Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns


**Context** It is a challenge to predict which infants will need early follow-up for hyperbilirubinemia. The present authors previously developed a model using elements from the history and physical (exclusive breastfeeding, bruising, race, cephalohematoma, maternal age, sex, jaundice in previous sibling, and gestational age) to predict which infants would have a total serum bilirubin (TSB) of 25 mg/dL or higher.

**Objectives** (1) To validate the previously reported risk index for predicting TSB levels of 25 mg/dL or higher in a separate population of infants; and (2) to combine a subset of this index with TSB levels measured at less than 48 hours to predict subsequent development of TSB levels of 20 mg/dL or higher.

**Design** Nested case-control study using electronic and paper records (study 1). Retrospective cohort study using electronic records only (study 2).

**Setting** Northern California Kaiser Permanente hospitals.

**Participants** Subjects for both studies were newborns weighing ≥2000 g born at a gestational age ≥36 weeks. The validation study included 67 cases born between 1997-1998 who developed TSB levels of 25 mg/dL or higher at less than 30 days and 208 randomly-selected control subjects. Subjects for study 2 included 5706 newborns born between 1995-1996, who were discharged from the hospital and had a TSB level measured at less than 48 hours.

**Main Outcome Measure** Performance of the risk index, measured as the area under the receiver operating characteristic (ROC) curve.

**Results** The risk index was shown to be similar in the validation group and the derivation group (area under the ROC curve=0.83 vs 0.84, respectively). Of the 5706 newborns with TSB levels measured before 48 hours, 270 (4.7%) developed a TSB level of 20 mg/dL or higher. Of these, 254 (94%) had a TSB level at the 75th percentile or higher at less than 48 hours. Application of the risk index improved prediction over using TSB level alone, largely owing to the effect of gestational age. For example, for those infants with a TSB level at the 95th percentile or higher at less than 48 hours, the risk increased from 9% for newborns born at 40 weeks or more gestation to 42% for those born at 36 weeks.

**Conclusions** Clinical risk factors significantly improve prediction of subsequent hyperbilirubinemia compared with early TSB levels alone, especially in those with early TSB levels above the 75th percentile.

**Comment** Newman et al. statistically link the diagnostic performance of two tests: pre-discharge bilirubin (TSB) risk zone assignment and a clinical risk factor index to predict excessive hyperbilirubinemia (TSB ≥20 mg/dL and ≥25 mg/dL). Both predictive tests, as independent variables, intend to provide surrogate measures for the bilirubin load: a composite of bilirubin production plus enterohepatic circulation minus bilirubin elimination. The latter is often a "wild card" with a paucity of surrogate indices other than TSB. Validation for the discriminative ability of a combined approach would reinforce the time-honored dictums for clinical practice: relevant history, astute physical examination, and objective verification. The study design is limited by choices for outcome (dependent) and predictors (independent) variables and population sample to develop safer and validated predictive rules that achieve a sensitivity of 100% and a positivity criterion with the most optimal specificity. Some challenges to achieving that goal are listed here. First, based on perceived risks of neurotoxicity, well infants with TSB between 18 and 25 mg/dL (beyond age 72 hours) are in need of hospital-based intensive phototherapy and preparation for exchange transfusion; thus, an outcome severity. It is not evident why severely affected infants (based on aEEG criteria) were included as participants in this trial, when Gluckman et al. hypothesized that based on evidence from experimental models they were unlikely to benefit from this intervention. It may be one explanation for the overall negative result of this trial. More importantly, this study was not adequately powered to assess subgroup effects definitively.

The practical aspects of the selection of infants and the application of therapeutic hypothermia remain challenging. It is clear from experimental data that early initiation of therapeutic hypothermia is critical to its success, and yet the mean age at randomization in this trial was 4.8 hours. In addition, the participants are not easily recognizable, and the methods difficult to apply in everyday clinical practice. The majority of newborn infants around the world with hypoxic-ischemic encephalopathy are not born in tertiary care perinatal centers with aEEG monitors, or in centers with the expertise to apply or interpret the aEEGs. Further, many centers do not have access to the complicated type of cooling device used in this study, and probably never will. Results of current randomized controlled trials of therapeutic hypothermia of a more pragmatic design with straightforward clinical eligibility criteria, a simple method of cooling, and without the need for complicated equipment will be important.

As clinicians caring for infants with hypoxic-ischemic encephalopathy and its devastating sequelae, we want to embrace therapies that may help these infants and their families. Does this trial by Gluckman et al. provide the necessary evidence to initiate therapeutic hypothermia in all asphyxiated, encephalopathic newborn infants? Clearly, the answer is no. It does, however, give us a reason to continue and to participate in current trials, to await their results as well as their synthesis into systematic reviews, and, above all, to remain patiently optimistic.
variable should correspond to safer thresholds of hyperbilirubinemia (such as those recommended for initiation of home phototherapy). Second, clinical history and physical signs, as predictive factors, are limited by lack of standardized definitions, vagaries of charting, and propensity to observer error. Alternatively, Keren et al. report practice-based objective factors: use of vacuum aspiration and oxytocin induction in lieu of the frequently unrecognized or unrecorded cephalhematoma and bruising. Observer-independent factors identified by procedures (e.g., birthweight, vacuum assistance) allow for generalized results and avoid factors with inequity, such as “sibling with jaundice” as applied to the first-born infant, or “racial identity” as applied to a multiracial infant. In employing bilirubin screening and/or clinical risk measurements, measurement errors can arise and also affect predictive performance. Third, because simple interventions or aggressive management styles are likely to influence a pre-discharge hyperbilirubinemia experience, lack of consistent implementation and enforcement of pre-discharge guidelines during the course of the study is likely to influence the natural history of jaundice, and thereby the predictive performance of these tests. Actually, these two tests have a natural dynamic relationship rather than a static one as implied by the proposed linkage. Fourth, restrictions of infants to this study sample, a retrospective study with selective pre- and post-discharge TSB measurements for infants, who were presumably tested upon clinician’s recognition of jaundice, requires verification and introduces a spectrum bias: a form of selection bias. The sample also excludes a group of infants with very early onset of hyperbilirubinemia who were probably well managed at the study institutions, but who may not be identified at other birthing facilities. Finally, in such a select jaundiced population, the data may erroneously suggest a better performance, and therefore a higher area under the ROC curve. Prospective studies, regardless of jaundice recognition, would be useful to demonstrate the value of universally generated predictive rules, not merely to identify an infant who is at risk for severe hyperbilirubinemia (TSB >95th percentile), but to identify accurately and unambiguously, one who is not. Thus, infants with TSB <40th percentile, who have no (or minimal) clinical risk factors, may need a less rigorous follow-up than those who are suspected to be at any risk for severe hyperbilirubinemia. The challenge is to predict which infant needs early follow-up and ensure that a practicing clinician has no decision regret.

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REFERENCES

Effect of pneumococcal vaccination on quality of life in children with recurrent acute otitis media: a randomized, controlled trial


Context Limited effectiveness of current treatment strategies for recurrent acute otitis media (RAOM) and increasing antibiotic resistance have diverted attention to prevention of AOM by vaccination. Pneumococcal vaccination for AOM seems to have only modest clinical efficacy. Thus far, the effects on health-related quality of life (HRQoL) or functional health status (FHS) have not been studied.

Objective To assess the effect of vaccination on HRQoL or FHS.

Design Double-blind, randomized, controlled trial.

Setting Pediatric outpatient departments of a general hospital and an academic hospital in the Netherlands.

Participants 383 children 1 to 7 years old with RAOM.

Interventions Vaccination with either heptavalent pneumococcal conjugate vaccine followed by pneumococcal polysaccharide vaccine (pneumococcal group, n=190) or with hepatitis A or B vaccines (control group, n=193).

Main Outcome Measures Parents completed validated Dutch versions of 8 HRQoL and FHS instruments assessing generic FHS (Rand, Functional Status Questionnaire specific, and Functional Status Questionnaire generic), otitis media-specific FHS (OM-6), otitis media-specific child HRQoL (Numerical Rating Scale for Child), family functioning (Family Functioning Questionnaire), and otitis media-specific caregiver HRQoL (Numerical Rating Scale for Caregiver). Scores were compared at baseline and at 14 and 26 months’ follow-up.

Results At baseline, the average AOM incidence in the pneumococcal and control group was 5.0 (SD: 2.8) and 4.9 (SD: 2.6) episodes per year, respectively, with 38.4% and 36.8% having suffered from >6 episodes per year. AOM frequency decreased 4.4 episodes per year in both groups, with a considerable and comparable improvement in HRQoL and FHS. No substantial differences in HRQoL or FHS were found between the pneumococcal and the control group at baseline or at 14 or 26 months’ follow-up.

Conclusions Pneumococcal vaccination has no beneficial effect compared with control vaccination on either HRQoL or FHS in children 1 to 7 years old with RAOM.

Comment Immunization with pneumococcal conjugate vaccine (PCV) in infancy has proven highly effective in preventing invasive disease, but has proven only mildly effective in preventing acute otitis media (AOM). The authors conducted a randomized, controlled trial of pneumococcal vaccination in children aged 1-7 years with known history of recurrent AOM to investigate clinical endpoints as well as quality-of-life (QoL) measures (functional health status; health-related QoL).
Intervention and control children experienced similar declines in AOM rate during the study period, and QOL measures improved concomitantly (without significant differences between intervention and control).

Tracking QOL outcomes is common in instances where differences in clinical endpoints have proved elusive. The authors used parents as proxies for children's QOL measures, who are widely regarded as the most appropriate proxies but are not always used (some investigators use utilities estimated by physicians or other third parties). The problem with QOL measures in this trial, however, is that recurrent AOM occurred too infrequently to expect substantial variation in QOL in otherwise healthy children. QOL generally works better as a measure in individuals with chronic, not intermittent, conditions.

The negative findings of this trial suggest that continuing support for pneumococcal conjugate vaccination should be based on documented declines in rates of invasive pneumococcal disease in children and adults as well, rather than on effects related to otitis media.

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Oral versus intravenous rehydration of moderately dehydrated children: a randomized, controlled trial

Context Dehydration from viral gastroenteritis is a significant pediatric health problem. Oral rehydration therapy (ORT) is recommended as firstline therapy for both mildly and moderately dehydrated children; however, three-quarters of pediatric emergency medicine physicians who are very familiar with the American Academy of Pediatrics recommendations for ORT still use intravenous fluid therapy (IVF) for moderately dehydrated children.

Objectives To test the hypothesis that the failure rate of ORT would not be >5% greater than the failure rate of IVF. Secondary hypotheses were that patients in the ORT group will (1) require less time initiating therapy, (2) show more improvement after 2 hours of therapy, (3) have fewer hospitalizations, and (4) prefer ORT for future episodes of dehydration.

Design Randomized, controlled clinical trial (noninferiority study design).

Setting Emergency department of an urban children's hospital from December 2001 to April 2003.

Participants Children 8 weeks to 3 years old who were moderately dehydrated, based on a validated 10-point score, from viral gastroenteritis.

Interventions Patients were randomized to receive either ORT or IVF during the 4-hour study.

Main Outcome Measures Successful rehydration at 4 hours was defined as resolution of moderate dehydration, production of urine, weight gain, and the absence of severe emesis (>5 mL/kg).

Results 73 patients were enrolled in the study: 36 were randomized to ORT and 37 were randomized to IVF. Baseline dehydration scores and the number of prior episodes of emesis and diarrhea were similar in the 2 groups. ORT demonstrated noninferiority for the main outcome measure and was found to be favorable with secondary outcomes. Half of both the ORT and IVF groups were rehydrated successfully at 4 hours (difference: −1.2%; 95% confidence interval [CI]: −24.0% to 21.6%). The time required to initiate therapy was less in the ORT group at 19.9 minutes from randomization, compared with 41.2 minutes for the IVF group (difference: −21.2 minutes; 95% CI: −10.3 to −32.1 minutes). There was no difference in the improvement of the dehydration score at 2 hours between the 2 groups (78.8% ORT vs 80% IVF; difference: −1.2%; 95% CI: −20.5% to 18%). Less than one-third of the ORT group required hospitalization, whereas almost half of the IVF group was hospitalized (30.6% vs 48.7%, respectively; difference: −18.1%; 95% CI: −40.1% to 4.0%). Patients who received ORT were as likely as those who received IVF to prefer the same therapy for the next episode of gastroenteritis (61.3% vs 51.4%, respectively; difference: 9.9%; 95% CI: −14% to 33.7%).

Conclusions This trial demonstrated that ORT is as effective as IVF for rehydration of moderately dehydrated children due to gastroenteritis in the emergency department. ORT demonstrated noninferiority for successful rehydration at 4 hours and hospitalization rate. Additionally, therapy was initiated more quickly for ORT patients. ORT seems to be a preferred treatment option for patients with moderate dehydration from gastroenteritis.

Comment Evidence has been accumulating that oral rehydration therapy (ORT) is not inferior to intravenous therapy (IVT) and is more cost effective; however, for many reasons ORT is still underused in developed nations. This well-designed RCT is an important addition to the evidence as it demonstrates the non-inferiority in a North American Pediatric Emergency Department, the setting where ORT has had difficulty gaining acceptance. This study was of high quality because its authors noted and improved upon the limitations of studies previously done in the field, as evidenced by its method of randomization, use of allocation concealment, and accounting for all patients entered into the study. While a study in this area is impossible to double blind, the authors were innovative by being the first to blind treating physicians to treatment arms. New, previously unexplored outcome measures were defined, including time to initiation of therapy and number of unsuccessful vascular accesses. The question is no longer whether ORT is safe and effective, but rather how can child health care providers ensure that children, who deserve to
receive the painless and beneficial intervention of ORT, actually receive it.

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REFERENCES

Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials


Context Atopic dermatitis affects 15-20% of children and its treatment utilizes significant health care resources. Concerns about the safety of topical corticosteroids may affect patients' adherence to treatment.

Objective To determine the efficacy and tolerability of topical pimecrolimus and tacrolimus compared with other treatments for atopic dermatitis.

Design Systematic review and meta-analysis.

Main Outcome Measures Measures of efficacy: investigators' global assessment of response; patients' global assessment of response; proportions of patients with flares of atopic dermatitis; and improvements in quality of life. Measures of tolerability: overall rates of withdrawal; withdrawal due to adverse events; and proportions of patients with burning of the skin and skin infections.

Study Identification The authors electronically searched the Cochrane Library, Medline, and Embase for randomized controlled trials of topical pimecrolimus or tacrolimus. Trials were rated for methodologic quality and data was extracted by two authors.

Studies Reviewed 25 trials met inclusion criteria (11 for pimecrolimus and 14 for tacrolimus). 6897 participants were involved.

Results Both pimecrolimus and tacrolimus were significantly more effective than a vehicle control. Tacrolimus 0.1% was also more effective than hydrocortisone acetate 1% (NNT=4). Pimecrolimus 0.03% was more effective than hydrocortisone acetate 1% (NNT=5), but less effective than hydrocortisone butyrate 0.1% (NNT=8). Direct comparisons of tacrolimus 0.03% and tacrolimus 0.1% consistently favored the higher strength formulation, but efficacy differed significantly between the two strengths only after 12 weeks' treatment (rate ratio 0.80, 95% confidence interval 0.65 to 0.99). Pimecrolimus was far less effective than betamethasone valerate 0.1% (NNT=3 at three weeks). Pimecrolimus and tacrolimus caused significantly more skin burning than topical corticosteroids. Rates of skin infections in any of the comparisons did not differ.

Conclusions Both topical pimecrolimus and topical tacrolimus are more effective than placebo treatments for atopic dermatitis, but in the absence of studies that show long-term safety gains, any advantage over topical corticosteroids is unclear. Topical tacrolimus is similar to potent topical corticosteroids and may have a place for long term use in patients with resistant atopic dermatitis on sites where side effects from topical corticosteroids might develop quickly. In the absence of key comparisons with mild corticosteroids, the clinical need for topical pimecrolimus is unclear. The usefulness of either treatment in patients who have failed to respond adequately to topical corticosteroids is also unclear.

Comment Topical tacrolimus was initially studied in patients with moderate to severe atopic dermatitis. While it does seem to be moderately effective for these patients, it is clear that these agents are being used in patients with more mild disease. As pointed out by these authors, topical pimecrolimus appears to have no significant benefits over topical steroids. Topical tacrolimus may offer some benefit to some areas of the skin (notably the face and other areas where one would want to minimize high potency steroids) in patients with more significant disease. However, for most patients with atopic dermatitis, emollients and moderate potency corticosteroids will be effective, and at a lower cost. Concerns about the side effects of topical corticosteroids (skin thinning, potential for adrenal gland suppression) and general “steroid phobia” can affect adherence to treatment and need to be addressed with patients and families.

The long-term impact of topical tacrolimus and pimecrolimus is also unknown at this point. In March 2005, the US Food and Drug Administration issued a public health advisory regarding “a potential cancer risk from these agents, based on animal studies, a small number of case reports, and the drugs' mechanism of action.” Taken together, these concerns and the modest effectiveness of these agents would warrant limited use of in selected patients. At a minimum, a full discussion with families regarding benefits and risks is a necessity.
Objective assessment of pancreatic function in all patients with cystic fibrosis

To the Editor:

Borowitz et al. report the benefits of fecal elastase-1 to classify pancreatic status in patients with cystic fibrosis (CF), and Walkowiak emphasizes the importance of objectively ascertaining pancreatic function at the time of diagnosis irrespective of genotype. Although the authors point out that a “mild” mutation in the CF transmembrane conductance regulator gene does not exclude pancreatic insufficiency, clinicians need to be aware that a “severe” mutation does not always imply pancreatic insufficiency. At our tertiary care CF center, we have treated a male patient homozygous for delta F508 who presented at age 5 months with a productive cough and poor weight gain for the preceding 2 months. At age 19 years, he remains pancreatic sufficient with no symptoms of steatorrhea and with excellent weight gain (weight 98.8 kg and height 166.5 cm at age 19.5 years) and fecal chymotrypsin levels within the normal range. Although Borowitz et al. have not elaborated for their subjects, up to 4% of patients homozygous for delta F508 have been reported to be pancreatic sufficient in other studies.

In addition to defining pancreatic status in patients with a diagnosis of CF, fecal elastase-1 is also a useful investigation in children with poor weight gain and malabsorption, especially while awaiting a sweat test and CF gene analysis. Unlike a jejunal biopsy, fecal elastase-1 is noninvasive and helps differentiate exocrine pancreatic insufficiency from conditions such as celiac disease. Thus objective assessment of exocrine pancreatic function with a simple test such as fecal elastase-1 is important in all children diagnosed with CF, irrespective of genotype and whether neonatal screening or clinical manifestations led to the diagnosis, serial monitoring of pancreatic function in CF patients initially found to be pancreatic sufficient, and children being investigated for poor weight gain and malabsorption.

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REFERENCES

Reply

To the Editor:

Patel reports on a male patient with ΔF508 homozygous cystic fibrosis (CF) who at age 19 years is still pancreatic sufficient (PS), has no symptoms of steatorrhea, and whose fecal chymotrypsin is within the normal range. Stressing that the presence of “severe” CFTR mutations does not always imply pancreatic insufficiency (PI), Patel refers to 3 genotype-phenotype correlation studies. I fully agree that the presence of 2 severe CFTR mutations does not automatically imply, at least temporarily, the presence of steatorrhea in a subject with CF. However, pancreatic sufficiency is, in fact, rare in these patients. Keeping in mind the progression of PI in CF, clinicians should actively monitor for the possible changeover from PS to PI in those patients with CF with 2 severe CFTR mutations who are initially PS.

Lang et al. reported one case with PS among 163 subjects with ΔF508 homozygous CF (0.6%). In the study by The CF Genotype-Phenotype Consortium, 10 of 396 patients with AF508 homozygous CF (2.5%) were classified as PS. Exocrine pancreatic function was assessed exclusively by subjective methods in all subjects from the former study and in some patients from the latter study, which, in addition, did not document the absence of steatorrhea in an additional subset of patients. Moreover, some young patients with possible temporary or transient PS were also included. Therefore these data require confirmation. The importance of objective assessment of exocrine pancreatic function was nicely documented by Borowitz et al. The authors hypothesized and proved that some patients with CF are misclassified as PI. In addition, they documented that some patients were also misclassified as PS and consequently were not treated with pancreatic enzymes.

Kerem et al. assessed pancreatic function using reliable methods (pancreatic stimulation test and fecal fat balance study). In their study, 2 of 151 patients with CF who were homozygous for the ΔF508 mutation (1.3%) were documented to be PS. However, 12 years later the same group reported only one PS ΔF508 homozygous CF subject (0.2%) in a large cohort of their patients (1075 in total). In a Polish
multicenter study, no patients with this genotype were found to be PS. The measurement of fecal elastase-1 is simple, noninvasive, and reliable. However, the lack of differentiation between "primary" exocrine PI and exocrine pancreatic dysfunction caused by intestinal villous atrophy or duodenal atrophy is an important limitation of the fecal elastase-1 test. On the other hand, the fecal elastase-1 test is highly applicable in children with celiac disease on a gluten-free diet. In fact, villous atrophy also generally influences other indirect pancreatic function tests. Similarly, fecal elastase-1 concentrations may be low in acute episodes of diarrhea even when watery samples are excluded.

References


Does the effect of breast-feeding on atopic dermatitis depend on family history of allergy?

To the Editor:

Similar to the GINI group, we also studied the association between breast-feeding and atopic dermatitis (AD). We found no overall effects of exclusive or partial breast-feeding on risk of AD. However, the effect of exclusive breast-feeding for 4 months or more depended on parental history of allergic diseases. In children with no or one parent with allergic diseases (defined as self-reported history of asthma, hay fever, or AD), exclusive breast-feeding was associated with a slight increase in the risk of getting AD whereas among those with 2 parents with allergic diseases, there was a protective effect of breast-feeding.

Like us, the GINI group found no overall effect of exclusive breast-feeding for 4 months. However, in the intervention group, which consisted of children with 1, 2, or more family members with allergy, they found a significant protective effect of exclusive breast-feeding, whereas no such protective effect was found in the nonintervention group, which consisted mainly of children without a family history of allergy. The results might suggest a beneficial effect of exclusive breast-feeding in children with a family history, but no such effect in children without a family history, that is, a differential effect of exclusive breast-feeding depending on family history of allergy as found by us.

The authors stratified by family history of AD, but not on family history of allergy. They report that information about not only family history of AD but also asthma, hay fever, urticaria and food allergy was collected. Thus an analysis comparing the effect of exclusive breast-feeding in children with no, 1, or 2 parents with allergy should be feasible. We believe that such an analysis would add valuable information about whether our finding was a chance finding or indicative of a true differential effect of exclusive breast-feeding according to parental allergy.

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REFERENCES

Reply
To the Editor:

Dr Benn and colleagues present an interesting additional explanation for our finding that the protective effect of breast-feeding (versus cow’s milk formula) on atopic dermatitis (AD) is confined to the interventional subgroup. We followed their suggestions and stratified by parental history of atopic diseases (Table). In contrast to the analyses in our study,1 siblings were therefore not included in our stratification variable, and the atopic diseases definition comprised asthma, atopic dermatitis, and hay fever only, omitting the formerly used conditions urticaria and food allergy. In children of the interventional subgroup with a double-positive parental history of atopy, exclusive breast-feeding was associated with a decreased number of physician-diagnosed AD. However, in the noninterventional subgroup and the entire cohort, these associations were less clear than would have been expected from Dr Benn’s hypothesis. In our data, family history of atopy might possibly explain some of the differential effect in the interventional subgroup but is unlikely to explain all.

We also repeated the analyses stratified by parental history of AD (Table). There was no evidence of a differential protective effect of breast-feeding in those with a positive parental history of AD. Due to small numbers of children with a double-positive parental history of AD, stratification had to be based on any parental history of AD only. However, on the basis of the concept of gene-environment interaction, we would also expect the inverse associations between the environmental factor (breast-feeding) and AD to be more pronounced in children with a history of any parental AD than in children with no parental AD. Heredity of atopic diseases is strongest for the specific atopic disorders. Stratification on parental AD should therefore plausibly yield stronger effects than stratification on parental atopic diseases. We were intrigued by the thoughtful suggestions made by Dr Benn and colleagues. However, stratification by parental history of atopy cannot fully explain why the protective effect of breast-feeding on AD was only seen in the interventional subgroup and why stratification by parental atopy yielded stronger effects than stratification by parental AD.

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Reference

Cerebral infarction in diabetic ketoacidosis
To the Editor:
The report by Rosenbloom1 of a child with T1DM and heterozygosity for factor V Leiden who died of cerebral infarctions during diabetic ketoacidosis (DKA) raises several important points. The article stated that there is limited

Table. Association of exclusive breast-fed vs conventional cow’s milk formula during first 4 months and physician-diagnosed AD up to age 3 years by study group

<table>
<thead>
<tr>
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<th>Interventional subgroup</th>
<th>Non-interventional subgroup</th>
<th>Entire cohort</th>
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<tr>
<td></td>
<td>N</td>
<td>aOR (95% CI)</td>
<td>N</td>
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<tr>
<td>Parental atopy</td>
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<td>None</td>
<td>112</td>
<td>0.53 (0.16-1.82)</td>
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<td>2024</td>
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<tr>
<td>One/both parents</td>
<td>435</td>
<td>0.89 (0.49-1.63)</td>
<td>137</td>
</tr>
</tbody>
</table>

N: Number of observations in the model; Parental atopy, history of asthma, hay fever or AD in either parent; Parental AD: history of AD in either parent. aOR (95% CI): adjusted odds ratio with 95% confidence interval. Models are adjusted for geographic area, sex, maternal smoking first year, parental education, pets, introduction of solids during first 4 months.

Letters 129
information regarding coagulation factor abnormalities in this patient population. However, we have reported that children with uncomplicated but severe DKA have development of a prothrombotic state with a decrease in protein C activity and elevated levels of von Willebrand factor (vWF) antigen (Ag) and vWF activity both before and during treatment of DKA.\(^2\) Protein C activity and vWF (Ag) then reverted to normal by 96 hours after correction of DKA.

There is increased recognition that both hyperglycemia and DKA are accompanied by a proinflammatory state with elevated levels of cytokines, which also predispose to an acquired procoagulant state.\(^3,4\) The coagulation studies in this child limited to single determination, after correction of DKA revealed low protein C function and normal levels of protein S activity and factor VIII. An acquired procoagulant state contributing to the cerebral infarctions cannot be ruled out.

It is also important to note that both in vitro studies\(^5,6\) and clinical data\(^7\) indicate that cerebrovascular dysregulation occurs at several sites during DKA and its treatment. This supports the concept that cerebral thrombosis can occur unrelated to clinical cerebral edema. Thus it is likely that the cerebrovascular accidents in children with DKA are diverse in their pathophysiology.

In addition to special attention being given to the history of thromboembolic events in families of children with diabetes mellitus, studies involving a multispecialty approach are needed to develop prevention and treatment strategies for this therapeutic challenge and to improve the outcome of cerebrovascular crises in children with DKA.

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Reply

To the Editor:

The letter from Drs Carl, Ameri, and Hoffman provides interesting information about the prothrombotic diathesis of the ketoacidotic state, which amplifies the statement in my discussion that, in contrast to the extensively described abnormalities in coagulation factors in adults with diabetes, “The few studies in children with T1DM have described absence of coagulation factor abnormalities after metabolic stabilization.”¹

Obviously, the dehydration associated with diabetic ketoacidosis (DKA) increases the risk for thrombosis, as does any severe dehydration state, which in the case presented resulted in expression of a usually benign heterozygosity for factor V Leiden mutation. It is unclear whether the abnormalities that Carl et al²,³ have reported are primarily the result of dehydration or of the specific metabolic derangements of DKA. Nonetheless, cerebral thrombosis is, fortunately, a rare complication of DKA that may require subtle coagulation defects exacerbated by dehydration, as in my report. The few previously reported cases of cerebral thrombosis in DKA do not provide sufficient information about coagulation factors to implicate such an abnormality, but case series of cerebral venous thrombosis in children from various acute causes, including dehydration, indicate that thrombosis is unlikely to occur in the absence of background coagulopathy.⁴

Cerebrovascular dysregulation in DKA and the generation of pro-inflammatory cytokines may contribute to thrombosis or cerebral edema.⁵,6 Here again, however, demonstration of abnormalities in uncomplicated DKA describes the risk environment in which these rare events occur, but not their immediate cause.

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REFERENCES

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**Abstract.** Full-length papers for the Original Articles section of *The Journal of Pediatrics* must include a structured abstract of 200 words or less, to appear after the title page, in the general outline described by the Ad Hoc Working Group for Critical Appraisal of the Medical Literature (Ann Intern Med 1987; 106:598-604 and 1990; 113:69-76). The abstract must contain the following headings: Objective(s), Study design, Results, and Conclusion(s). The objective(s) reflects the purpose of the study, that is, the hypothesis that is being tested. The study design should include the type of study, the setting for the study, the subjects (number and type), the treatment or intervention, principal outcomes measured, and the type of statistical analysis. The results section should include the outcome of the study and statistical significance if appropriate. The conclusion(s) states the significance of the results.

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July 2005


August 2005

Charles E. Culpeper Scholarships in Medical Science, Goldman Philanthropic Partnerships is currently accepting applications for its 2006 Charles E. Culpeper Scholarships in Medical Science Program designed to support the career development of academic physicians.

Up to three awards of $108,000 per year for three years will be made to United States medical schools or equivalent United States educational institutions on behalf of candidates who are U.S. citizens or aliens who have been granted permanent U.S. residence (proof required), who have received their M.D. degree from a U.S. medical school or the equivalent of an M.D. degree from an educational institution equivalent to a United States medical school in 1997 or later, and who are judged worthy of support by virtue of the quality of their research proposals and their potential for successful careers in academic medicine. All scientific research relevant to human health is eligible for consideration; research that has relevance to cures for human disease is highly encouraged. No institution may nominate more than one candidate.

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Deadline for applications is Wednesday, August 17, 2005. Awards will be announced in January 2006, for activation on or about July 1, 2006. Application forms and instructions may be obtained on the Web at www.goldmanpartnerships.org or by contacting Amanda Morton, Charles E. Culpeper Program Manager, Goldman Philanthropic Partnerships, 155 North Pfingsten Road, Suite 109, Deerfield, IL, 60015, telephone: (847) 948-5512, fax: (847) 948-5516.

September 2005

World Congress of the World Society for Pediatric Infectious Diseases, “WSPID 2005,” Warsaw, Poland, September 1-4, 2005, Website: www.kenes.com/wspid, E-mail: wspid2005@kenes.com.

Pediatrics for the Practitioner - Update 2005, September 22-23, 2005, Johns Hopkins University School of Medicine, Thomas B. Turner Building, Johns Hopkins University School of Medicine Baltimore, Maryland. This conference is designed for pediatricians, family practitioners, pediatric nurse practitioners and physician assistants involved in providing primary care for infants, children and adolescents. The major focus will be on commonly encountered problems about which current controversies exist, and in areas, which recently have undergone changes in patient management.

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