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(Qaqundah et al, J Pediatr 2006;149:663-70)
A Preparticipation Screening Program Can Decrease the Incidence of Sudden Cardiac Death among Young Athletes

(JG Frohna, J Pediatr 2007;150:319-20)

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How do pediatricians deal with parents who smoke?

There is a growing body of evidence concerning the adverse effects of exposure to environmental tobacco smoke (ETS) in children. In fact, exposure to ETS is a leading cause of childhood morbidity and mortality. It is therefore reasonable to expect pediatricians to address the question of environmental tobacco smoke exposure with parents and to provide guidance on how to quit smoking.

In this issue of The Journal, Collins et al from Temple University and Children’s Hospital of Philadelphia investigated the current practice and attitudes of pediatric residents and their preceptors at a major academic children’s hospital. Results show that both residents and their preceptors intervened inconsistently and at fairly low rates. The most frequently cited barriers to their intervention were lack of time and low confidence in the effectiveness of interventions.

The authors conclude that training should be developed for pediatricians, and interdisciplinary collaboration facilitated with affiliated health professionals who might supervise intervention, referral, and follow up to sustain smoking behavior change. Collins et al are to be commended on their transparency. These findings are probably an accurate snapshot of current practice at many centers.

—Robert W. Wilmott, MD

Celiac disease and type 1 diabetes: To screen or not to screen?

Several groups have recommended that subjects with type 1 diabetes (T1DM) undergo screening for celiac disease (CD). In fact, serological screening for CD will yield positive markers in 10-15% of children with T1DM. However, because the vast majority of these individuals are asymptomatic, the question arises as to the value of screening and the benefit of early detection of CD. The long-term outcome for untreated, asymptomatic patients with CD, with or without T1DM, is not known. On the other hand, the contribution of variable nutrient intake and absorption due to concomitant CD on complications of T1DM (decreased bone mineral density, reduced growth, poor diabetic control) must be addressed.

Simmons et al evaluated the impact of screening-identified CD on growth, bone mineral density, and the course of diabetes. Weight, BMI, and anthropometric measures were reduced in patients with T1DM who were CD positive. There were no differences in height, bone mineral density, or in diabetes control indices.

In an editorial, Ivor Hill discusses the possible benefit of screening balanced against the negative impact and unintended consequences. It may be time to rethink the recommendations and to assess the true value of screening for CD in asymptomatic patients with T1DM.

—William F. Balistreri, MD
Abdominal obesity in prepubertal children

Excess fat in the abdominal region, which can be clinically demonstrated by increased waist circumference, has been associated with the metabolic syndrome and increased risk of cardiovascular disease and type 2 diabetes. However, overall adiposity is also associated with these abnormalities. It has not been completely clear, especially in children, whether the development of abdominal fat is associated with higher risk, what metabolic factors are associated with increased abdominal mass, and whether there are important developmental aspects to the increase in abdominal fat.

In this issue of The Journal, Barat et al report on a study of prepubertal French children. They found that after adjusting for total body fat mass, truncal fat was associated with fasting insulin levels. Truncal fat was also associated with morning plasma cortisol and, in girls, was negatively associated with the rise of cortisol after a standard meal. These cross-sectional results suggest that the hypothalamic-pituitary-adrenocortical axis may be involved in factors associated with the metabolic syndrome. This deserves future study with a longitudinal approach to better sort out the timing of these relationships and with the timing of puberty.

—Stephen R. Daniels, MD, PhD

Fish oil supplements and PKU

For patients with phenylketonuria (PKU), dietary treatment requires a limited natural protein intake and, therefore, a low intake of long-chain omega-3 polyunsaturated fatty acids (LC-PUFA). Despite the restricted phenylalanine intake, patients with PKU have demonstrable neurological deficits and may have impaired specific motor function. The mechanisms behind these less than perfect outcomes may, in part, be related to fluctuations in plasma phenylalanine levels. However, an unintended consequence of the diet may be to induce metabolic imbalance, specifically LC-PUFA deficiencies. Indeed, there is a wealth of recent data indicating the important role for LC-PUFA in neurological development and function.

In this issue of The Journal, Beblo et al report that supplementation of the “PKU diet” with fish oil (a rich source of LC-PUFA) normalized plasma levels of phospholipids (LC-PUFA) and improved motor skills. These results should stimulate further thought regarding the optimal nutrient intakes in children with PKU.

—William F. Balistreri, MD

Cerebral edema in DKA: First do no harm!

The development of cerebral edema during the acute treatment of diabetic ketoacidosis (DKA) is a rare but potentially devastating complication. Over the past few years, The Journal has published a number of studies that have attempted to elucidate the cause and prevention of this life-threatening disturbance.

In the current issue, our knowledge about cerebral edema in DKA is expanded upon with a careful observational study by Hoorn et al. These workers undertook a retrospective examination of data from cohorts of children treated at their center for DKA who either did or did not develop cerebral edema. The major difference noted between the two groups was an early drop in effective plasma osmolality in the cerebral edema group. The group that did not develop this fall in osmolality had either a smaller drop in plasma glucose, a slight rise in plasma sodium, or both. The cerebral edema group tended to receive more fluid early in treatment.

These observations are put into a very helpful perspective in an accompanying editorial by Friedman. Although it is likely that there are a host of causes of cerebral edema in DKA—indeed there may be vascular abnormalities at presentation that are predisposing—these publications suggest that the initial fluid therapy may play a role as well. This observation is somewhat in conflict with current consensus statements on the topic. From a practical standpoint, the thrust of these articles suggests that avoiding precipitous drops in plasma glucose, and avoiding overly aggressive rehydration, particularly with less-than-isotonic fluid, are important strategies in the management of DKA.

—Thomas R. Welch, MD

Obstructive sleep apnea and behavior

There have been many studies that have documented an association between obstructive sleep apnea and adverse behavior and developmental delay. There is no doubt that, in most cases, relief of upper airway obstruction results in improved sleep and reduced obstruction. Constantin, and others at Montreal Children's Hospital have completed an investigation of whether adenotonsillectomy for obstructive sleep apnea improves behavior. This was assessed retrospectively using the Conner's Parent Rating Scale-Revised. In the 138 complete questionnaires that were returned, compared to controls, parents of children who had adenotonsillectomy reported improvements in sleep, breathing, and quality of life, but no improvements in concentration, school performance, and intellectual or developmental progress, either short or long-term. The authors discuss the lack of improvement in behavioral outcomes and whether recall or observer bias could explain the lack of effect.

—Robert W. Wilmott, MD
Children with β thalassemia major have substantial psychosocial maladjustment

This issue of The Journal features two studies in which investigators have addressed some of the “non-medical” morbidity affecting children with chronic hematologic disorders and their families. In one, Klaassen et al describe the development and validation of a simple quality of life instrument specifically designed for use with children with acute and chronic ITP. There have been a number of new interventions described for these disorders, and the use of this instrument is another way in which studies can demonstrate one dimension of effectiveness of these. In the other, Saini et al, using a cross-sectional case-control validated questionnaire study design, show substantial psychosocial maladjustment and comparatively poor school performance in children with β thalassemia major. Findings are similar to those in children with other chronic conditions requiring continuous medical interventions.

The conclusions of these studies are clear. Screening and therapy for psychosocial morbidities should be an active and integral part of medical management for children with chronic disorders such as these. We now have increasingly sophisticated methods for undertaking this screening.

—Sarah S. Long, MD, and Thomas R. Welch, MD

Hyperthyroidism: Impact on bone

Thyroid hormone is known to result in increased osteoclastic activity, resulting in negative skeletal calcium balance and osteopenia in adults. The precise geometry of this bone loss, however, has not been clear.

As readers of The Journal know from a number of recent articles, although DEXA continues to be a popular measurement of bone density in children, the modality has significant limitations. Especially in growing children, quantitative CT (qCT) has the advantage of providing more detailed data on bone geometry.

With this background, Numbenjapon et al used qCT to examine bone in 18 children with untreated hyperthyroidism. These children had preferential loss of cortical bone as determined by this methodology. The authors provide a number of testable hypotheses which might explain this observation. Regardless of the underlying physiology, their study reminds us that bone mineral loss is a common accompaniment of hyperthyroidism in children as well as adults.

—Thomas R. Welch, MD

Ventilation with CPAP

Continuous positive airway pressure (CPAP) is being used more frequently as the initial therapy for preterm infants with respiratory distress syndrome (RDS). Failures occur because of the need to treat progressive RDS with surfactant and because of apnea and inadequate breathing effort. An advancement in conventional ventilation for infants with RDS has been the ability to synchronize the mechanical ventilatory cycle with the infant’s inspiratory effort. A number of reports suggest that a mechanical ventilatory cycle can be superimposed on nasal CPAP with the goal to assist spontaneous ventilation and to avoid intubation and traditional mechanical ventilation.

Kugelman et al report a single site trial of CPAP in comparison to CPAP plus nasal mechanical ventilation for infants with RDS. The supplemental mechanical ventilation decreased the number of infants requiring intubation and decreased bronchopulmonary dysplasia. A weakness of the study was the lack of validation of the effectiveness of synchronization of the ventilatory cycles with spontaneous ventilation. This report is an example of the foment in the field of neonatal ventilation to develop new devices and strategies to improve outcomes.

—Alan H. Jobe, MD, PhD
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18th Annual Spring Conference on Pediatrics. May 16-19, 2007, Marriott Frenchman’s Reef Beach Resort, St. Thomas, United States Virgin Islands. Sponsored by Symposia Medicus. For more information, contact Symposia Medicus; phone: 925-969-1789, 800-327-3161; E-mail: info@symposiamedicus.org; Website: www.symposiamedicus.org.

July 2007

29th Annual Aspen Conference on Pediatric Gastrointestinal Disease: Pediatric Gastrointestinal Disease and Intestinal Transplantation. July 22-27, 2007, Snowmass Conference Center, Snowmass (Aspen), CO. Sponsored by Cincinnati Children’s Hospital Medical Center. The conference will be devoted to the diagnosis and management of gastrointestinal disease in children. Specific topics include inflammatory bowel disease (diagnosis, complications, and management), diarrhea (acute and chronic), celiac disease, h. pylori and peptic ulcer disease, gastroesophageal reflux, abdominal pain/irritable bowel syndrome, constipation, obesity and NAFLD/NASH, TPN-associated cholestasis, allergic gastroenteropathies, motility disorders, short gut syndrome/NEC, pancreatic disease/cystic fibrosis, and various aspects of small bowel transplantation. For more information, contact Laura Werts, CME Office, Cincinnati Children’s Hospital Medical Center; phone 513-636-6732; E-mail: laura.werts@cchmc.org; Website: www.cincinnatichildrens.org.

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Leadership in Academic General Pediatrics

TINA L. CHENG, MD, MPH, AND PETER G. SZILAGYI, MD, MPH

As the environment in academic medicine becomes increasingly complex and as new healthcare delivery systems, technologies, and scientific advances stimulate change, the need for effective leaders becomes paramount. Leadership has been defined as “creating the future by initiating and sustaining change in areas where there is no precedent, as well as seizing the opportunities offered in the present.”

There is emerging interest and movement toward physician leadership. Physicians, however, receive little training in administrative, management, and leadership skills. Medical school and residency education changes lag behind clinical practice and system change. Lane and Ross state that “physician leadership is critical for attaining balance among conflicting pressures for quality of care versus cost containment, prevention versus high-technology medical intervention, and application of specialized versus primary care.”

The changing landscape for children and adolescents highlights unique issues requiring leadership. The growing number of children in poverty, threats to health insurance coverage, and the rising burden of chronic physical, mental, and social disorders all directly affect clinical care. Clinical programs increasingly consist of multidisciplinary teams with physicians as leaders but others as experts in specific fields. Similarly, funding of the education and research missions in pediatrics is precarious. Successful research programs have become multi-faceted, requiring leaders who manage people as well as scientific investigation.

More than 15 years ago pediatric leaders highlighted the emerging role of the division chief. Fiser noted that “division leaders in academic medicine today must have many of the preferred requirements for chief executive officers of large corporations . . . [they] must have some working knowledge of business administration, must be sensitive to the changing circumstances of the medical marketplace, and must also understand that marketplace pressures cannot be permitted to detract from or interfere with the work of individuals in research, excellence of care, or teaching.” Stapleton added: “Division chiefs are expected to develop clinical programs, administer budgets, supervise office personnel, educate medical students and residents, recruit faculty, develop research programs, train subspecialty fellows, and maintain their personal academic productivity.”

NEED FOR LEADERSHIP TRAINING IN AGP

Academic General Pediatrics (AGP) is a relatively new field, having established its national organization—the Ambulatory Pediatric Association (APA)—in 1960. AGP has progressed through the 1990s when the field was characterized as potentially “endangered,” to its current state as an established field facing new challenges of expansion and integration with other fields within healthcare. General pediatric divisions play a significant role in clinical care, education, research, and advocacy in their institutions. The generalist orientation, including individual and population health, research translation to practice and policy, and a broad view of health systems, is critical for our nation to achieve Healthy People 2010 goals of improving quality of care and eliminating disparities in health.

Leadership in visioning and preparing for the future is a continuing challenge. Workforce concerns include declining resident interest in primary care and in academic fellowships, reduction in funding of Title VII primary care programs that support many training efforts including fellowships, and concern that many fellowship-trained pediatricians are choosing clinical-oriented careers rather than traditional academic careers. As a relatively young field with predominance of junior faculty in AGP divisions, leadership development is of particular importance.

Turnover rates of leaders in pediatrics emphasize the need for leadership development and succession planning. A recent survey of pediatric department chairs found that the mean annual turnover rate was 17%. A survey of division directors of AGP divisions found a similar rate with many interim directors. Not surprisingly, when AGP division directors were asked about training needs, leadership skill development was most frequently mentioned. A recent survey of the 1800 APA members asked about new initiatives APA might sponsor to support their professional goals. Leadership skills were frequently mentioned including “training on how to run a division” and “faculty development programs that can be replicated and potentially offered regionally.”

From the Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland (T.L.C.); and the Department of Pediatrics, the University of Rochester School of Medicine, Rochester, New York (P.G.S.).

(J Pediatr. 2007;150:451-2)
NEW SKILLS FOR FUTURE LEADERS

McKenna and Pugno delineate four types of physician leadership needed in healthcare today including leadership to enhance clinical excellence, promote organizational effectiveness, advance and disseminate evidence-based innovations, and advocate for reform of healthcare policy, laws, and regulation. Much literature exists on healthcare leadership but less on competencies specific for physician leaders. Some have delineated physician competencies to include skills in communication, leadership, interpersonal skills, self-motivation/management, organizational knowledge, organizational strategy, administrative skills, and thinking. One survey noted that interpersonal and communication skills, professional ethics, and social responsibility were most important for effective physician leadership.

Leaders of today need to be more knowledgeable and sophisticated to function in an increasingly collaborative and global world and to lead new technological and scientific initiatives. Training needs focused on the changing healthcare environment include quality assurance, clinical benchmarking, decision-making, strategic planning, communication skills, organizational change, effective listening, and systems thinking. Medical practice executives identified key future needs including a population and broad perspective on healthcare, strong planning, conflict management, financial management, team building, and communication skills.

In AGP there are particular leadership skills relevant for future roles. Emerging roles for primary care pediatricians include chronic care coordinators, multidisciplinary team players, genomic interpreters, community collaborators, and hospitalists. These roles suggest that team building, and interpersonal and cross-disciplinary communication skills may be particularly important.

Leadership skills have been described as the “process skills that provide the framework for accomplishing all other professional responsibilities.” General skills are critical; however, a challenge in leadership training is making it relevant across disciplines and to local circumstances. Training must include specific technical skills, reflection and enhancement of personal leadership characteristics, and must emphasize application across disciplines and institutions.

THE LEADERSHIP TRAINING “GAP”

Though record numbers of physicians are earning degrees in management, business, health administration, and public health, many in MD dual degree programs, concern remains about a leadership “gap.” Management, administration, and leadership training is not a formal part of medical training despite the importance of these skills in practice. Some suggest that training of clinicians and managers is culturally different in norms and values. For instance, clinicians are trained to be autonomous decision-makers, whereas managers are planners, team players, and delegators. Schwartz also notes that private industry focuses on the internal development of leaders, whereas academic medicine fills many leadership positions by outside recruitment, potentially disrupting continuity of institutional goals. It is widely recognized that leadership skills can be taught and medicine must transcend cultural differences and develop leaders.

Current leaders are often chosen because of excellence in clinical care, teaching, or research, not necessarily for demonstrated administrative or leadership skill. Although leadership programs have been developed at some institutions or through organizations such as the American College of Physicians Executives and the Association of American Medical Colleges, many leaders have not had the benefit of this training and much learning occurs experientially on the job. Many advocate that the undergraduate medical curriculum introduce and reiterate topics of healthcare economics, organizational behavior, financial imperatives, outcome measures, and leadership training.

Developmental educational opportunities must address the leadership gap and focus on other leadership gaps including women and minorities.

STRATEGIC PLANNING FOR THE FUTURE

The need for leadership development in AGP has led to the convening of the first National Leadership Conference in Academic General Pediatrics in Spring 2007. The APA has led this effort with involvement of the American Medical School Pediatric Department Chairs, Inc. (AMSPDC) leadership. This conference targets division directors, current and future leaders in AGP, will teach leadership skills and discuss the future of AGP. Department chairs were asked to nominate current and future leaders to participate in the conference, and the response has been overwhelming. In pediatrics, other leadership development efforts have been initiated including the American Academy of Pediatrics’ Pediatric Leadership Alliance. These efforts offer models for ongoing planned efforts to develop leaders to influence the future.

Leadership conferences, however, are not enough. Ongoing development that addresses general, discipline, and institution-specific issues are needed. Education on leadership must be developed as a core competency and begun in medical school. Multimodal methods for training beyond degree programs and conferences must be developed and evaluated including Web training, mentoring programs, and community service experiences. Some feel that coaching or mentoring from an experienced leader and on-the-job experience are the most effective means for developing physician leadership. Leadership training requires a commitment of resources and release time for individuals to develop expertise. Finally, academic physician leaders often require unique skills and different measures of academic productivity. This role must be valued and recognized in academic promotion.

Although recent activity in leadership development is promising, research is needed on its effectiveness including the knowledge, skills, and attitudes necessary for change. There has been progress in the development of evaluation measures of pediatric leadership training, however more work is needed on outcomes. Long-term tracking of individuals and outcomes and developing best practices must be part of this effort. To address the future, continuous strategic planning and quality improvement mechanisms, creation of developmental opportunities for future leaders, and explicit succession planning are crucial. Forward-thinking leaders and their development are of strategic importance for improving the health of children, adolescents, and families.

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Serologic Testing for Celiac Disease: Primum Non Nocere!

The decision to place a child on a strict gluten-free diet (GFD) for life should not be taken lightly. For the family, it involves a modification of their daily lives with significant additional expense. For the children, it has potential quality-of-life implications, setting them apart from their peers and forever impacting their social interactions. In symptomatic children with histologically confirmed celiac disease (CD), the benefits of maintaining a strict GFD are irrefutable. In the short term, there will be complete symptom resolution with repair of the intestinal mucosal damage. In the long term, there should be normal growth and development and the same expectations for health as in the general population. In contrast, the benefits of maintaining a GFD for those who are asymptomatic and identified with CD through a serological screening program are less clear.

There are certain groups of persons at increased risk for CD.\(^1^2\) These include first-degree family members of an index case and those with specific autoimmune and non-autoimmune conditions. Of the autoimmune conditions associated with CD, type 1 diabetes (T1D) is best known, with up to 12% being affected. Many persons with CD in at-risk groups are asymptomatic at the time of diagnosis. Such cases were initially identified during studies using serological tests to screen for the condition, and, consequently, it has become common practice to test all persons in at-risk groups, even if they are asymptomatic. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) advocates such a policy in their Clinical Practice Guidelines on CD.\(^1\)

The National Institutes of Health (NIH) Consensus Statement on CD also recommends screening asymptomatic at-risk persons but excluded those with T1D\(^3\) because there are no data to show that treatment of those with diabetes with asymptomatic CD has any benefit in the short term. Neither NASPGHAN nor the NIH advise mass screening of the general population for CD, even though as many as 1% may be affected, and this approach would probably not be cost effective.

The major reason for recommending testing of asymptomatic persons stems from the belief that early identification and treatment of CD will prevent long-term adverse health consequences. These include an excess in mortality rate, increased rates of malignancies (particularly intestinal lymphoma) and osteoporosis, and possibly onset of other autoimmune diseases.\(^2^4\)\(^6\) In children, there is concern that delays in treatment may permanently stunt growth. Based on standardized mortality rates, there is an excess of deaths associated with CD.\(^4\) However, this seems confined to those with severe symptoms of malabsorption who had delayed diagnosis and poor compliance with treatment.\(^4\) Persons with mild symptoms or symptomless CD had no excess mortality.\(^4\) Intestinal malignancies are relatively more common in those with untreated CD, but recent data suggest the relative risk for such malignancies is lower than initially reported.\(^5^6\) In terms of absolute numbers, intestinal lymphomas are relatively rare and account for a small proportion of all malignancies.\(^5\) Most malignancies in persons with CD occur in those with symptomatic disease who remain untreated, and there are little data demonstrating asymptomatic persons are at increased risk for cancer. Similarly, many patients with symptomatic CD have decreased bone mineralization at the time of diagnosis, but there are little data on the prevalence of osteoporosis in asymptomatic persons. Finally, the data suggesting that early diagnosis and treatment of CD can prevent onset of other autoimmune diseases are relatively weak.\(^6\) Although this is an attractive theory, there is need for more robust data before such a concept can be accepted.

The study by Simmons et al reported in this issue of The Journal attempts to address the need for testing children with T1D.\(^8\) By looking for antibodies to tissue transglutaminase (TG) in children with T1D they identified 71 TG+ subjects and compared them with 63 TG− controls matched for age, sex, and duration of diabetes. TG+ subjects were advised to undergo small intestinal biopsy to confirm the diagnosis of CD. The groups were compared for height, weight, body mass index (BMI), triceps skinfold thickness, and midarm circumference using age- and sex-specific Z scores. Additional comparisons included measures of bone mineral density and markers of...
bone turnover rates, HbA1C levels, records of insulin requirements, hypoglycemic events, and thyroid function tests. A subgroup analysis for these measurements compared those who agreed to have a biopsy and had characteristic histologic features of CD (n = 35) with TG− subjects matched for age, sex, and duration of diabetes. A symptom questionnaire was administered to all subjects.

TG+ subjects had lower weight, BMI, and midarm circumferences Z scores but no difference for height and skinfold thickness scores. Comparing those with biopsy-confirmed CD with TG− subjects; only the BMI scores were lower in the TG+ group, and there was no longer a difference in weight and midarm circumference scores. The groups were similar for bone mineral density, but the TG+ subjects had increased parathyroid hormone and urine n-telopeptides levels suggesting possible increased bone resorption. TG+ subjects had lower levels of free T4 and thyroid stimulating hormone, but the clinical significance of this finding is uncertain. There was no identifiable difference between the two groups for glucose control or frequency of hypoglycemic episodes. TG+ subjects reported an increased frequency of symptoms, but this finding is open to bias as the questionnaire was administered only after the subjects were identified as TG+ or TG−. There was no comparison between truly asymptomatic TG+ and TG− subjects.

Does this study clarify whether all children with T1D should be screened for CD? Unfortunately not, and the authors acknowledge this fact. On the other hand, the results also do not permit us to renounce the recommendations of NASPGHAN and other authorities in the field. In their discussion, the authors note that available data on growth effects of CD in children with T1D are conflicting, as are those relating to impact of CD on glycemic control.9,10 One study has shown improved growth rates on a GFD over a 2-year period in children with T1D and CD.11 However, most of the subjects with CD in this report had symptoms before starting treatment, and therefore the results may not apply to the truly asymptomatic person. There are some who question the benefits of screening all children with T1D for CD.12 First, by labeling them with a second chronic illness requiring another significant lifelong diet change, we may be imposing an unnecessary psychological burden on some children. Second, because asymptomatic children identified through screening programs are less likely to be compliant with the GFD, subjecting them to an intestinal biopsy may place them at unnecessary risk. Similar concerns regarding the benefit of CD screening in children with Down syndrome have also been raised recently.13

As physicians, we constantly make treatment decisions that have the potential to significantly impact the lives of our patients. In doing so, we weigh the potential benefits against the possible risks. When the benefits clearly outweigh the risks our treatment decisions are justified. This approach embodies the principle of primum non nocere—first do no harm. With this in mind, perhaps it is time to reconsider the recommendations to screen asymptomatic persons for CD. We simply do not yet know the natural history of CD in such cases. Prospective studies comparing asymptomatic, screening-identified patients who maintain a strict GFD with those who do not are much needed. In addition, solid data are essential to justify the need for a strict lifelong GFD and to convince our patients to comply. A recent review and medical position statement issued by the American Gastroenterology Association (AGA) does not recommend routine testing of asymptomatic persons belonging to an at-risk group.14 Instead, the American Gastroenterology Association recommends testing when there are symptoms of CD. Physicians need to appreciate the variable clinical manifestations and know the conditions associated with CD. Testing those belonging to an at-risk group only when they have symptoms is a reasonable consideration until there is good evidence to recommend otherwise.7

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REFERENCES
Choosing the Right Fluid and Electrolytes Prescription in Diabetic Ketoacidosis

The acute management of children with diabetic ketoacidosis (DKA) is a complex blend of urgent therapy and underlying disease management. A serious, potentially life-threatening complication of DKA and its treatment is cerebral edema.1

Cerebral edema in DKA usually is noted within 12 hours after therapy begins.2 Some have suggested that cerebral edema may be present before the start of therapy.3 The etiology of cerebral edema in DKA is complex, with ischemia and reperfusion, inflammation, increased blood flow, intracellular osmolyte generation and osmotic “imbalance,” and cytotoxins all implicated. Risk factors associated with the development of cerebral edema include: new onset type 1 diabetes mellitus, younger age, longer duration of symptoms, severity of acidosis, greater hypocapnia, and elevated blood urea nitrogen.3,4 Physicians caring for a child with DKA reasonably are concerned with assuring that treatment does not worsen the outcome. The hallmarks of treatment—provision of fluids, electrolytes, and insulin—are at the same time life-saving and potentially life-threatening. The article by Hoorn and colleagues5 points to observations regarding fluid therapy and cerebral edema in children with DKA. These observations fall into two categories: (1) those that corroborate previously published information; and (2) those that advance or may advance our understanding of cerebral edema in DKA.

CORROBORATIVE INFORMATION

The study compares patients with DKA and clinical and/or imaging evidence of cerebral edema with control patients with DKA and hypernatremia but no cerebral edema, and with control patients with DKA, no hypernatremia, and no cerebral edema. The demographic and biochemical/hemodynamic data in the article show that the patients with cerebral edema and the control without cerebral edema but with hypernatremia, were younger (smaller), had a higher serum glucose at presentation, had somewhat lower blood pressures, and had higher blood urea levels than the control nonhypernatremic, no cerebral edema patients. Serum pH was not different among the three groups. Interestingly, the hematocrits of patients with DKA, no cerebral edema, and no hypernatremia at admission were higher than the cerebral edema group or hypernatremic, noncerebral controls. This presumably is because of the lower serum glucose and blood urea levels found in the no cerebral edema, no hypernatremia group, and therefore a smaller shift of water from the intracellular space to the extracellular and plasma spaces.

OBSERVATIONS THAT MAY ADVANCE OUR UNDERSTANDING

The article by Hoorn et al5 found that children who developed cerebral edema were more likely to receive an insulin bolus of ≥0.1 units/kg and were more likely to receive more fluid and more solute in the first 6 hours of therapy than patients who did not develop cerebral edema. Further, the fluid-given patients who developed cerebral edema were of a lower tonicity than the controls. The consensus statement of the European Society of Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society published in 20046 states: “There is little evidence, however, to show associations between the volume or sodium content of intravenous fluid” and the development of cerebral edema. The observation by Hoorn and colleagues does provide evidence to suggest that the fluid volume and sodium content of IV fluids may impact the risk of cerebral edema. Indeed, as the Hoorn et al article states, “A more moderate regime (fluids and electrolytes) may therefore be advisable if there is no compelling evidence to be aggressive.” The consensus statement6 also says “there is evidence that an attenuated rise in measured serum sodium concentrations during therapy for DKA may be associated with increased risk of cerebral edema.” Here, too, the article by Hoorn et al5 adds to our knowledge. A gradual decline in effective plasma osmolality as reflected by a decrease on serum glucose and a concomitant increase in serum sodium appears to decrease the likelihood of cerebral edema. This finding may not teach us precisely why cerebral edema occurs or progresses in children with DKA. Many of the proposed pathogenic mechanisms or risk factors may be in place when the patient presents to the physician. Our responsibility is to assure that the therapy we provide does not exacerbate the risk of cerebral edema. Here attention to insulin therapy and the fluid and electrolyte prescription (both therapies over which we have control) become important in reducing the risk of cerebral edema associated with DKA.

The study by Hoorn et al is descriptive. The observations are from two sites over a period of 11 years. It was not possible to match controls so as to single out the effect of a slow fall in effective plasma osmolality alone. The authors admit they could not control for...
oral intake of fluids among the groups. Oral intake could have been different enough to influence outcomes. Nonetheless, the study affirms that fluid and electrolyte therapy during DKA should restore extracellular volume—but not too aggressively or quickly. Second, it confirms that fluid therapy should aim to decrease gradually the effective plasma osmolality. This gradual decrease is manifest by an increase in the serum sodium concentration. Hypernatremia per se may not protect against cerebral edema, but it may indicate that the effective plasma osmolality is falling at a rate that reduces the risk of developing cerebral edema. Such an approach is prudent and could further reduce the risk of cerebral edema in DKA.

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Muscle Memory

In this issue of The Journal, Cyrulnik et al report that patients with Duchenne muscular dystrophy (DMD) often have delayed milestones, both language and motor.1 This is the first systematic study of a large cohort of patients to document that early delay does occur and can be correlated with later cognitive function.

The year 2006 marked the 20th anniversary of the discovery of the dystrophin gene and mutations that cause DMD and the allelic disorder, Becker muscular dystrophy (BMD).2,3 In the 2 decades since, we have seen molecular explanations for facts we knew but didn’t understand, such as holes in the sarcolemma visible at the electron microscopic level. We have also learned some new things, such as there are many patients with BMD who have no weakness, but present with other manifestations such as cardiomyopathy or autism.4,5 This knowledge has reinforced a concept that, although progressive muscle weakness is the hallmark of DMD/BMD, it is a multi-system disease.

Although the association between DMD/BMD and cognitive deficits was recognized in the earliest clinical descriptions, the role that dystrophin deficiency might play in brain dysfunction remains a mystery. Debate in the 1970s centered on whether the cognitive deficit was progressive and somehow related to loss of mobility and socialization; we now know this is not true (Hinton; personal communication). Studies of brain structure yielded little information, but positron emission tomography studies suggested a relationship between glucose utilization and dystrophin deficiency in the cerebellum.6 Few studies focused on the specifics of clinical brain dysfunction in DMD/BMD.

However, the cognitive deficits seen in DMD/BMD are not seen in other neuromuscular disorders. Spinal muscular atrophy, another common cause of weakness in infancy and childhood, is associated with excellent higher cortical function and often advanced language development.7 Likewise, children with various forms of congenital myopathies tend to perform extremely well academically.

Cyrulnik et al previously showed that DMD is associated with significant deficits in verbal memory that can explain poor school performance.8 Now, as part of their large and ambitious study of cognitive function in DMD, they have focused in this report on developmental milestones. Most neuromuscular specialists who care for patients with DMD know empirically that boys who are affected often have a history of delayed milestones and, in particular, language delay.

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However, many families experience inappropriate diagnosis and management because of failure to recognize the presence of the muscular abnormality before they get to the neuromuscular specialist. It is very important that pediatricians be aware that DMD is a common cause of developmental delay and school failure in the absence of or before the development of weakness. Serum creatine kinase levels should be included in the first screening tests for boys with developmental delay; creatine kinase screening is a cheap and quick test that will always have abnormal results in DMD/BMD during the first decade of life. Moreover, newborn screening and early diagnosis might make it possible to enroll young affected boys in early childhood intervention and appropriate classroom placement by age 3 years.

Although treatment with prednisone has been very effective in slowing the progression of weakness and preventing some of the medical complications of DMD, steroids may disrupt school performance by causing decreased attention span and irritability. The authors of the report by Cyrulnik et al do not mention whether any of their patients were taking steroids at the time of neuropsychological testing. It is clear from their work that the search for new treatments as effective as prednisone should include a consideration for effects on cognitive function, especially verbal memory.

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Omega-3 Long-Chain Polyunsaturated Fatty Acids in Older Children

Phenylketonuria (PKU), the most prevalent inborn error of metabolism, is usually caused by low hepatic activity of phenylalanine hydroxylase, the enzyme that catalyzes conversion of phenylalanine to tyrosine. It is characterized by a high plasma phenylalanine concentration and, in the absence of adequate tyrosine intake, a low plasma tyrosine concentration. Management of patients with PKU includes early detection, primarily by mandatory neonatal screening programs, followed by a low protein diet supplemented with a low-phenylalanine or phenylalanine-free formula. Frequent monitoring and appropriate dietary changes in response to this monitoring are necessary to maintain plasma phenylalanine and tyrosine concentrations within the desired range.

Growth and development of infants and children with PKU who are treated as aforementioned do not differ appreciably from population norms. However, the IQ of treated children with PKU is somewhat lower than that of their unaffected siblings. These children also perform less well in school than their unaffected siblings, they tend to exhibit more behavioral problems, and they have problems concentrating. However, current outcomes of infants and children with PKU are far superior to the severe psychomotor retardation that occurs without treatment.

A major question concerns the extent to which the residual developmental deficits of optimally treated infants and children with PKU are an inevitable consequence of the condition. A study reported by Beblo et al in this issue of the Journal suggests that at least...
some of the residual deficits can be further reduced or perhaps abolished by dietary supplementation with fish oil, a rich source of omega-3 long-chain polyunsaturated fatty acids (LC-PUFA), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The latter fatty acid has received considerable attention in the past 20 years. It is present in high concentrations in the developing brain and retina, and failure to provide a dietary source of this fatty acid results in low plasma, erythrocyte, and brain lipid levels of DHA. Many studies also show that failure to provide a dietary source of DHA adversely affects cognitive and visual development. Thus, most infant formulas throughout the world contain DHA or this fatty acid plus arachidonic acid (AA). The amounts present reflect the content of these fatty acids in human milk. Although most studies have involved short periods of supplementation during early life, usually for only a few months and almost never beyond the first year of life, these supplemented formulas appear to be safe.

Despite the rate of deposition of DHA in the developing brain not slowing appreciably until well after a year of age, little is known about the need for a dietary source of this fatty acid in children older than 12 to 18 months. This is unfortunate, because the endogenous production of DHA from its precursor, alpha-linolenic acid, is thought to be inefficient, and intake of preformed DHA (eg, fish) by most children (and many adults) is quite low.

Beblo et al studied 1- to 11-year-old (mean, 6.3 ± 0.6 years) children with PKU who had been in good metabolic control for at least 6 months and a control group of unaffected age- and sex-matched children. After determining plasma phospholipid fatty acid pattern and administering the motoric Rostock Oseretzki Scale, a standardized scale that assesses coordination and fine motor skills of children between 4 and 11 years old, the patients received fish oil (approximately 15 mg/kg/d of DHA and 22.5 mg/kg/d of EPA) for 90 days, after which the baseline studies were repeated. Baseline plasma phospholipid DHA content of both the children with PKU and the control subjects was low but not different from that of a reference population from the same geographic region. Fish oil supplementation of the children with PKU resulted in a 3-fold increase in plasma phospholipid DHA content, an 8-fold increase in plasma phospholipid EPA content, and a 25% decrease in plasma phospholipid AA content. Baseline performance assessed with the standardized test of coordination and fine motor skills was within the reference range in both patients and control subjects, but performance of the children in the control group was better than that of the children with PKU. However, after fish oil supplementation, performance of children with PKU was markedly improved, whereas the performance of control subjects (who did not receive fish oil or have plasma phospholipid fatty acids repeated) was not different from baseline.

These investigators and other groups have previously shown that omega-3 LC-PUFA supplementation of patients with PKU lowers visual evoked potential (VEP) latency and that the magnitude of decrease in latency is associated with the observed increase in DHA content of erythrocyte lipids. Other studies have shown that the difference in VEP latency is not apparent 3 years after terminating supplementation, suggesting that a continuous supply of omega-3 LC-PUFA may be required. In contrast, children with PKU who were breastfed and, hence, received DHA for as long as 6 weeks before beginning dietary therapy had a 12.9-point higher IQ at 9 years of age (after adjustment for social class and maternal education) than infants who were formula-fed for the same period. Metabolic control of the 2 groups after diagnosis and beginning dietary therapy did not differ.

In toto, the study of Beblo et al adds considerably to an existing body of data suggesting that omega-3 LC-PUFA may be conditionally essential for infants and children with PKU. This, presumably, is because the usual PKU diet is low in protein and, hence, low in the common dietary sources of omega-3 LC-PUFA (eg, fish, meat, eggs). This also appears to be true for other nutrients; for example, formulas for patients with PKU are supplemented with several essential trace minerals and vitamins that have been shown to be low in low protein diets or poorly available from these diets.

The improvement of older children with PKU because of omega-3 LC-PUFA supplementation, without changes in plasma phenylalanine concentration, suggests that still other groups might benefit from dietary omega-3 LC-PUFA. Certainly, the brain continues to grow well beyond infancy, and there likely is considerable turnover of brain components, including DHA, after adult size is reached; thus, there may be benefits of omega-3 LC-PUFA supplementation, not only during infancy and early childhood, but also, perhaps, during adolescence and adulthood.

Currently, evidence that children with PKU might benefit from omega-3 LC-PUFA supplementation, perhaps as a component of their low phenylalanine formula, is reasonably strong. However, whether this supplement should be EPA, DHA, or perhaps both, as studied by Beblo et al, is not clear. The amount of these fatty acids that should be provided also is not clear. An 8% increase in plasma phospholipid EPA content, as reported by Beblo et al, seems somewhat excessive. Further, considering the 27% decrease in plasma phospholipid AA observed by Beblo et al, the supplement perhaps should also include omega-6 LC-PUFA.

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Bipolar disorder is a serious mental illness that affects approximately 3% of the adult population. Additional epidemiological surveys have indicated incidence rates up to 7%. In contrast to previous thought, two-thirds of adult patients diagnosed with bipolar disorder began having symptoms in childhood or adolescence, and between 25% and 33% of youth who initially present with depression will ultimately become manic.

The diagnosis of bipolar disorder suffers from two common phenomena in medicine: overdiagnosis and underdiagnosis. Clinicians faced with seriously disturbed and aggressive youth may make a serious diagnosis, that is, bipolar disorder, to obtain needed care for these children and adolescents. Not making the diagnosis, on the other hand, may result from clinicians not wanting to “label” a child or frequently not adequately assessing for the condition. Most people identified as having bipolar disorder in epidemiological surveys had either no diagnosis (50%) or were incorrectly diagnosed with depression (31%).

The failure of clinicians to identify bipolar disorder is frequently a result of the cross-sectional nature of episodes of care. Few patients complain during the early stages of mania. Instead, they frequently present for medical treatment because of somatic complaints associated with depression. Without direct, pointed inquiry, symptoms of mania may go undetected for many years.

In this issue of The Journal, Leverich et al from the Stanley Medical Research Institute Bipolar Centers describe findings that significant delay in treatment of bipolar disorder results in negative consequences on outcome and a more treatment-resistant form of the illness. In this important study, 480 adults with bipolar disorder were evaluated to determine their age at first onset of manic or depressive symptoms and the age of first treatment in relationship to the course of the illness. Patients who had earlier onset of illness (childhood or adolescence), in general, had longer delays to appropriate treatment. In addition, these same patients suffered more episodes of affective illness, had more co-morbidities, and experienced rapid mood cycling (a predictor of poor outcome and treatment refractory status).

This long delay to diagnosis and treatment is unfortunately very common. Prolonged illness and recurrent episodes of illness appear to have the effect of making the condition more difficult to treat. Long delays in treatment, as described in this article, can have detrimental effects on patient outcomes, similar to many other illnesses.

Geller et al have described a group of youth with prolonged symptoms of mania and poor outcomes, including failure to recover from mania. Unfortunately, in this group the poor outcome may be more easily explained by the poor quality of treatment received including many not receiving any mood stabilizer. The failure to recover was most likely the effect of treating physicians not using mood stabilizers in many of the youth. Whether this was because of diagnostic differences or lack of knowledge about the treatment of bipolar disorder is unclear. These findings are in contrast to emerging data that suggest that youth diagnosed with bipolar disorder and given adequate treatment respond in a similar manner to those with adult-onset illness. In regards to the older patients in the Leverich article, there are now many new and possibly safer treatments FDA approved for adults with bipolar disorder. Many of these agents have positive studies in youth with bipolar disorder. FDA approval for use in youth is still lacking with the exception of lithium, which is now formally being studied.

The childhood onset of bipolar disorder symptoms is apparently more common in the United States than in Europe. A possible theory is that immigration status differences (group selection) may account for some of the differences noted across the Atlantic Ocean. Selection regarding those who chose the risky path of transatlantic immigration may have resulted in some differences in conditions where impulsivity plays a role.
a significant role, that is, bipolar disorder. It is also possible that other forms of selection bias or reasons for lack of recognition of bipolar disorder could account for the differences between identified rates in the United States and Europe.

The information contained in this article and additional evidence suggest that early detection, diagnosis, and treatment are essential for determining effective treatment outcomes and subsequently, quality of life for those afflicted with bipolar disorder. Collaboration between primary care and psychiatry is essential in making an impact upon bipolar disorder and other serious psychiatric conditions. Screening and early identification by primary care providers and early treatment or referral to psychiatric care, when available, can have a positive impact upon the outcome for these youth.

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Impact of Celiac Autoimmunity on Children with Type 1 Diabetes

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Objective Children with type 1 diabetes (T1DM) are at increased risk for celiac disease (CD); however, the benefits of screening for IgA tissue transglutaminase autoantibodies (TG), a marker for CD, are unclear.

Study design We compared 71 screening-identified TG+ with 63 matched TG– children with TIDM. Growth, bone density, and diabetes control measures were obtained.

Results The group was 10 ± 3 years of age, 46% male, with TIDM for 4 ± 3 years. Z scores for weight (0.3 ± 1 vs 0.7 ± 0.8, P = .024), body mass index (BMI) (0.3 ± 0.9 vs 0.8 ± –0.8, P = .005), and midarm circumference (0.3 ± 1.1 vs 0.6 ± 0.9, P = .031) were lower in the TG+ group. Bone mineral density and diabetes control measures were similar. When limiting the analysis to the 35 TG+ subjects with biopsy changes of CD, the BMI Z score was lower than the control group (0.4 ± 0.9 vs 0.7 ± 0.7, P = .05).

Conclusions In children with TIDM, screening-identified evidence of CD is associated with altered body composition, but not bone mineral density or diabetes control. Further study is needed to determine the benefit of early diagnosis and treatment of CD in TIDM children. (J Pediatr 2007;150:461-6)

Up to 16% of children with type 1 diabetes (T1DM) express the highly specific serological markers of celiac disease (CD)—autoantibodies to endomysium or tissue transglutaminase.1-5 The majority of these children are asymptomatic or do not have symptoms severe enough to seek medical attention.6-10 These patients are identifiable only through screening. However, they have the same genetic background (HLA DQ2, DQ8) and characteristic changes on small bowel biopsy as those who present with clinical signs or symptoms. The long-term consequences of untreated subclinical CD remain unclear.11-18

Manifestations of CD include diarrhea, abdominal pain, iron deficiency anemia, pubertal delay, growth failure, decreased bone mineralization, and villous atrophy on small bowel biopsy.3,12-16 A diet free of gluten leads to complete clinical resolution and mucosal healing.12-16 in the majority of children. If a gluten-free diet (GFD) is initiated late in childhood or adolescence, bone mineralization may not normalize.16 Although a GFD is effective, only a minority of patients achieve long-term compliance; patients diagnosed because of clinical manifestations have higher compliance rates13 than those identified through screening.17,18

In poorly controlled T1DM, poor growth,19,20 delayed sexual development,21-23 and diminished bone mineralization24-27 have been reported. Thus, CD places the child with T1DM at increased risk for these complications.3,28 In addition, variable nutrient absorption because of CD-associated intestinal injury may destabilize diabetic control, leading to recurrent hypoglycemia.29

See editorial, p 453

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The primary aim of this study was to determine the impact of screening-identified CD on growth, bone mineralization, and diabetes control.

METHODS

Research Design/Methods

Since 1998, patients with T1DM followed at the Barbara Davis Center have undergone routine screening for CD with testing for IgA anti-tissue transglutaminase autoantibodies (TG).4,10 Those with elevated TG levels were offered small bowel biopsy, enrollment into this study, and dietitian instruction in the GFD. Patients or their parents self-selected to a regular diet or GFD. Subjects 2 to 18 years of age and with well-controlled thyroid disease were not excluded (Table I). Patients with chronic glucocorticoid use, had another systemic illness, or required medications known to adversely affect linear growth or bone mineralization (patients with well-controlled thyroid disease were not excluded).

Anthropometrics/Bone Densitometry

Height, weight, body mass index (BMI), triceps skinfold measurements, and midarm circumference were converted to age- and sex-specific Z scores ([value-mean value for sex and age]/standard deviation).30,31 Bone densitometry was performed in the anteroposterior direction at the lumbar spine (L2-L4) using a Lunar XRC1 version 4.7E bone densitometer with smart scan (Granite Microsystems, Mequon, Wis). Data were expressed as age- and sex-specific Z scores for both bone age and chronologic age. Areal lumbar bone mineral density (LBMDA, grams per square centimeter) was obtained and volumetric lumbar bone mineral density (LBMDV, grams per cubic centimeter) was calculated based on the LBMDA and the width of the lumbar vertebrae using the formula LBMDA × (4/[π × width]) = LBMDV.32

Small Bowel Biopsy

Small bowel biopsy was performed on TG+ subjects consuming a normal gluten-containing diet. At upper intestinal endoscopy, two biopsies from the distal duodenum and two biopsies from the proximal duodenum were obtained. A pediatric pathologist, unaware of the clinical and laboratory results, interpreted the sample according to the criteria defined by Marsh,33 as previously described.10 A normal biopsy is Marsh 0, increased intraepithelial lymphocytes is Marsh 1, crypt hyperplasia is Marsh 2, and villous atrophy is Marsh 3. A Marsh score ≥2 is considered to be evidence for CD.

Table I. Demographic and clinical data at enrollment of children with diabetes with (TG+) and without (TG–) serologic evidence of celiac disease

<table>
<thead>
<tr>
<th></th>
<th>TG+ n = 71</th>
<th>TG– n = 63</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>10.1 ± 2.9</td>
<td>10.2 ± 3.3</td>
<td>.738</td>
</tr>
<tr>
<td>T1DM duration (y)</td>
<td>4.3 ± 3.3</td>
<td>4.4 ± 3.2</td>
<td>.0614</td>
</tr>
<tr>
<td>Sex (males)</td>
<td>33 (46.4%)</td>
<td>29 (46%)</td>
<td>.959</td>
</tr>
<tr>
<td>TG index</td>
<td>0.56 ± 0.50</td>
<td>-0.004 ± 0.02</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HbA1c (4.2-6.3%)</td>
<td>8.3 ± 1.3%</td>
<td>8.3 ± 1.0%</td>
<td>.680</td>
</tr>
<tr>
<td>Insulin dose/kg/day</td>
<td>0.78 ± 0.32</td>
<td>1.18 ± 2.90</td>
<td>.322</td>
</tr>
<tr>
<td>% subjects with severe hypoglycemic event*</td>
<td>14.9%</td>
<td>7.9%</td>
<td>.412</td>
</tr>
<tr>
<td>Wt Z score</td>
<td>0.29 ± 1.0</td>
<td>0.68 ± 0.84</td>
<td>.024</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>0.34 ± 0.9</td>
<td>0.75 ± 0.76</td>
<td>.005</td>
</tr>
<tr>
<td>Height Z score</td>
<td>0.02 ± 1.45</td>
<td>0.34 ± 1.02</td>
<td>.369</td>
</tr>
<tr>
<td>Triceps skinfold Z score</td>
<td>1.0 ± 0.85</td>
<td>0.93 ± 0.77</td>
<td>.612</td>
</tr>
<tr>
<td>Midarm circumference Z score</td>
<td>0.31 ± 1.15</td>
<td>0.60 ± 0.91</td>
<td>.031</td>
</tr>
<tr>
<td>L-spine Z score for bone age</td>
<td>-0.69 ± 1.46</td>
<td>-0.41 ± 1.49</td>
<td>.073</td>
</tr>
<tr>
<td>Volumetric L-spine Z score for bone age</td>
<td>-0.21 ± 1.22</td>
<td>0.07 ± 1.3</td>
<td>.237</td>
</tr>
<tr>
<td>Bone age delay (y)</td>
<td>0.05 ± 1.7</td>
<td>0.006 ± 0.92</td>
<td>.304</td>
</tr>
<tr>
<td>PTH (13-54 pg/mL)</td>
<td>24.8 ± 8.5</td>
<td>21.5 ± 7</td>
<td>.022</td>
</tr>
<tr>
<td>Vitamin D 25OH (15-45 ng/mL)</td>
<td>29.0 ± 7.9</td>
<td>31.2 ± 7.8</td>
<td>.099</td>
</tr>
<tr>
<td>Urine n-telopeptides†</td>
<td>105.3 ± 60.2%</td>
<td>69.0 ± 33.2%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Vitamin B12 (211-911 pg/mL)</td>
<td>714.7 ± 297.6</td>
<td>759.7 ± 311.9</td>
<td>.299</td>
</tr>
<tr>
<td>Prealbumin (18-357 mg/dL)</td>
<td>20.2 ± 2.8</td>
<td>21.0 ± 4.0</td>
<td>.064</td>
</tr>
<tr>
<td>Ferritin (15-119 ng/mL)</td>
<td>36.6 ± 22.2</td>
<td>39.8 ± 18.4</td>
<td>.164</td>
</tr>
<tr>
<td>Urine microalbumin/creatinine ratio (0-30 ug/mg creat)</td>
<td>12.5 ± 16.8</td>
<td>17.7 ± 34.4</td>
<td>.882</td>
</tr>
<tr>
<td>Free T4 (0.8-1.7 mg/dL)</td>
<td>1.18 ± 0.21</td>
<td>1.31 ± 0.25</td>
<td>.001</td>
</tr>
<tr>
<td>TSH (0.36-5.4 mg/dL)</td>
<td>2.45 ± 1.93</td>
<td>2.55 ± 6.79</td>
<td>.002</td>
</tr>
<tr>
<td>IGFl Z score</td>
<td>-2.12 ± 0.99</td>
<td>-1.82 ± 1.02</td>
<td>.037</td>
</tr>
<tr>
<td>IGF-BP3 Z score</td>
<td>-0.78 ± 1.0</td>
<td>-0.68 ± 1.23</td>
<td>.999</td>
</tr>
</tbody>
</table>

*% of subjects with severe hypoglycemic event in the 2 years prior to enrollment
†Urine N-telopeptides: % of age- and sex-specific reference mean (evaluated for bone age)
Laboratory Tests and Bone Age

The IgA TG radioassay has been previously described and compared with commercially available enzyme-linked immunosorbent TG assays. Briefly, in vitro transcribed and translated full-length human recombinant transglutaminase was used. Radiolabeled samples were measured in the fluid phase with duplicates in 96-well plates using a Top Count β-counter (Packard Instrument Company, Meriden, Conn). A TG index >0.05 is considered elevated. A TG index of >0.05 has a positive predictive value for histologic confirmation of CD of 76%, and a TG index of >0.5 has a positive predictive value of 96%. Hemoglobin A1c (HbA1c) was measured by the DCA 2000™ (Bayer Diagnostics, Elkhart, Ind) by latex agglutination procedure. Insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein 3 (IGF-BP3) were determined by enzyme-immunoassay (R&D Systems, Minneapolis, Minn) and evaluated as Z scores adjusted for bone age (SD from the mean for age- and sex-matched laboratory methods). Bone age was determined in masked conditions by a single investigator (JS) using the method of Greulich and Pyle.

Hypoglycemia/Other Assessments

Episodes of severe hypoglycemia, defined as seizures, altered consciousness, emergency department visits, or hospitalizations as a result of hypoglycemia within 2 years prior to study enrollment were obtained from the Barbara Davis Center clinical electronic database. Additionally, the percentage of blood glucose levels <70 mg/dL from home glucose meter downloads at the visit before enrollment were obtained. These downloads provide information regarding the month before the download. A questionnaire ascertaining each subject’s daily insulin regimen was administered and daily dose of insulin per kilogram was then calculated. A symptom questionnaire regarding the presence of diarrhea, abdominal pain, constipation, vomiting, irritability, decreased energy, gas, itch/rash, edema, bleeding disorder, pubertal delay, failure to gain weight, short stature, or bone fracture was administered by a study dietitian.

Statistics

Log transformations were applied to highly skewed variables. Chi-square test of independence or Fisher’s exact test was used to test the distribution of discrete variables. The Wilcoxon’s rank sum test was used to test the difference among groups in continuous variables at baseline. There were no P value adjustments for multiple tests. A subanalysis was performed with pair-matched TG– and TG+ subjects with Marsh scores ≥2. These subjects were matched for age, sex, and diabetes duration. A matched group analysis was performed using the rank sum test. Symptoms were analyzed using a χ² test; Fisher’s exact test was used when the frequency of a symptom was <5.

RESULTS

There were 71 TG+ and 63 TG– children enrolled, all with T1DM. The TG+ group was 10 ± 3 years of age, 46% male, 94% self-described non-Hispanic white, and had a T1DM duration of 4 ± 3 years. Because of frequency matching, age, sex, and diabetes duration were similar in the TG+ and TG– groups (Table I). The median duration of GFD was 0 months in the TG+ group (mean 5.4 ± 11.2 months). Twenty percent of TG+ subjects stated that they had been following a GFD for ≥6 months; the mean TG index of this group was similar to the mean of the remainder of the TG+ group (0.50 ± 0.47 vs 0.58 ± 0.51, P = .768). The TG+ group reported increased frequency of decreased energy, flatulence, itching/rash, failure to gain weight, and short stature (data not shown, results obtained after TG results were known).

The TG+ group had lower weight, BMI, and midarm circumference Z scores than the TG– group, but the groups were similar for bone mineral density. There were no differences between the TG+ and TG– groups in HbA1c at the baseline visit (Table I) or in the average HbA1c during the 2 years before enrollment between the TG+ (8.4 ± 1.5%) and TG– groups (8.6 ± 1.0%), P = .245. There were also no differences in episodes of severe hypoglycemia, as 14.9% of subjects in the TG+ group and 7.9% in the TG– group had a single episode of severe hypoglycemia during the 2 years before enrollment (P = .412). No subject had more than one episode of severe hypoglycemia during the 2 years before enrollment. The TG+ group had 9.7 ± 6.0% of blood glucose values <70 mg/dL (obtained from glucose meter downloads at the visit before enrollment), compared with 9.0 ± 5.8% in the TG– group (P = .470). There were no differences between groups in insulin dose/kg.

The TG+ group had lower IGF-I Z scores than the TG– group, but both were decreased compared with control values. The TG+ group had higher PTH and urine NTX levels and lower free T4 and TSH levels. Five subjects in the TG+ group (7%) and four subjects in the TG– group (6%) had hypothyroidism and were receiving replacement therapy. There were no other differences between groups in any other variables. A subanalysis of TG+ subjects on GFD <6 months (n = 57, mean 1 ± 1.6 months and median 0 months) at enrollment compared with TG– controls demonstrated the same differences in weight, BMI, midarm circumference Z scores, PTH, urine NTX, free T4, and TSH levels; there was no longer a statistically significant
Table II. Demographic and clinical data at enrollment of children with diabetes with histologic (Biopsy+) and without serologic (TG−) evidence of celiac disease

<table>
<thead>
<tr>
<th></th>
<th>Biopsy + n = 35</th>
<th>TG− matched controls n = 35</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>10.52 ± 2.70</td>
<td>10.13 ± 3.07</td>
<td>.488</td>
</tr>
<tr>
<td>Diabetes mellitus duration (y)</td>
<td>4.00 ± 3.22</td>
<td>4.12 ± 3.25</td>
<td>.660</td>
</tr>
<tr>
<td>Sex (males)</td>
<td>17 (48.6%)</td>
<td>17 (48.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>TG index</td>
<td>0.67 ± 0.55</td>
<td>-0.001 ± 0.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HbA1c (4.2-6.3%)</td>
<td>8.1 ± 1.3%</td>
<td>8.2 ± 1.2%</td>
<td>.919</td>
</tr>
<tr>
<td>Insulin dose/ kg/ day</td>
<td>0.80 ± 0.40</td>
<td>1.39 ± 3.89</td>
<td>.835</td>
</tr>
<tr>
<td>Wt Z score</td>
<td>0.35 ± 1.09</td>
<td>0.53 ± 0.75</td>
<td>.431</td>
</tr>
<tr>
<td>BMI Z score</td>
<td>0.36 ± 0.87</td>
<td>0.68 ± 0.67</td>
<td>.050</td>
</tr>
<tr>
<td>Height Z score</td>
<td>0.25 ± 1.17</td>
<td>0.12 ± 0.92</td>
<td>.445</td>
</tr>
<tr>
<td>Triceps skinfold Z score</td>
<td>1.08 ± 0.85</td>
<td>0.86 ± 0.79</td>
<td>.594</td>
</tr>
<tr>
<td>Midarm circumference Z score</td>
<td>0.41 ± 1.29</td>
<td>0.51 ± 0.82</td>
<td>.208</td>
</tr>
<tr>
<td>L-spine Z score for bone age</td>
<td>-0.41 ± 1.57</td>
<td>-0.54 ± 1.71</td>
<td>.831</td>
</tr>
<tr>
<td>Volumetric L-spine Z score for bone age</td>
<td>0.04 ± 1.24</td>
<td>-0.0001 ± 1.37</td>
<td>.960</td>
</tr>
<tr>
<td>Bone age delay (y)</td>
<td>0.22 ± 2.24</td>
<td>-0.04 ± 0.90</td>
<td>.648</td>
</tr>
<tr>
<td>PTH (13-54 pg/mL)</td>
<td>25.7 ± 7.5</td>
<td>21.4 ± 6.2</td>
<td>.021</td>
</tr>
<tr>
<td>Vitamin D 25OH (15-45 ng/mL)</td>
<td>31.3 ± 7.7</td>
<td>31.9 ± 6.2</td>
<td>.689</td>
</tr>
<tr>
<td>Urine n-telopeptides*</td>
<td>107.6 ± 58.2%</td>
<td>70.7 ± 36.3%</td>
<td>.0004</td>
</tr>
<tr>
<td>Vitamin B12 (211-911 pg/mL)</td>
<td>769.5 ± 301.2</td>
<td>839.1 ± 330.9</td>
<td>.065</td>
</tr>
<tr>
<td>Prealbumin (18-35.7 mg/dL)</td>
<td>20.4 ± 2.2</td>
<td>21.0 ± 2.9</td>
<td>.384</td>
</tr>
<tr>
<td>Ferritin (15-119 ng/mL)</td>
<td>30.9 ± 16.3</td>
<td>39.1 ± 18.0</td>
<td>.065</td>
</tr>
<tr>
<td>Urine microalbumin/creatinine ratio</td>
<td>9.0 ± 9.6</td>
<td>19.9 ± 40.9</td>
<td>.572</td>
</tr>
<tr>
<td>Free T4 (0.8-1.7 ng/dL)</td>
<td>1.16 ± 0.23</td>
<td>1.33 ± 0.31</td>
<td>.015</td>
</tr>
<tr>
<td>TSH (0.36-5.4 ng/dL)</td>
<td>2.42 ± 1.58</td>
<td>3.33 ± 9.06</td>
<td>.029</td>
</tr>
<tr>
<td>IGFB-1 Z score</td>
<td>-1.84 ± 1.10</td>
<td>-1.99 ± 0.96</td>
<td>.834</td>
</tr>
<tr>
<td>IGFBP-3 Z score</td>
<td>-0.50 ± 0.99</td>
<td>-0.86 ± 1.20</td>
<td>.091</td>
</tr>
</tbody>
</table>

*Urine N-telopeptides: % of age- and sex-specific reference mean (evaluated for bone age).

difference between groups in IGF-1 Z scores (data not shown).

Small bowel biopsy was performed in 48 of the 71 TG+ subjects (68%). Villous atrophy (Marsh score 3) was found in 33 and crypt hyperplasia (Marsh score 2) in an additional 2 subjects. Thus 73% of those with a biopsy and 50% of all screening-identified TG+ subjects had confirmation of CD on small bowel biopsy. None of the TG− group had a small bowel biopsy. A subanalysis was performed comparing these 35 TG+ subjects with biopsy evidence of CD with TG− subjects matched for age, sex, and diabetes duration (Table II). The group with biopsy evidence of CD, as the entire TG+ group, had lower BMI Z scores and similar HbA1c and bone mineral density compared with the TG− group, but no difference in weight or midarm circumference Z scores. As in the total TG+ group, the biopsy positive group had higher PTH and urine NTX and lower free T4 and TSH than the group without TG. The biopsy positive group had increased frequency of flatulence (28.6% vs 5.7%), P = .023, but there were no other differences in reported symptoms (data not shown).

**DISCUSSION**

This study evaluated a large number of children with T1DM and celiac autoimmunity. In children with T1DM, celiac autoimmunity is associated with decreased weight and BMI Z scores. These findings are important for several reasons.

First, whether to screen children with T1DM for CD is controversial. The 2004 National Institutes of Health consensus statement on CD reported that for those with T1DM “current data do not indicate a clear outcome benefit for early detection and treatment of asymptomatic individuals.” Routine screening was not recommended. However, areas for future research included “a cohort study to determine the natural history of untreated celiac disease, especially silent celiac disease” and to “analyze the benefit of screening high-risk groups relevant to clinically important outcomes.” This study from a large single-center group of subjects provides much-needed information to guide clinical practice.

Second, there is uncertainty regarding the optimal timing of therapy for CD in children with T1DM. In children with recently diagnosed T1DM, the psychological burden of a second chronic illness requiring significant life-long diet change was emphasized. Third, the clinical impact of CD in children seems to vary from person to person, probably because of the variable severity of the disease process. The multiple terminologies used in the literature (latent, subclinical, mild, screening-identified) exemplify the limited understanding of the natural history, pathogenesis, and modifying factors in CD. Continued follow-up of this cohort will eval-
ulate the effect of early initiation of GFD on screening-identified patients as well as the effect of GFD over time.

Although the results of our study are not decisive enough to assert that universal screening is justified, the evidence is also not conclusive enough to renounce the position statements by the American Diabetes Association and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition that the T1DM population should undergo screening for CD. This study extends to children with T1DM our previous finding of mild differences in BMI and is in agreement with one other study. However, others found no differences in anthropometrics. Of note, we and others did not find an impact of CD on height in patients with T1DM, although one other study found improvement in height with GFD. Some studies have suggested that CD has an impact on glycemic control, but we and others have not confirmed this. IGF-I values were low in both TG+ and TG− patients with T1DM. Circulating IGF-I levels are reduced in T1DM and levels are dependent on the degree of metabolic control. However, our study demonstrated lower values in those T1DM patients who also have CD; this may have adverse implications for both final height and bone mineralization.

We did not find any differences in bone density in these relatively young patients, although decreased bone mineral density has been associated with childhood CD. However, we did find increased urine NTX, a marker of bone resorption, in patients with T1DM and evidence of CD. Our patient population may be too young to have abnormalities demonstrated by dual-energy x-ray absorptiometry, and bone turnover markers may precede these abnormalities. Importantly, Vitamin D levels were normal; therefore, Vitamin D deficiency is not the cause of increased bone turnover.

Through screening, we identified 35 patients (49.3% of the TG+ patients) who had small bowel biopsy–confirmed CD. These patients had abnormalities in anthropometric measures and in bone turnover markers, as did the entire TG+ group. Importantly, it does not appear that having histologic evidence of CD has a more profound clinical effect than having TG.

An important limitation of this study is that 20% of the subjects in the TG+ group claimed to be following a GFD for at least 6 months before enrollment. This could result in a type II error, of finding no difference when one does exist. However, the mean TG index in the TG+ group at enrollment was >0.5 and not different from those recently begun on a GFD, suggesting that the GFD was not strictly followed. Additionally, analysis excluding those reporting a GFD for >6 months before enrollment revealed results similar to the analysis of the entire cohort.

Another limitation is that not all patients underwent biopsies, and they did not therefore all have biopsy-proven CD. However, our primary aim was to investigate the significance of having evidence of CD as measured by TG+, as not all patients in clinical practice agree to a small bowel biopsy. We demonstrated that those with histologic evidence of CD had similar clinical and laboratory differences from the TG− group as did the entire TG+ group.

In conclusion, we demonstrated differences in weight and BMI Z scores between TG+ and TG− T1DM patients. There were no differences in bone density or in diabetes control between these groups. Differences in urine NTX between these groups is of uncertain significance. There continues to be evidence for screening patients with T1DM for TG at regular intervals, as it aids in identifying patients for small bowel biopsy. Further longitudinal studies are needed to describe the natural history of untreated CD, to assess the mechanisms of decreased bone mineral density, and to determine the optimal timing of dietary therapy.

REFERENCES


Preventing a Drop in Effective Plasma Osmolality to Minimize the Likelihood of Cerebral Edema During Treatment of Children with Diabetic Ketoacidosis

Ewout J. Hoorn, MD, Ana P. C. P. Carlotti, MD, Leila A. A. Costa, MD, Beth MacMahon, MB, Gareth Bohn, BSc, Robert Zietse, MD, Mitchell L. Halperin, MD, and Desmond Bohn, MB

Objectives To test whether a drop in effective plasma osmolality (PEff osm; 2 × plasma sodium [PNa] + plasma glucose concentrations) during therapy for diabetic ketoacidosis (DKA) is associated with an increased risk of cerebral edema (CE), and whether the development of hypernatremia to prevent a drop in the PEff osm is dangerous.

Study design This study is a retrospective comparison of a CE group (n = 12) and non-CE groups with hypernatremia (n = 44) and without hypernatremia (n = 13).

Results The development of CE (at 6.8 ± 1.5 hours) was associated with a drop in PEff osm from 304 ± 5 to 290 ± 5 mOsm/kg (P < .001). Control patients did not show this drop in PEff osm at 4 hours (1 ± 2 and 2 ± 2 vs –9 ± 2 mOsm/kg; P < .01), because of a larger rise in PNa and/or a smaller drop in plasma glucose. During this period, the CE group received more near-isotonic fluids (69 ± 9 vs 35 ± 2 and 27 ± 3 mL/kg; P < .001). The CE group had a higher mortality (3/12 vs 0/57; P = .003), and more neurologic sequelae (5/12 vs 1/57; P < .001).

Conclusions CE during therapy for DKA was associated with a drop in PEff osm. An adequate rise in PNa may be needed to prevent this drop in PEff osm. (J Pediatr 2007;150:467-73)

Although cerebral edema (CE) is the most common cause of morbidity and mortality in diabetic ketoacidosis (DKA) in pediatric patients,1-3 there is a lack of consensus on how to prevent its development.3-6 Because CE usually occurs during the first 5 to 15 hours of treatment of DKA,7 it is possible that therapy contributes to its development.8 Several associations with CE have been identified, including younger age,9 newly diagnosed diabetes,3,9 higher initial plasma urea concentration,1,7 higher initial plasma glucose concentration (PGlucose),1,9 severe acidosis,1,7,10,11 and therapy with sodium bicarbonate.7

In addition to the aforementioned factors, fluid and electrolyte disturbances and their management may increase the risk of developing CE during treatment of DKA.1,7,10-15 One important observation in this regard is that a smaller increase in the plasma sodium concentration (PNa) during therapy is associated with CE.7,10,15 Because PNa is the most important determinant of the “effective” plasma osmolality (PEff osm), our objective was to test the hypothesis that a drop in PEff osm (defined as 2 × PNa + PGlucose) during therapy for DKA is associated with the development of CE. Furthermore, because a rise in PNa is necessary to maintain PEff osm, when the PGlucose drops, we also wanted to evaluate whether hypernatremia in this context had any untoward effects.

METHODS

Approval was obtained from the respective institutional research ethics boards to conduct a retrospective review of patients who were admitted with DKA to the Hospital...
CE, or specific treatment for CE (hyperosmolar therapy combination with radiographically or pathologically confirmed abatement in mental status (obtundation or disorientation) in combination with radiographically or pathologically confirmed CE, or specific treatment for CE (hyperosmolar therapy and/or controlled ventilation) that was followed by prompt clinical improvement. P Eff osm was calculated as 2 × P Na + P Glucose (in mmol/L).18

Study Groups

Three groups of DKA patients were included in this study. The CE group comprised all patients who developed CE during therapy for DKA and were admitted to the pediatric intensive care units (ICUs) of HSC between 1994 and 1999 or USP between 1996 and 2005. These data were collected from the 2 institutions by the same physician (APCP) to get a sufficiently large group. The characteristics of HSC and USP patients were similar (data not shown). The CE group was compared with 2 control groups of patients who did not develop CE during DKA and who were admitted to HSC in the same years as the cases. The first group (controls with hypernatremia) comprised ICU and non-ICU patients who had at least 1 P Na ≥ 150 mmol/L (hypernatremia) during the first 8 hours of hospitalization. The second group (controls without hypernatremia) comprised ICU patients who did not have hypernatremia during DKA treatment.

Data Collection

A retrospective chart review was performed using a computer database (for ICU patients), and/or a “diabetes mellitus flow sheet” (for other departments). The first 24 hours of treatment of DKA were reviewed, starting at the point at which therapy began. Data for patients who were originally admitted to other hospitals before transfer were also included in our analysis. Data collection included biochemical and hemodynamic measures, medication, all input values (intravenous [IV] fluids and/or oral fluids, including those received at the referral hospitals), available output values, and outcome. With regard to biochemical measurements, we focused on the P Eff osm, P Na, and P Glucose, which were recorded at 4-hour intervals; other measures are reported at the time of admission only. The amounts of sodium (Na+) and potassium (K+) and the volume and tonicity of the fluids (ie, amount of Na+ + K+ per liter) administered through the IV and/or oral routes were evaluated. All urinary values were analyzed, and fluid balances were calculated when data were available. Outcome measures included neurologic sequelae and mortality during or shortly after treatment of DKA.

Statistical Analysis

Group comparisons of normally distributed variables were performed by 1-way analysis of variance (ANOVA) with least significant difference post hoc tests (with P values of the latter reported). Categorical data were analyzed using Fisher’s exact test (analyzing the control groups separately and together). A repeated-measures generalized linear model was used to compare changes in biochemical measures over time. A P value ≤ .05 was considered significant. Data are expressed as mean ± standard error of the mean.

RESULTS

Patients

The CE group consisted of 12 patients with DKA (7 from HSC and 5 from USP), who developed CE 6.8 ± 1.5 hours after therapy for DKA began (range, 0.5 to 20 hours). A total of 44 control patients with hypernatremia (peak P Na 161 ± 1 mmol/L) and 13 control patients without hypernatremia were also identified; all had been directly admitted to HSC. Six patients were excluded because of a central nervous system infection and/or substance abuse; an additional 11 patients were excluded because they were admitted for less than 24 hours and/or had incomplete data. CE was diagnosed clinically in all patients in the CE group and was confirmed by computed tomography (CT) scan in 9 patients and by autopsy in 1 patient. In contrast, there was no clinical suspicion of CE in the control patients; in 3 patients, CT scans confirmed the absence of CE. Treatment for CE consisted of mannitol and ventilation in 6 patients; mannitol, hypertonic saline, and ventilation in 2 patients; hypertonic saline and ventilation in 1 patient; mannitol only in 2 patients; and ventilation only in 1 patient.

Biochemistry Data and Hemodynamics

Biochemical and hemodynamic data for the 2 groups at the time of admission are given in Table I. P Eff osm and P Na were significantly higher in the control patients with hypernatremia. Other differences included a lower P Glucose and plasma urea and a higher hematocrit and systolic and diastolic blood pressure in the control patients without hypernatremia (Table I).

Treatment and Outcomes

The CE group received a bolus of insulin significantly more often than the control patients (11/12 vs 9/57; P < .001); treatment with fluid boluses or sodium bicarbonate was comparable (Table II). Outcome was poorest in the CE group, as evidenced by a higher number of deaths (3/12 vs 0/57; P = .003), and a greater prevalence of neurologic sequelae (5/12 vs 1/57; P < .001). Neurologic sequelae included hemiparesis in 2 patients, other motor disturbances in 3 patients, visual disturbances in 3 patients, speech disturbances in 3 patients, and cognitive problems in 2 patients. One control patient developed severe hypernatremia (P Na
increase from 149 mmol/L to 189 mmol/L) with neurologic sequelae (speech disturbances and cognitive problems).

Course of Effective Plasma Osmolality

Figure 1 shows the time courses for changes in $P_{\text{Eff osm}}$, $P_{\text{Na}}$, and $P_{\text{Glucose}}$ in the 3 groups during the first 24 hours in the hospital. In the CE group, there was a significant decrease in $P_{\text{Eff osm}}$ in each patient as well as in the group average (304 ± 5 mOsm/kg vs 290 ± 5 mOsm/kg at the time of CE; $P < .001$). The $P_{\text{Eff osm}}$ dropped during the first 8 hours of therapy (after which hyperosmolar therapy was given to treat CE), whereas it remained constant or decreased minimally in the control groups. This difference was statistically significant ($P = .002$), as analyzed by a generalized linear model. The drop in $P_{\text{Eff osm}}$ in the CE group was most prominent in the first 4 hours after admission ($-9 ± 2$ mOsm/kg) and was significantly greater than in the controls with hypernatremia ($1 ± 2$ mOsm/kg; $P = .003$) and without hypernatremia ($2 ± 2$ mOsm/kg; $P = .001$) (Fig 2). In the hypernatremic control patients, the small change in $P_{\text{Eff osm}}$ was the result of a larger rise in $P_{\text{Na}}$ ($7 ± 1$ vs $3 ± 1$ mmol/L; $P = .03$), whereas in random control patients, it was mainly the effect of a smaller drop in $P_{\text{Glucose}}$ ($-4 ± 2$ vs $-14 ± 2$; $P = .01$) (Fig 2).

Input and Output Values

The time interval from 4 to 8 hours was when $P_{\text{Eff osm}}$ reached its nadir and CE developed in most of these patients.

Table I. Biochemistry and hemodynamics at time of admission

<table>
<thead>
<tr>
<th></th>
<th>CE group (n = 12)</th>
<th>Controls with hypernatremia (n = 44)</th>
<th>Controls without hypernatremia (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective osmolality</td>
<td>304 ± 5</td>
<td>342 ± 4†</td>
<td>301 ± 2</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>133 ± 2</td>
<td>149 ± 1†</td>
<td>136 ± 1</td>
</tr>
<tr>
<td>Glucose, mmol/L (mg/dL)</td>
<td>38 ± 4 (684 ± 72)</td>
<td>40 ± 3 (720 ± 54)</td>
<td>20 ± 2‡ (360 ± 36)</td>
</tr>
<tr>
<td>pH</td>
<td>7.09 ± 0.05</td>
<td>7.11 ± 0.02</td>
<td>7.09 ± 0.04</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>8.0 ± 1.6</td>
<td>7.7 ± 0.9</td>
<td>6.6 ± 0.8</td>
</tr>
<tr>
<td>Creatinine, μmol/L (mg/dL)</td>
<td>109 ± 11 (1.2 ± 0.1)</td>
<td>100 ± 10 (1.1 ± 0.1)</td>
<td>59 ± 8 (0.7 ± 0.1)</td>
</tr>
<tr>
<td>Urea, mmol/L (mg/dL)</td>
<td>11.6 ± 1.2 (4.1 ± 0.4)</td>
<td>10.0 ± 0.7 (3.6 ± 0.3)</td>
<td>4.8 ± 0.7† (1.7 ± 0.3)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>39 ± 4</td>
<td>31 ± 3</td>
<td>46 ± 2‡</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>115 ± 7</td>
<td>137 ± 4</td>
<td>130 ± 5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>107 ± 4</td>
<td>105 ± 2</td>
<td>120 ± 5‡</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67 ± 3</td>
<td>63 ± 2</td>
<td>76 ± 5‡</td>
</tr>
</tbody>
</table>

*Calculated as $2\times P_{\text{Na}} + P_{\text{Glucose}}$.
†Values higher (effective osmolality and sodium) or lower (urea) compared with the 2 other groups ($P < .05$ by ANOVA).
‡Values higher (hematocrit, systolic and diastolic blood pressure) or lower (glucose) compared with the control patients with hypernatremia ($P < .05$ by ANOVA).

Table II. Treatment and outcome characteristics

<table>
<thead>
<tr>
<th></th>
<th>CE group (n = 12)</th>
<th>Controls with hypernatremia (n = 44)</th>
<th>Controls without hypernatremia (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>6.2 ± 1.2</td>
<td>7.7 ± 0.9</td>
<td>10.8 ± 1.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>21.2 ± 4.1*</td>
<td>32.1 ± 3.3</td>
<td>42.5 ± 6.3</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>8 (67)</td>
<td>29 (66)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>New-onset diabetes, n (%)</td>
<td>6 (50)</td>
<td>31 (71)</td>
<td>9 (69)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid bolus, n (%)†</td>
<td>6 (50)</td>
<td>17 (39)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Insulin bolus, n (%)‡</td>
<td>11 (92)§</td>
<td>8 (18)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Sodium bicarbonate, n (%)</td>
<td>8 (67)</td>
<td>15 (34)</td>
<td>4 (31)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic sequelae, n (%)</td>
<td>5 (42)§</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>3 (25)§</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Values lower compared with control patients without hypernatremia ($P < .05$ by ANOVA).
†Defined as ≥ 10 mL/kg in 30 to 60 minutes.
‡Defined as ≥ 0.1 U/kg in single application.
§Values higher compared with both control groups ($P < .05$ by Fisher’s exact for control groups separately and combined).
Therefore, we were interested in evaluating input and output values from admission until a time point within this interval (the 6-hour time point was selected). At 6 hours of therapy, the CE group received more fluid (69 ± 9 vs 35 ± 2 and 27 ± 3 mL/kg) and more Na⁺ and K⁺ (10 ± 2 vs 6 ± 0.5 and 4 ± 0.5 mmol/kg) compared with the control groups with and without hypernatremia (Fig 3; P < .001 for all). The tonicity of these fluids was lower for the CE group compared with the controls with hypernatremia (142 ± 7 vs 163 ± 4; P = .05). A similar analysis was performed for urinary output and balance data, which were available in 6 of the 12 CE patients, in 39 of the 44 controls with hypernatremia, and in all of the controls without hypernatremia. The CE group had a more positive balance (52 ± 19 mL/kg vs 8 ± 2 and 3 ± 4 mL/kg; P < .001 for both) and a higher urine output (64 ± 27 mL/kg vs 23 ± 2 and 24 ± 5 mL/kg; P < .001 for both) compared with the control groups. The administration of hypertonic saline to treat CE was not included in these calculations, because it was always administered after the 6-hour time point.

**DISCUSSION**

Patients who developed CE had a larger drop in PEff osm early during therapy, which was not present in controls because of either a larger rise in PNa or a smaller drop in PGlucose. The changes in PEff osm became most prominent during the first 8 hours after the start of therapy, which appeared to be a time window with a large risk for the development of CE. We also found that the CE group received a larger volume of near-isotonic fluids during this period. Finally, they had a higher urine output and a more positive fluid balance than the
control patients. Thus, this study adds to the evidence that, at least in some settings, fluid and electrolyte management during DKA might be causally linked to the development of CE.1,7,10-15 In addition, our data confirm results from 2 previous studies, 1 by Bello et al,9 who found that CE was related to a marked reduction in measured plasma osmolality, and the second by Durr et al,10 who found that CE correlated with a small rise in PNa and a large drop in PEff osm. However, because not only osmotic factors, but also vasogenic19 and cytotoxic factors20 have been implicated in the formation of brain edema, we are hesitant to conclude that the large drop in PEff osm alone caused CE. Finally, because the development of hypernatremia during DKA in patients who had near-normal PNa values on admission prevented a large drop in PEff osm and was associated with better outcome, it might be a goal of therapy for this subset of patients.

The next important issue is to define how fluid and electrolyte management may have caused the large drop in PEff osm in the CE group. We consider 4 possibilities based on the available evidence. First, the drop in PEff osm may have been caused by increased infusion of IV fluids with a lower Na+/K+ concentration.21 Because the tonicity of the infusate was somewhat hypotonic to the patients, the infusion of larger volumes may have resulted in a positive electrolyte-free water balance, which prevented an adequate rise in PNa in the face of decreasing PNa levels.

Second, if the infused volume was sufficiently high to cause expansion of the extracellular fluid volume, this may have triggered a “desalination” process.22 To produce a drop (or a smaller rise) in PNa in these patients, a negative balance for Na+/K+ and/or a positive balance for water must be achieved. What is known about the composition of the urine in patients with DKA is that the Na+ concentration in the urine is ~40 to 50 mmol/L during the osmotic diuresis phase.23 Nevertheless, once the PNa drops appreciably, glucosuria diminishes, and the Na+ + K+ concentration in the urine can rise appreciably. It is at this time that desalination of infused saline could contribute to the smaller rise in the PNa. Of relevance, patients who developed CE in our study received almost twice as much intravenous saline.

Third, although not obvious on clinical grounds, a factor that merits attention is the role of hypotonic fluid retention in the upper gastrointestinal tract. When fruit juice and/or sweetened pop are ingested, there may be a large volume of water with little Na+ in the stomach, and its rate of emptying could be rapid early during therapy, as described in a previous case.24 If the CE group drank predominantly water before coming to the hospital and their stomach emptying was more rapid, this may have caused a smaller rise in the PNa.

The fourth potential contributing factor to CE identified in this study was the higher incidence of insulin bolus administration. Giving a bolus of insulin activates the sodium:hydrogen ion (H+) exchanger,25 resulting in a gain of Na+ and a loss of H+ in the intracellular fluid compartment. This results in an increased number of intracellular solutes, because exported H+ will be largely bound to intracellular buffers. This increase in the number of solute molecules inside cells could expand the intracellular volume, because water moves rapidly across cell membranes to achieve osmotic equilibrium. This could explain how insulin bolus administration could contribute to CE, especially when insulin was given at the onset of treatment, when the blood-brain barrier might be more permeable.26-28

Clinically, an important question is how these ideas could aid in optimizing fluid and electrolyte management in...
pediatric patients who present with DKA. The 2 major goals of IV fluid therapy should be to deal with hemodynamic emergencies due to low extracellular fluid volume (at the outset recognizing that true emergencies are not common) and to avoid a rapid drop in $P_{\text{Eff osm}}$ to minimize the risk of developing CE.16,17,29

With regard to the first goal, based on the available biochemical and hemodynamic data on admission, it is questionable that there was a hemodynamic indication to infuse such a large amount of $\text{Na}^+ + K^+$. For example, the amount of infused $\text{Na}^+ + K^+$ in the CE group exceeded 9 mmol/kg, roughly equal to 30% of the extracellular fluid volume.28 Thus a more moderate fluid regimen may be advisable if there is no compelling evidence to warrant being aggressive.15,30-33 We previously showed that the degree of extracellular fluid contraction during hyperglycemia is best assessed by serial plasma hematocrit or total protein levels;34 thus, these should be determined more frequently during fluid resuscitation in DKA.

With regard to the second goal, the $P_{\text{Eff osm}}$ was not maintained in the patients who developed CE. Regularly assessing $P_{\text{Eff osm}}$ and paying more attention to the urine volume and its electrolyte concentrations in these potentially vulnerable groups might help define whether the $P_{\text{Eff osm}}$ is likely to drop. In addition, a low $P_{\text{Na}}$ on admission may serve as a warning sign. If $P_{\text{Eff osm}}$ drops, infusing an appropriate volume of hypertonic saline is a therapeutic option to consider.35 Because the $P_{\text{Eff osm}}$ was remarkably well maintained in the control patients, the development of hypernatremia might be needed in those patients with a high $P_{\text{Gluose}}$ and near-normal $P_{\text{Na}}$ to prevent an excessive drop in the $P_{\text{Eff osm}}$ early in therapy. This is further supported by the good clinical outcome and few adverse events in all but 1 unusual case, in which a lesser rise in $P_{\text{Na}}$ and a small drop in $P_{\text{Eff osm}}$ may have been needed. We speculate that most of the control patients developed hypernatremia because they either had a greater osmotic diuresis (with the consequent loss of more electrolyte-free water) and/or received isotonic fluids while excreting a hypotonic urine.48 Another way to maintain $P_{\text{Eff osm}}$ is to establish a smaller drop in $P_{\text{Gluose}}$, as occurred in the controls without hypernatremia, although it must be noted that these patients’ degree of hyperglycemia on admission was less severe.

Because of the descriptive nature of this study, some limitations should be mentioned. First, the study was designed to test a single hypothesis in relation to CE, and thus other factors were not weighed in a multivariate approach. Second, the way in which cases and controls were selected does not allow a representative estimate of the incidence of CE and hypernatremia during DKA.

In conclusion, this study suggests that the production of a modest degree of hypernatremia might be needed to prevent a drop in $P_{\text{Eff osm}}$ and the development of CE in children with DKA. This may explain why a smaller rise in $P_{\text{Na}}$ might be associated with CE.7,10,15 If a drop in $P_{\text{Eff osm}}$ were prevented during therapy of DKA, and this required the presence of hypernatremia, then perhaps achieving this abnormal electrolyte concentration should be a goal of therapy when $P_{\text{Na}}$ is not appreciably low in a patient with serious hyperglycemia.

REFERENCES


50 Years Ago in The Journal of Pediatrics

Serious Complications of Varicella, Including Fatalities
Blattner RJ. J Pediatr 1957;50:515-18

In 1957, Blattner reported on the recognition of serious complications of varicella-zoster virus (VZV) infection in children. He reviewed known complications of VZV infection but also commented on pathologic and clinical findings described in the deaths of 2 immunocompromised children. Both cases demonstrated diffuse vasculitis and acute encephalitis at autopsy, constituting an early description of severe central nervous system complications of varicella.

What we know now about VZV prevention, treatment, and outcomes helps put these early findings into perspective. The most significant development in the management of VZV infection was the development of a live, attenuated varicella vaccine, licensed in 1996 and recommended in 1997 for routine vaccination of susceptible children aged 12 to 18 months. According to a 2003 report by the Centers for Disease Control, national varicella vaccination rates increased from 26% in 1997 to 85% in 2003 for children aged 19 to 35 months. Simultaneously, the incidence of acute chickenpox infection in the United States decreased ≤84% between 1990 and 2001 in reporting states. A 70% decline in varicella hospitalization rates from 1995 to 2003 and a 78% decline in varicella-related deaths for all age groups during 1999 to 2001, as compared with 1990 to 1994, were documented in 2 regional reporting sites. Efforts to provide booster doses of vaccine to prevent breakthrough infection and utilization of an adult zoster vaccine will likely further reduce VZV-related morbidity.

Immunocompromised children with acute VZV infection suffer disproportionate morbidity and death relative to healthy children. Encephalitis, hepatitis with fulminant liver failure, and pneumonitis remain deadly. Advances in prevention and treatment, including the use of vaccine, varicella-zoster immune globulin, and antiviral therapy have led to reductions in mortality rates for these patients. However, rates of solid organ transplantation, HIV infection, and use of immunosuppressive therapy have increased dramatically since 1957, and opportunistic infection remains the most common cause of death for immunocompromised patients. Thus, public health initiatives toward primary prevention of VZV infection must be prioritized. There remains great variation in immunization rates across states, as well as wide variation in immunization requirements for school and child care entry, which may constitute lost opportunities for disease prevention.

Whereas great progress toward reducing the burden of VZV infection in children has occurred since Blattner’s report in 1957, the rate of death associated with severe varicella-related complications remains significant, especially for immunocompromised patients. Care must be taken not to forget that these dangers remain just as scary and real as they were in 1957.

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Delayed Developmental Language Milestones in Children with Duchenne’s Muscular Dystrophy

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Objectives To document the attainment of developmental milestones in children with Duchenne’s muscular dystrophy (DMD) and to determine whether early delays are associated with later performance on measures of cognition.

Study design Retrospective parental report was utilized to document the acquisition of 10 common developmental milestones in children with DMD (n = 130) and their unaffected siblings (n = 59). Children completed tests of cognitive functioning.

Results Parents rated children with DMD as delayed on achieving both language and motor milestones more frequently than their unaffected siblings. Furthermore, those children with DMD who were rated as late talkers or late walkers performed more poorly on tests of cognitive function than their on-time peers.

Conclusions In addition to the commonly reported delays in motor milestones, the current study documents delays in the acquisition of language milestones as well. These early delays are associated with significant impairments in later cognitive functioning. (J Pediatr 2007;150:474-8)

Duchenne’s muscular dystrophy (DMD) is an X-linked disorder that occurs in 1 in 3500 male births.1 It is known primarily as a disease of the muscle, as children present with progressive muscular weakness. DMD is also associated with delays in the acquisition of motor milestones.1,2 Interestingly, in some cases delayed language milestones—not motor milestones—may be the earliest signs of DMD that give rise to clinical concern. Unfortunately, those early indications of DMD often go unnoticed because most clinicians still do not associate early language impairment with DMD.4 Indeed, with the exception of several case studies,5,6 this link has never been studied systematically. Given the ubiquitous screening for general milestone attainment, determining how children with DMD present from a cognitive perspective may provide a promising avenue for improving the likelihood of early diagnosis and intervention.

There is ample evidence of cognitive involvement in DMD, although the presentation is much more variable than the motor symptoms of the illness. On average, the mean IQ in children with DMD is shifted down one standard deviation from the population mean, and verbal IQ scores are more compromised than performance IQ scores.7 However, no relationship has been documented between levels of muscular degeneration and cognitive impairment,8-12 nor is there a relationship between creatine kinase levels and cognitive impairment.9

There are considerable data attesting to specific verbal deficits in children and adolescents with DMD.13-25 Moreover, there is a clear association between brain function and cognition in DMD.26,27 Few studies have focused on early development (<5 years of age) in this population.28-30

The purpose of the current study, therefore, is to examine reports of early developmental milestones in children with DMD. We hypothesize that children with DMD will be reported as having more early language delays than their unaffected siblings or than expected for the general population. We also hypothesize that evidence of early language delays will be associated with lower scores on cognitive tests administered after 4 years of age.

METHODS

Children with DMD (n = 130) and unaffected sibling controls (n = 59) participated in a large-scale study investigating cognitive skills in boys with muscular dystrophy.
Diagnosis of muscular dystrophy was based on clinical onset of progressive weakness before 5 years of age, and either molecular assessment of mutation in the DMD gene or muscle biopsy that was deficient in dystrophin and compatible with DMD. Siblings were within 5 years of age of the proband. When more than one comparison child was available, preference was given first to male sex and then to closeness in age. Children with DMD were between 4 and 14 years of age, with a mean age of 9.00 years (SD = 2.52), and sibling controls ranged from 3 to 16 years of age, with a mean age of 9.85 years (SD = 3.61). Approximately one third of the probands (38%) were in a wheelchair at the time of assessment, and none of the sibling controls were wheelchair bound. Racial composition of the sample consisted of persons who identified themselves as Caucasian (88%), Hispanic (7%), African-American (3%), and Indian (2%).

Participants for this study were recruited through the Muscular Dystrophy Association clinics of Columbia Presbyterian Hospital, New York, and Children’s Healthcare of Atlanta at Scottish Rite Children’s Medical Center. Additionally, newsletters with a description of the study were sent to Parent Project Muscular Dystrophy, regional Muscular Dystrophy Association clinics, and parent support groups. Interested persons returned the response form directly to the investigator.

This study was approved by the Columbia University and New York Presbyterian Hospital Institutional Review Board, by the Queens College of the City University of New York Institutional Review Board, and by the Children’s Healthcare of Atlanta at Scottish Rite Children’s Medical Center Institutional Review Board.

As part of several ongoing studies, parents completed a developmental milestone questionnaire; they were asked to indicate whether their child was “on-time” or “late” for 10 developmental milestones listed. These included when the child first began to: smile, sit, crawl, stand, walk, say single words, construct complete sentences, read, and become bowel and bladder trained. In addition, parents had the option of recording the month at which their child achieved each milestone. Parents also completed the Child Behavior Checklist, a 118-item questionnaire in which parents rate the frequency with which their child engages in a variety of behaviors.

Children enrolled participated in different neuropsychological studies involving a number of measures of language, memory, and visuospatial skills. Measures included in the battery required minimal motor involvement. Some of the test measures have been described in detail elsewhere. This article will report results from two tests used across batteries to ensure the largest sample size: the Peabody Picture Vocabulary Test, 3rd edition, and the Raven’s Colored Progressive Matrices. Both tests were scored twice to ensure consistency; discrepancies were resolved by consensus.

After obtaining written informed consent from the participant and verbal assent from the child, parents completed questionnaires while their children were administered the complete battery of neuropsychological tests. Testing was done in English. Most testing was completed at the Columbia Presbyterian Medical Center. In some cases, however, children were tested in their home, in a quiet room.

Based on the retrospective history of early developmental milestones provided by the parents, children were classified as either “on-time” or “late” in achieving developmental milestones. In the event that the parent did not indicate whether their child was on-time or late, but recorded the month at which their child achieved each milestone, the data were converted to on-time or late by determining whether the child achieved the milestone within the same period or after 90% of the general population did. Norms for the general population were based on the Denver Developmental Screening Test, with the exception of bowel and bladder control norms, which were extracted from Copeland and Kimmel. In the event that a parent both endorsed on-time or late and recorded the month, preference was given to the on-time/late variable; however, these data were checked for accuracy. Because of the variable manner in which parents responded to items on this questionnaire, the total number of responses for each developmental milestone is different. As such, data are presented as percentages, and the lowest number of responses (n = 130) was used as the total N.

To determine the percentage of children with DMD (n = 130) reported to be on-time versus late for each developmental milestone, a frequency count was used.

To determine whether the likelihood of delay for each developmental milestone was equivalent between the probands and their siblings, analyses were performed only on those probands with unaffected siblings controls (n = 59). The null hypothesis predicted an equal likelihood of delay among children with DMD and their siblings as reported by their parents. Alpha was set at .005 to account for the multiple comparisons (.05/10 = .005).

To determine whether early delay was associated with later cognitive functioning, two variables with the largest values were chosen: when the child first began to walk and construct complete sentences (hereafter referred to as “walk” and “sentence”). These variables were chosen because of their discriminative ability among the sibling pairs, and for the current analysis, were applied to the larger group of DMD probands only. A series of independent sample t tests were performed among DMD children to determine whether delay on the above-mentioned two variables was related to performance on the Peabody Picture Vocabulary Test, 3rd edition, the Raven’s Colored Progressive Matrices, and parental report on the Child Behavior Checklist. The null hypotheses were that there would be no differences in test scores between children rated late or on-time on early milestones.

**RESULTS**

The percentage of children with DMD reported to be on-time versus late for each developmental milestone can be found in Table I. Data show variable ranges of responses across items. Only 3% of the children with DMD were rated late on developing their smile, and 67% were rated late on
beginning to walk independently. For most items, between 30% and 50% of the group were rated late.

Results of \( \chi^2 \) analyses revealed that children with DMD were rated as late more often than their unaffected siblings on most, but not all, developmental milestones (Table II). Specifically, parents reported that their children with DMD were more often late in motor milestones such as sitting (\( \chi^2 = 28.37, P < .001 \)), crawling (\( \chi^2 = 40.53, P < .001 \)), standing (\( \chi^2 = 44.79, P < .001 \)), and walking (70% vs 2%, \( \chi^2 = 52.14, P < .001 \)) than their siblings. Furthermore, a greater percentage of children with DMD than siblings were also rated as delayed on language milestones. More children with DMD were reportedly late in speaking their first word (\( \chi^2 = 24.12, P < .001 \)) and in speaking in full sentences (49% vs 4%, \( \chi^2 = 29.73, P < .001 \)) than their siblings. No between-group differences were observed on other aspects of development, such as when their children first smiled, or when they achieved bowel or bladder control.

Results of independent sample t tests revealed that children with DMD whose parents rated them as late in constructing complete sentences were more likely to perform poorly on measures of single-word vocabulary (mean [SD]: late = 94.29 [22.26], on-time = 107.00 [17.07]; \( t = 3.75, P < .001 \)) and visuospatial reasoning (mean [SD]: late = 90.87 [25.26], on-time = 101.62 [13.21]; \( t = 3.17, P = .002 \)) than children with DMD who were on-time in this regard. There was no significant difference in behavioral difficulties between the two groups of children with DMD.

Children with DMD who were rated as delayed on walking performed significantly more poorly on a measure of visuospatial reasoning (mean [SD]: late = 94.35 [22.08], on-time = 103.07 [12.12]; \( t = 2.38, P = .02 \)); however, there was no relationship between delayed walking and performance on a measure of single-word vocabulary. Furthermore, children with DMD who rated as delayed on walking did not exhibit later behavioral issues when compared with children with DMD who achieved this milestone on-time.

### Table I. Percentage of children with DMD rated as “on-time” or “late” for each developmental milestone*

<table>
<thead>
<tr>
<th>Milestone</th>
<th>On-time (%)</th>
<th>Late (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smile</td>
<td>97</td>
<td>3</td>
</tr>
<tr>
<td>Sit</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>Crawl</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>Stand</td>
<td>43</td>
<td>53</td>
</tr>
<tr>
<td>Walk</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>Speak</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td>Sentence</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>Bowel trained</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Bladder trained</td>
<td>59</td>
<td>40</td>
</tr>
<tr>
<td>Read</td>
<td>51</td>
<td>47</td>
</tr>
</tbody>
</table>

*Percentages have been rounded up and may not equal 100% in all cases.

### Table II. Comparison of children with DMD and sibling controls on developmental milestones: percentage late for each milestone as per parental report

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Proband: % late</th>
<th>Control: % late</th>
<th>( \chi^2 )</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smile</td>
<td>3%</td>
<td>2%</td>
<td>.34</td>
<td>NS</td>
</tr>
<tr>
<td>Sit</td>
<td>38%</td>
<td>0%</td>
<td>28.37</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Crawl</td>
<td>60%</td>
<td>6%</td>
<td>40.53</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Stand</td>
<td>56%</td>
<td>0%</td>
<td>44.79</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Walk</td>
<td>70%</td>
<td>2%</td>
<td>52.14</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Speak</td>
<td>42%</td>
<td>4%</td>
<td>24.12</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Sentence</td>
<td>49%</td>
<td>4%</td>
<td>29.73</td>
<td>P &lt; .001</td>
</tr>
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<td>Bowel trained</td>
<td>28%</td>
<td>8%</td>
<td>7.77</td>
<td>NS</td>
</tr>
<tr>
<td>Bladder trained</td>
<td>25%</td>
<td>10%</td>
<td>5.97</td>
<td>NS</td>
</tr>
<tr>
<td>Read</td>
<td>94%</td>
<td>6%</td>
<td>25.89</td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>

NS, Not significant.

### DISCUSSION

Results of the current investigation indicate that children with DMD are more likely than their siblings to be rated as delayed on most language and motor milestones. Consistent with previous reports of motor delay, children with DMD tend to be delayed in sitting, crawling, standing, and walking. The current investigation also documented delays in language milestones; children with DMD are more likely than their siblings to exhibit delays in speaking their first word and in constructing sentences. Not all aspects of development were rated as delayed. For example, parents reported that children with DMD and their siblings were equally capable of mastering bladder and bowel control at similar ages. The selectivity of these findings indicates that reports of delay among affected children are unlikely to be attributed solely to a bias in reporting.

The second goal of this study was to examine, in more detail, the relationship between early developmental delay and cognitive functioning among children with DMD. Results of this investigation revealed that late talkers performed significantly more poorly on select measures of intellectual functioning. It is important to emphasize that these findings, although statistically robust, represented subtle differences in performance. For example, children with DMD who were reported to be late talkers scored slightly below average (mean standardized score of 95) on the test of vocabulary, although those who were on-time in learning to speak scored slightly above average (mean standardized score of 107). These findings were statistically significant at the P < .001 level. There were no significant differences between the two groups on reports of behavior.

A similar analysis was performed on children who had been rated as delayed in walking; in contrast to late talkers, it was hypothesized that late walkers would not exhibit cognitive delays or behavioral problems. Unexpectedly, however, late walkers did significantly more poorly on the test of reasoning than their on-time peers. Although the reason for...
this finding is unclear, it is not uncommon to observe impaired motor skills associated with cognitive disorders. For example, children with specific language impairment often present with poor motor skills. It can be conjectured that the same part of the brain that is responsible for learning coordinated movement (ie, cerebellum) also contributes to cognitive functioning in this disorder. Tentative support for this hypothesis is offered by a positron emission tomography scan study in which children with DMD exhibited reduced glucose metabolism in areas normally rich in dystrophin, namely, the cerebellum.

The current study employed retrospective parental report as the primary method of investigating the attainment of developmental milestones in a large group of children with DMD and their siblings. Although the investigators are mindful of the potential drawbacks associated with the use of retrospective parental report in ascertaining timing of developmental milestones, several features of the design of the current study serve to increase the likelihood of accurate parental report. The investigators chose to focus on broad categories such as “on-time” and “late” to increase the likelihood of accurate parental report. The fact that the control group consisted of siblings also enhanced the investigators' confidence in the accuracy of parental report because the accuracy of the parent likely remained consistent between siblings. Indeed, there is substantial support for the hypothesis that most parents are capable of judging whether their child's development is on par with other children of the same age, even when they are poor, uneducated, or lack parenting experience.

The use of siblings as controls is, in fact, one of the strengths of the current design. This method of control helps account for genetic, familial, and socioeconomic variables, and, thus, permits detection of subtle neuropsychological deficits unique to children with this disorder. Previously published data have demonstrated subtle, yet statistically robust, differences in neuropsychological test performance between children with DMD and their unaffected siblings. Some of the cognitive deficits observed might not ordinarily suggest a need for clinical intervention, but, when compared with those of siblings, their significance is highlighted.

The findings of this study are important for several reasons: Early delays in the development of language and motor skills (ie, before the onset of significant motor weakness) demonstrate that poor performance on measures of cognition cannot be attributed solely to muscle fatigue, emotional reactions to DMD, or the loss of educational opportunities because of limited ambulation. Moreover, early delay implicates an underlying central nervous system component to DMD. Finally, the current findings underscore the need for early intervention services in this population. The initiation of early intervention may help limit later learning problems, potentially enhancing the quality of life for a group of children who face adversity in the form of enormous physical and emotional challenges.

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Effect of Fish Oil Supplementation on Fatty Acid Status, Coordination, and Fine Motor Skills in Children with Phenylketonuria

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Objective To investigate effects of long-chain omega-3 polysaturated fatty acids (LC-PUFA) on motor skills in patients with phenylketonuria (PKU).

Study design Thirty-six patients with PKU (1-11 years of age, good metabolic control: plasma phenylalanine ≤360 μmol/L for ≥6 months). We determined plasma phospholipid fatty acids, and in patients >4 years of age (N = 24) the mototmetric Rostock-Oseretzky Scale (ROS), before and after supplementation with fish oil for 3 months (15 mg docosahexaenoic acid [DHA]/kg body weight daily). ROS was also assessed in 22 age-matched controls.

Results Patients had low n-3 LC-PUFA in plasma phospholipids (DHA, 2.37 ± 0.10%; eicosapentaenoic acid [EPA], 0.4 ± 0.03%) and poorer ROS performance than controls (motor development index [MQ] 107 ± 3 vs 117 ± 3, P = .010). Supplementation increased phospholipid n-3 LC-PUFA (DHA 7.05 ± 0.24%; EPA 3.31 ± 0.19%; P < .001), decreased n-6 LC-PUFA (arachidonic acid, 9.26 ± 0.23% vs 6.76 ± 0.16%; P < .001), increased plasma branched-chain amino acids (0.24% vs 0.19%; P < .001), and improved ROS (MQ 115 ± 3.54, P = .011, paired t test). ROS was unchanged in 11 retested controls (MQ 115 ± 5.16, P = NS, paired t test multivariate analysis of variance [MANOVA] for time by group, P = .027). Patients tolerated fish oil well. Plasma phenylalanine remained unchanged.

Conclusion In patients with PKU, fish oil supplementation enhances n-3 LC-PUFA levels and improves motor skills. (J Pediatr 2007;150:479-84)

Phenylketonuria (PKU) caused by deficient activity of hepatic phenylalanine hydroxylase affects about 1 in 7000 live newborns in Caucasians. If left untreated, children with PKU suffer from severe psychomotor retardation. Postnatal diagnosis by newborn screening programs and early initiation of treatment based on strictly limited natural protein intake and supplemented phenylalanine-free synthetic amino acid mixtures result in a largely normal cognitive development. However, patients with PKU continue to have subtle but measurable neurological deficits. The IQ of these patients tends to be slightly lower than that of their healthy siblings, and they show inferior average school achievements. Many patients suffer from disturbance of concentration ability and a prolonged reaction time. Slight impairments in specific motor functions have been shown, especially in hand-wrist steadiness, finger-hand dexterity, and hand-wrist speed.

The reasons for these subtle dysfunctions remain unclear. Fluctuations of plasma phenylalanine concentrations can influence cognitive performance, but other factors seem to contribute as well. The mainstay of therapy, strict dietary treatment, may induce metabolic imbalances. Vitamin and trace element depletions have been reported in patients with PKU. Long-chain polyunsaturated fatty acids (LC-PUFA), particularly docosahexaenoic acid (DHA, 22:6n-3) are also poorly supplied because natural food sources of LC-PUFA such as meat, liver, fish, and eggs are rich in protein and hence avoided with the PKU diet. Therefore, patients with PKU rely almost exclusively on endogenous production of DHA and other LC-PUFA by elongation and desaturation of the precursors linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3). Low plasma or

<table>
<thead>
<tr>
<th>ANOVA</th>
<th>Analysis of variance</th>
<th>MANOVA</th>
<th>Multivariate analysis of variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
<td>MQ</td>
<td>Motor development index</td>
</tr>
<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</td>
<td>PKU</td>
<td>Phenylketonuria</td>
</tr>
<tr>
<td>LC-PUFA</td>
<td>Long-chain polysaturated fatty acids</td>
<td>ROS</td>
<td>Rostock-Oseretzky Scale</td>
</tr>
</tbody>
</table>

See editorial, p 457

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serum concentrations of LC-PUFA, especially of DHA, have been described in patients with classic PKU.14,15

LC-PUFA are essential components of all cell membranes and modulate membrane functions. Animal studies have established that LC-PUFA availability modulates visual and behavioral development.16,17 In controlled trials supplementation of healthy formula-fed infants with preformed LC-PUFA led to beneficial effects on visual and psychomotor development in some but not all reported studies.18-20 Little is known on potential effects of LC-PUFA status on neurological functions beyond infancy.

We hypothesized that children with PKU who have a poor LC-PUFA supply may benefit from supplementation with fish oil providing n-3 LC-PUFA. We have previously shown that LC-PUFA supplementation in 36 children with PKU has enhanced information processing in the central nervous system, as assessed by visual evoked potential latencies.21 Here, we report the effect of LC-PUFA supplementation on fatty acid status and motor skills in the same study group.

METHODS

Trial Design

This open clinical trial included patients with classic PKU 1 to 11 years of age and was performed in accordance with the Declaration of Helsinki/Somerset West and ICH-GCP guidelines. The protocol was reviewed by the ethics committee of the Bavarian Board of Physicians, Munich, Germany. Information of patients and/or parents and acquisition of their consent was carried out in writing. Inclusion was restricted to patients with a documented average blood phenylalanine level, determined at least monthly over the previous 6 months, <360 μmol/L. Patients with additional diseases or abnormal signs in the general or neurological examination were excluded.

At baseline, patients were examined clinically, blood was taken for plasma phospholipid fatty acid status, routine blood tests, and phenylalanine concentration. The Rostock-Oseretzky Scale (ROS) was performed as described below.

Patients were then supplied with fish oil capsules (Ameu®, Omega Pharma, Berlin, Germany) providing 500 mg fish oil per capsule (35% omega-3 fatty acids including 18% eicosapentaenoic acid [EPA] and 12% DHA); the coating (gelatin) contained 3 mg phenylalanine. To ensure a dose of >15 mg DHA/kg body weight, patients received one capsule per day for each 4 kg body weight, rounding up to the next full capsule. Thus, patients received 2 to 10 capsules per day in two divided doses. All other aspects of dietary treatment remained unchanged. After 90 days of fish oil supplementation, a follow-up examination was performed in the same way as the baseline examination.

Healthy, age-matched children without special diets volunteered as controls. Written informed consent was obtained from the guardians. Controls were examined clinically, the motometric scale (ROS) was assessed at baseline, and again after 90 days in a subgroup. For ethical reasons, no blood sample was taken in controls, and they did not receive fish oil.

Subjects

Sixty-five patients, 1 to 11 years of age, were screened. Thirty-eight patients were enrolled, and 36 completed the protocol (6.3 ± 0.6 years of age, 19 females, two dropouts). The diagnosis of PKU had been established by newborn screening and confirmed by further testing and, in most patients, by molecular genetics. Dietary treatment had been initiated within the first 3 weeks of life. All patients were regularly seen in our clinic and followed a strict protein-restricted diet. The mean daily phenylalanine intake was 13.9 ± 0.6 mg/kg and did not change during the study. The dosage of synthetic amino acids followed current recommendations for protein intake in children22 with an added surplus of 20% to account for possible differences in biological value of synthetic amino acid mixtures relative to natural protein.

Controls were 30 healthy, age-matched children (6.6 ± 0.5 years of age, 15 females).

Fatty Acid Analysis

Venous blood with sodium-ethylene-diamine-tetraacetate as anticoagulant (1 mg/mL) was taken at least 4 hours after the last meal, at baseline, and after 90 days of fish oil supplementation. Plasma was separated immediately and frozen at −80°C until further analysis. Total lipids were extracted from 0.25 mL plasma with chloroform/methanol after addition of internal standard (C15:0), according to the method of Folch. Lipid classes were separated by one-dimensional thin layer chromatography on silica gel plates (Merck, Darmstadt, Germany) with development in n-heptane:diisopropylether:acetic acid (60:40:3). The band containing phospholipids (PL) was identified by comparison to standards, removed by scraping, and transesterified with methanolic hydrochloric acid. Fatty acids were analysed by high-resolution capillary gas liquid chromatography with a Hewlett-Packard 5890 Series II gas chromatograph (Hewlett-Packard, Boeblingen, Germany), equipped with a 50 m × 0.32 mm (inside diameter) polar cyanopropyl silicone-coated column (SGE, Weiterstedt, Germany). Fatty acid determination was performed at a column-head pressure of 1.3 bar and an initial temperature of 130°C increasing by 3°C per minute to 180°C and then by 4°C per minute to 220°C. Peak identification was performed by comparison with authentic standards (Nu-Chek-Prep, Elysian, Minnesota).

Motometric Rostock-Oseretzky Scale by Kurth (ROS)

The ROS is a reliable test battery of body coordination and fine motor skills in children 5 to 11 years of age.23 The test was performed in the subgroup of 24 children with PKU and 11 controls within this age range.

The test battery contains five subtests of specific motor functions (static balance with and without optic control, dynamic balance, fine motor ability with consideration of velocity and accuracy, and motoric–rhythmic coordination). Every
subtest is demonstrated and explained until the proband has a complete understanding of the task, but there is no training phase. The subtests are first evaluated separately to yield test-specific C-values, based on the child’s age. The C-values are added to a total C-score, which serves to determine the motor-development index (MQ). Similar to the IQ, the MQ is normalized to a median score of 100, derived from the normative population. The minimal total C-score of 1 represents a MQ of 28, the highest achievable C-score is 50 and represents an MQ of 149.

Subtests:

1. Coins: Twenty coins are placed in two lines at the edge of a table. The proband picks up the coins using the dominant hand one at a time and puts them into a small box placed behind the coin line. The number of coins put into the box within 15 seconds is counted.

2. Maze: With a soft pencil, the proband follows a small maze printed on paper. Evaluation criteria are touching, crossing, or interruption of the predicted line (maze mistakes) and the time required to finish the task (maze time).

3. Dynamic balance: The proband balances heel-to-toe over wooden ledges of different width (8, 7, 6, 5, 4, 3, 2 cm), starting with the widest. The end of the test is determined by either stepping aside, or by finishing all ledges without stepping aside. The number of balanced ledges is recorded.

4. Static balance: Standing on heels or toes on both feet (arranged in tandem, with eyes open and closed), standing on the toes (feet arranged next to each other, with eyes open or closed), standing on one foot (right and left, with eyes open and closed), and standing on one foot while crossing the hands behind the back. Evaluation criterion is the number of fulfilled tasks without losing equilibrium.

5. Motoric-rhythmic coordination: Clapping and stamping of six different rhythms. Evaluation criterion is the accuracy of the clapped rhythm for four measures.

The test was always performed under the same circumstances. One investigator (H.R.) examined all tested children (PKU and controls) at baseline and follow-up, each time in the same room of the hospital. Only the proband, the investigator, and the guardian were in the room. The guardian was allowed to watch the procedure but not to speak or gesture to proband or investigator. The raw data (raw scores, mistakes, time) were recorded on a standardized worksheet. Calculation of the C-value and MQ test were performed by a different investigator (S.B.) who was masked with respect to the identity of the person tested and the test date (baseline/follow-up).

Data Analysis

Comparisons between patients and controls were performed by analysis of variance (ANOVA) and Student’s t test. To test treatment effects, MANOVA for repeated measures was used, with “group” as a between-subjects factor with two levels (patients and controls) and “time” as within-subjects factor with two levels (baseline and follow-up). After verification for normal distribution in all data sets, cases were weighted by group where appropriate. T test for paired samples was applied in addition for comparisons of baseline and follow-up evaluations. The Statistical Package for the Social Sciences for Windows 11.0 (SPSS Inc., Chicago, Ill.) was used for all statistical operations. Significance was accepted for P < .05. Data are given as mean ± SEM unless otherwise mentioned.

RESULTS

Plasma Phospholipid Fatty Acid Profiles

Compared with data of healthy children of the same ethnicity and from the same region,24 children with PKU showed a similar fatty acid composition of plasma phospholipids. Somewhat lower values were found in patients for total n-3 fatty acids and especially DHA (2.37 ± 0.1%) than in the reference population (2.62 ± 0.99%), whereas there were higher levels for total n-6 fatty acids (36.19 ± 0.49% vs 32.82 ± 2.68% in healthy children) and linoleic acid. Therefore, the n3 to n6 ratio tended to lower values in the patients. However, mean fatty acid levels in the patients were within the range of values observed in healthy omnivorous children in Europe.24

Fish oil supplementation increased the DHA concentration almost threefold and the EPA concentration about eightfold. This pronounced increase of DHA and EPA over time indicates a good compliance with the fish oil capsules. Total concentration of the n-6 fatty acids decreased by approximately 20% because of a decrease of especially arachidonic acid (AA) (by about 25%) and of its precursors 18:2n6 and 20:3n6. Mead acid (20:3n9) decreased by almost 50%, consistent with an increasing n-3 pool (Table I).

Coordination and Fine Motor Skills

At baseline, ROS was performed in 24 patients and 22 controls. Although all patients achieved results within the normal range, they showed poorer mean motor skills than controls with a significantly lower overall MQ (Table II). The children with PKU performed worse in all but one subtest, with particular marked differences in coin sorting and maze mistakes (testing finger-hand dexterity, hand-wrist speed, and eye-hand coordination) as well as in dynamic balance (Table II).

All 24 patients and 11 controls were retested after 3 months. During this interval, only the patients received fish oil supplements. At follow-up, the children with PKU showed a marked improvement in overall MQ (Table III) and in the subtests coin sorting and dynamic balance (Table IV), and there was no change in controls.

Relationship between Fatty Acid Status and Motometric Test Results

Using linear regression or bivariate correlation, no significant correlations were found between the plasma concentrations of the fatty acids analyzed (DHA, EPA, AA; total n3, total n6, n3 to n6 ratio) and the motometric performance (MQ and subtest C-values). Changes in the fatty acid concentrations during the supplementation period did not correlate to changes in the MQ or the ROS subtests. Plasma
phenylalanine levels did not correlate to motometric test results at baseline ($P = .45$) or at follow-up ($P = .69$).

**Tolerance**

Fish oil supplementation for 90 days showed no serious adverse effects. Even though the fish oil capsules contained small amounts of phenylalanine (3 mg/capsule), plasma phenylalanine concentrations did not change during the intervention period (Table I). Patients judged the overall tolerance as very good in 83%, good in 11%, and moderate in 6%. Six minor adverse events were observed during the course of the study (mild acute viral gastroenteritis), but a dose reduction or an interruption of fish oil administration was not considered necessary in any case.

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### Table I. Plasma concentration of phenylalanine (μmol/L) and major fatty acids in plasma phospholipids (% weight/weight, mean ± SEM) in children with PKU before and after 3 months of fish oil supplementation

<table>
<thead>
<tr>
<th></th>
<th>N = 35</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Mean change</th>
<th>P (paired t test)</th>
</tr>
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<tbody>
<tr>
<td>Phe</td>
<td></td>
<td>266 ± 14.4</td>
<td>271 ± 21</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>SFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>44.93 ± 0.32</td>
<td>44.63 ± 0.14</td>
<td>-0.41 ± 0.30</td>
<td>NS</td>
</tr>
<tr>
<td>Mead</td>
<td></td>
<td>20:3n9</td>
<td>0.21 ± 0.02</td>
<td>0.13 ± 0.01</td>
<td>-0.09 ± 0.1</td>
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<tr>
<td>MUFA</td>
<td></td>
<td>total</td>
<td>13.62 ± 0.42</td>
<td>13.05 ± 0.32</td>
<td>-0.60 ± 0.33</td>
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<td>21.47 ± 0.57</td>
<td>18.37 ± 0.54</td>
<td>-2.97 ± 3.06</td>
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<td></td>
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<td>-0.00 ± 0.10</td>
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<tr>
<td>n-3 to n6</td>
<td></td>
<td>0.11 ± 0.01</td>
<td>0.45 ± 0.02</td>
<td>+0.33 ± 0.002</td>
<td>&lt; .001</td>
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</table>

Total SFA: sum of 14:0, 16:0, 18:0, 20:0, 22:0, 24:0.
Total MUFA: sum of 16:1n7, 18:1n9, 18:1n7, 20:1n9, 20:3n9, 22:1n9, 24:1n9.
Total n6 PUFA: sum of 18:2n6, 18:3n6, 20:2n6, 20:3n6, 20:4n6, 22:2n6, 22:4n6, 22:5n6.
MUFA, Monounsaturated fatty acids; Phe, phenylalanine; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

---

### Table II. Results of the Rostock-Oseretzky Scale subtests (C-values) at baseline and after 3 months in children with PKU and controls

<table>
<thead>
<tr>
<th>C-values</th>
<th>PKU (N = 24)</th>
<th>Controls (N = 22)</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coins</td>
<td>6.2 ± 0.4</td>
<td>7.4 ± 0.5</td>
<td>.061</td>
</tr>
<tr>
<td>Maze time</td>
<td>8.1 ± 0.5</td>
<td>7.4 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Maze mistakes</td>
<td>4.7 ± 0.4</td>
<td>6.1 ± 0.4</td>
<td>.030</td>
</tr>
<tr>
<td>Dynamic balance</td>
<td>4.1 ± 0.5</td>
<td>5.5 ± 0.5</td>
<td>.042</td>
</tr>
<tr>
<td>Static balance</td>
<td>6.0 ± 0.5</td>
<td>6.9 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Motor-rhythm coordination</td>
<td>3.9 ± 0.5</td>
<td>4.9 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>C-score</td>
<td>33.0 ± 1.3</td>
<td>38.2 ± 1.4</td>
<td>.009</td>
</tr>
<tr>
<td>MQ</td>
<td>107 ± 3</td>
<td>119 ± 3</td>
<td>.010</td>
</tr>
</tbody>
</table>

---

### Table III. Motor development index (MQ) in children with PKU and controls at baseline and after 3 months show an improvement in patients following fish oil supplementation but no change in controls

<table>
<thead>
<tr>
<th>MQ</th>
<th>PKU (N = 24)</th>
<th>Controls (N = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>107 ± 3.25</td>
<td>116 ± 3.96</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>115 ± 3.54</td>
<td>115 ± 5.16</td>
<td></td>
</tr>
</tbody>
</table>

Paired t test†: $P = .027$

†Baseline vs follow-up within the same group (PKU or controls).

### Table IV. Results of the Rostock-Oseretzky Scale subtests (C-values) at baseline and after 3 months in children with PKU and controls

<table>
<thead>
<tr>
<th>C-values</th>
<th>PKU (N = 24)</th>
<th>Controls (N = 11)</th>
<th>MANOVA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coins</td>
<td>6.2 ± 0.4</td>
<td>6.7 ± 0.9</td>
<td>0.046</td>
</tr>
<tr>
<td>Maze time</td>
<td>7.9 ± 0.4</td>
<td>7.1 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Maze mistakes</td>
<td>8.1 ± 0.5</td>
<td>8.1 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Balance dynamic</td>
<td>4.7 ± 0.4</td>
<td>5.1 ± 0.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Balance static</td>
<td>4.7 ± 0.4</td>
<td>5.1 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Motor-rhythm coordination</td>
<td>5.2 ± 0.5</td>
<td>5.6 ± 0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*For repeated measures by group, with between-subject factor “group” and within-subject factor “time.”
DISCUSSION

Significant deficits in body coordination and fine motor skills were found in this group of children with PKU under good metabolic control with treatment since the newborn period following current standards. A supply of fish oil with high amounts of DHA and EPA for 3 months significantly increased both the plasma phospholipid n-3 fatty acids and results of the motometric test. The change of the MQ is not likely to constitute a normal developmental process or a training effect because there was no change in the age-matched control group after the same follow-up period. Thus, our data indicate that LC-PUFA supply may exert a benefit on body coordination and fine motor skills in patients with PKU.

The prerequisite for the normal development of proper hand motor function is the maturation of corticomotoneuronal connections. In healthy children, the development of motor function is variable and probably not complete before entering puberty. The various components of motor control appear to mature by 8 to 12 years of age. The reduced MQ values in our patients may reflect either a structural deficit or a developmental delay, but the latter seems more likely given the response to fish oil. A study in adult patients with early treated PKU, with completed psychomotor development, may help clarify this question.

Chronically elevated phenylalanine concentrations are known to have an impact on brain function, but the concurrent phenylalanine level seems to contribute as well. Therefore, we chose to include only patients with good metabolic control, that is, an average phenylalanine level <360 μmol/L, over 6 months. Plasma phenylalanine concentration remained stable over the study period, and there was no correlation between current phenylalanine concentrations and the motometric test results. Thus, the improved motor function is not a result of changes in current metabolic control.

Dietary treatment of patients with PKU may contribute to the observed deficits. Depending on the individual phenylalanine tolerance, the PKU diet provides roughly one-sixth of the usual intake of natural proteins in healthy children. Concomitantly, all other components of protein rich foods are avoided. Clinically relevant deficiencies have been recognized for calcium, iron, zinc, and vitamin B12, which are currently supplied with amino acid substitutes for PKU. More recently, LC-PUFA depletion of plasma lipids has been reported in patients with PKU. DHA is considered the functionally most relevant LC-PUFA because it has decisive functions in the assembly, maintenance, and proper function of brain cell membrane lipids. The endogenous synthesis of DHA from the precursor α-linoleic acid found in vegetable oil is rather inefficient in humans. Several studies in healthy newborn infants have recognized the role of DHA supply as an important factor in postnatal psychomotor development.

The observed significant improvement of the MQ with fish oil supply supports a beneficial role of DHA. Abnormalities in the brain white matter are found in untreated and even early treated patients with PKU on magnetic resonance imaging. Electrophysiological studies revealed prolonged latencies of visual and somatosensory evoked potentials in varying proportions, which responded to LC-PUFA supply in two recent studies. High-dose DHA may directly or indirectly revert these abnormalities. In generalized peroxisomal disorders, DHA supplementation reduced MRI signs of dysmyelination, which supports this notion. The lack of significant correlations between the increase of LC-PUFA concentrations and improvement of motor function only partially argues against a biological relationship because plasma concentrations do not necessarily represent fatty acid availability in relevant tissues. Further, the assumed effect involves several steps in the uptake and metabolism of fatty acids by the brain, a process probably too complex to be represented by a linear relationship with plasma levels.

Given the functional consequences, we consider n-3 LC-PUFA conditionally essential substrates that should be supplied with the diet even beyond infancy. Since early and continuously treated patients with PKU benefit from dietary supplementation with n-3 LC-PUFA, their addition to the synthetic amino acid mixtures appears advisable. The dosage used in this study resulted in supranormal plasma n-3 LC-PUFA levels and was associated with a reduction of arachidonic acid values, hence a lower dosage of supplementation appears to be preferable and should be evaluated.

We are grateful for invaluable support by the patients and their families and the staff of the Dr. von Hauner Children’s Hospital.

REFERENCES


The Poor Prognosis of Childhood-Onset Bipolar Disorder

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Objective  We examined age of onset of bipolar disorder as a potential course-of-illness modifier with the hypothesis that early onset will engender more severe illness.

Study design  A total of 480 carefully diagnosed adult outpatients with bipolar disorder (mean age, 42.5 ± 11.6 years) were retrospectively rated for age of illness onset, time to first pharmacotherapy, and course of illness. Clinicians prospectively rated daily mood fluctuations over 1 year.

Results  Of the 480 patients, 14% experienced onset in childhood (12 years or younger); 36% in adolescence (13 to 18 years); 32% in early adulthood (19 to 29 years); and 19% in late adulthood (after 30 years). Childhood-onset bipolar illness was associated with long delays to first treatment, averaging more than 16 years. The patients with childhood or adolescent onset reported more episodes, more comorbidities, and rapid cycling retrospectively; prospectively, they demonstrated more severe mania, depression, and fewer days well.

Conclusions  This study demonstrates that childhood onset of bipolar disorder is common and is associated with long delays to first treatment. Physicians and clinicians should be alert to a possible bipolar diagnosis in children in hopes of shortening the time to initiating treatment and perhaps ameliorating the otherwise adverse course of illness.

(J Pediatr 2007;150:485-90)

The recent follow-up studies of Geller et al1,2 suggest a relatively difficult course of illness in children with bipolar disorder treated naturalistically in the community. Although 65% of the patients studied recovered for 2 weeks by the end of 2 years, 55% relapsed within this 2-year period, and 64% relapsed during the 4-year follow-up. Birmaher et al3 reported extremely long delays to achieving acute remission, along with relatively high subsequent relapse rates, in children with bipolar I, bipolar II, and especially bipolar NOS (not otherwise specified) disorders. Controlled clinical trial findings in long-term prophylaxis of childhood bipolar illness have reported high dropout rates due to inefficacy of either lithium or valproate monotherapy.4

There remains much controversy about the quality of symptoms and severity/duration thresholds sufficient for diagnosing childhood-onset bipolar illness.5-8 Given this ongoing controversy, many children with bipolar-illness are not being identified until after many years of psychopathology. In some instances, these children are being treated with stimulants or antidepressants for their comorbid attention deficit hyperactivity disorder (ADHD) without the recommended coverage of a mood stabilizer or atypical antipsychotic.6

Much of the diagnostic controversy derives from the lack of characteristic discrete episodes so often seen in adult-onset bipolar disorder.9 In contrast, many of the youngest children with otherwise profound manic and depressive mood and behavioral swings associated with considerable social or educational dysfunction show brief bursts and rapid changes in mood, sometimes several times within a 24-hour period, a phenomenon called “ultradian” cycling.1,2,10,11 A second reason underlying the controversy is that the extremes...
of activation, impulsivity, irritability, and anger that these children exhibit can occur in other childhood disorders, such as ADHD, oppositional defiant disorder, or major depressive disorder.12

In this article, we examine the proportion of adults who had childhood and adolescent onset of their illness and assess the illness outcomes related to these different ages of onset. One retrospective study by Perlis et al13 based on the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) cohort of 983 patients found that 27.7% had on onset of bipolar illness in childhood (age ≤ 12) while another 37.6% had their onset in adolescence (from ages 13 to 18). They found that both of these groups had a much more difficult course of illness compared with those with adult onset, including faster cycling, more days depressed, greater number lifetime of manic and depressive episodes, an increased risk of substance abuse and other comorbidities, and a greater lifetime risk of suicide attempts. We also revisit this issue in another adult outpatient cohort with several new methodological approaches. We obtained daily prospective clinician ratings for 1 year during naturalistic treatment of adult bipolar illness by experts to supplement the retrospective self-report findings. We also examined data on the lag between the onset of first symptoms likely meeting DSM-IV diagnostic criteria and the onset of first drug treatment for either mania or depression.

METHODS

The methods of study of this outpatient cohort have been presented in detail elsewhere.14-18 Outpatients were recruited between 1995 and 2002 largely from local advertisements and outpatient settings located near 4 research clinic sites in the United States (Los Angeles, Dallas, Cincinnati, and Bethesda) and 3 sites in Europe (Utrecht, Freiburg, and Munich). All patients provided informed written consent for participation in naturalistic follow-up. The population was a broad and representative sample, because patients were not excluded for the presence of comorbidities; the only exclusions were for active ongoing substance abuse that required separate treatment in another facility or other serious medical illnesses that might preclude participation in subsequent treatment protocols if this became necessary.

Patients were diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)19 and completed questionnaires about the extent of their previous course of illness.16-18,20 The self-report questions included (1) age of onset of first depressive symptoms associated with dysfunction, (2) age of onset of first hypomanic or manic symptoms, and (3) age of first treatment for either mania or depression. Age of onset was also obtained from the SCID19 interviews by trained clinicians based on an assessment of when symptoms similar to those experienced in adulthood first occurred. Ages of onset as assessed by these 2 methods were highly correlated (r = .80; P ≤ .001). In this study, we used patients’ self-reported age, because it was derived from the same patient assessment instrument that also provided retrospective data on course of illness and time to first treatment.

The 480 patients were assessed on various cross-sectional measures18,20 during each visit, as well as on the daily prospective National Institutes of Mental Health Life Chart Method (NIMH-LCM).21 Because the severity of mania and depression ratings on the NIMH-LCM are based on the degree of mood-related functional impairment in a patient’s usual social, educational, or occupational roles,21 they are readily remembered by the patient and rated by a clinician during the clinical interview. Such prospective NIMH-LCM clinician ratings are highly reliable over a period of several weeks to 1 month between visits and have been validated against more conventional cross-sectional rating scales, as described by Denicoff et al.22,23

Sequentially admitted patients who also had a full year of prospective daily clinician ratings were included in the analysis. Because preliminary analysis suggested potential nonlinear relationships between age of onset and various outcome measures, age of onset was divided into 4 groups as was done by Perlis et al.13 Onset at age 0 to 12 years was considered childhood onset; at 13 to 18 years, adolescent onset; at 19 to 29 years, early-adult onset; and after 30 years, late-adult onset.

Average severity of days ill (with euthymic days included) for the prospective year was calculated using the mood ratings for mania and depression on the NIMH-LCM on a scale of 0 to 4, with 0 = euthymic (not ill); 1 = mild severity, with little or no role dysfunction; 2 = low moderate (some dysfunction); 3 = high moderate (much dysfunction); and 4 = severe (essentially incapacitated).21 Days with ultradian cycling (ie, switching between mania and depression within a 24-hour period) were recorded separately and not counted in the assessment of number of episodes.

The normality of continuous measures was examined using the Kolmogorov-Smirnov test, and homogeneity of variance was examined using Levene’s test. Continuous demographic and outcome measures were examined using 1-way analysis of variance with the 4 onset groups. Bonferroni-corrected pairwise comparisons were used post hoc. A χ² test was used with categorical measures, with omnibus significance followed up with a 2 × 2 χ² test to determine the location of differences. All P values were evaluated for significance at <.05 (2-tailed). Results were Bonferroni-corrected for the 15 measures compared across onset groups.

RESULTS

The mean age at network entry (42.5 ± 11.6 years) was not significantly different among the patients with childhood, adolescent, and early-adult onset; however, the late-adult onset group was significantly older at network entry than the other groups (Table I). Of the 480 individuals with at least 1 year of complete prospective daily ratings, 65 (14%) reported onset at age 12 years or younger, 171 (36%) reported onset during adolescence, 154 (32%) reported early-adult onset, and 90 (19%) reported late-adult onset.
The duration from onset of illness to first pharmacologic treatment for depression or mania, available in 420 patients, was strongly inversely related to age of onset (Figure). The lag averaged $16.8 \pm 11$ years in those with childhood onset and $11.5 \pm 10$ years in those with adolescent onset. In contrast, those with onsets in early and late adulthood received their first treatment after average delays of only $4.6 \pm 7$ years and $2.6 \pm 5$ years, respectively.

As shown in Table I, patients with childhood-onset bipolar disorder had the highest incidence of parental history of bipolar illness and unipolar depression, and these percentages declined progressively in patients with later age of onset. Environmental adversity, also a potential vulnerability factor, was higher in those with early onsets of bipolar disorder, as revealed by the incidence of physical or sexual abuse in childhood.

A higher percentage of patients with childhood and adolescent onset reported having more than 20 affective episodes before network entry compared with those with adult onset. The incidence of dysphoric (as opposed to euphoric) mania was also substantially higher in patients with childhood onset (ie, mania was unpleasant, with more anxious and depressive symptoms). Among the comorbidities, patients with childhood onset had a higher prevalence of lifetime anxiety disorders and of drug abuse, with a nonsignificant trend in the same direction for alcohol abuse.

As shown in Table II, in the first year of daily prospective ratings during naturalistic treatment, patients with childhood onset remained substantially more ill than those with adult onset. The childhood-onset group had greater severity of both mania and depression, as well as more days depressed and days with ultradian cycling. They also had more total

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**Table I. Patient demographics and retrospective illness variables as a function of age of onset**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Childhood (0 to 12 years)</th>
<th>Adolescent (13 to 18 years)</th>
<th>Early adulthood (19 to 29 years)</th>
<th>Late adulthood (30+ years)</th>
<th>$\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (percent)</td>
<td>65 (14%)</td>
<td>171 (36%)</td>
<td>154 (32%)</td>
<td>90 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age at first symptom, years $\pm$ SD</td>
<td>9.57 ± 2</td>
<td>15.92 ± 2</td>
<td>22.60 ± 3</td>
<td>38.51 ± 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age at network entry, years $\pm$ SD</td>
<td>39.95 ± 11</td>
<td>40.37 ± 12</td>
<td>40.95 ± 11</td>
<td>51.20 ± 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>42 (65)</td>
<td>98 (57)</td>
<td>78 (51)</td>
<td>45 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>54 (83)</td>
<td>132 (80)</td>
<td>125 (83)</td>
<td>63 (73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>11 (17)</td>
<td>33 (20)</td>
<td>26 (17)</td>
<td>23 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabitating</td>
<td>28 (46)</td>
<td>82 (50)</td>
<td>78 (50)</td>
<td>49 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental history of bipolar disorder</td>
<td>23 (47)</td>
<td>52 (37)</td>
<td>27 (21)</td>
<td>12 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental history of depression</td>
<td>25 (52)</td>
<td>60 (43)</td>
<td>39 (29)</td>
<td>18 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical abuse as a child</td>
<td>22 (36)</td>
<td>36 (22)</td>
<td>21 (15)</td>
<td>10 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual abuse as a child</td>
<td>19 (31)</td>
<td>33 (20)</td>
<td>15 (11)</td>
<td>8 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphoric mania</td>
<td>48 (79)</td>
<td>94 (59)</td>
<td>68 (46)</td>
<td>46 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid cycling (lifetime)</td>
<td>45 (70)</td>
<td>83 (51)</td>
<td>66 (45)</td>
<td>35 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of mood episodes ($&gt;20$ lifetime)</td>
<td>50 (83)</td>
<td>105 (66)</td>
<td>63 (44)</td>
<td>30 (38)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comorbidities:**

- Lifetime anxiety disorder: 38 (60) vs 63 (37) vs 56 (37) vs 21 (24) vs 21.07 $< .001$
- Lifetime alcohol abuse or dependence: 27 (42) vs 60 (35) vs 46 (30) vs 22 (25) vs 5.77 .12
- Lifetime drug abuse (excluding alcohol): 16 (25) vs 42 (25) vs 30 (20) vs 7 (8) vs 11.14 .01

Includes patients with 1 full year (365 days) of prospective life chart data.
affection episodes during the prospective year and fewer days well (euthymic).

**DISCUSSION**

Our findings reveal that approximately 50% of adult outpatients with bipolar disorder had an onset of illness in either childhood or adolescence (ie, before age 19), and these individuals had long lags before initial treatment for mania or depression. These findings in a clinically identified cohort are convergent with recent epidemiologic data reported by Kessler et al demonstrating a substantial incidence of early onset and long lag to treatment. However, Kessler et al could not determine whether or not the lag to first treatment reflected the presence of mild symptomatology and had little functional impact. Our combined retrospective and prospective data indicate that early onset of bipolar disorder is associated with an adverse lifetime course of illness that extends into 1 year of naturalistic treatment in adulthood. When we analyzed data by site, we found that the sites in the United States had a significantly greater rate of childhood- and adolescent-onset bipolar disorder than those in Europe, as discussed in detail elsewhere.28 When considering only the US sites, our findings (62% onset in childhood or adolescence) are even more similar to those of Perlis et al,13 who found this onset pattern in 65% of their US participants.

Our data are also consistent with findings of Perlis et al indicating that earlier age of onset was associated with a more difficult and complicated course of illness, including faster cycling, more days depressed, greater lifetime manic and depressive episodes, increased risk of substance abuse and other comorbidities, and greater lifetime risk of suicide attempts. In our study, those with childhood onset had more mood episodes, as well as more anxiety disorder and substance abuse comorbidity (Table I). Furthermore, they also experienced more dysphoric mania and more ultradian cycling than the other groups.

These 2 retrospective accounts and the report by Lish et al of a more severe course of bipolar disorder in patients with earlier illness onset are now validated by clinician-rated daily prospective follow-up as adults. During naturalistic treatment (i.e., treatment as usual), those patients with early onset had more time depressed and more severe mania and depression, as well as less time well. The fact that these patients experienced a greater number of episodes in this 1 year of prospective follow-up indicates that the greater proportion of early-onset patients with high numbers of episodes reported retrospectively is not just an artifact of a greater number of years of potential exposure (ie, duration of illness).

Kessler et al,60,31 in their epidemiologic data from 983 community survey participants in the National Comorbidity Study Replication, found that 13% of bipolar patients had an onset of illness by age 10 and that time lags between illness onset and first treatment correlated inversely with age of onset.

The data from our cohort and that of Perlis et al indicate that 14% to 28% of patients with bipolar disorder experience onset of illness before age 13 and that 50% to 67% experience onset before age 19. Lish et al,29 in a study of bipolar patients surveyed from an affective illness advocacy group, also found that early onset of illness and long delay to appropriate diagnosis and treatment were very common. All of these findings taken together with the longest lags in onset of first treatment in those with the earliest onsets27-29 suggest that very–early-onset bipolar disorder was quite common even a generation ago, but was relatively underrecognized and undertreated at that time. Lange and McGinnis reviewed evidence likely indicating both cohort (year of birth) and anticipation (generational) effects in childhood-onset bipolar illness, possibly yielding even more children with early onset today than were found several decades ago when the adults in our study were at risk.

Consequently, providers who assess and treat children and adolescents in various health care settings, including primary and family practice, pediatrics, and neurology, who see many children with ADHD and other externalizing disorders, should be particularly alert to the possibility of bipolar disorder in the differential diagnosis. Such vigilance may begin to shorten what were the extraordinary long delays to first treatment some 20 years ago. Keep in mind, however, that even in adults, in whom there is much less diagnostic controversy, only 9.8% of those in a primary care clinic who screened positive for bipolar symptomatology were recognized as potentially having this disorder.33 Similarly, the underdi-

### Table II. Outcome in childhood- and adolescent-onset bipolar disorder: One-year prospective follow-up on the NIMH-LCM (n = 480)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Childhood (0 to 12 years)</th>
<th>Adolescent (13 to 18 years)</th>
<th>Early adulthood (19 to 29 years)</th>
<th>Late adulthood (30+ years)</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total days (hypo-) manic</td>
<td>51.4 ± 49</td>
<td>51.9 ± 59</td>
<td>34.7 ± 43</td>
<td>39.7 ± 51</td>
<td>37.56</td>
<td>.01</td>
</tr>
<tr>
<td>Total days depressed</td>
<td>162.2 ± 97</td>
<td>139.3 ± 96</td>
<td>108.5 ± 98</td>
<td>128.6 ± 105</td>
<td>5.29</td>
<td>.001</td>
</tr>
<tr>
<td>Days cycling</td>
<td>26.7 ± 50</td>
<td>11.6 ± 32</td>
<td>8.7 ± 23</td>
<td>4.6 ± 18</td>
<td>6.59</td>
<td>.001</td>
</tr>
<tr>
<td>Days euthymic</td>
<td>125.74 ± 91</td>
<td>162.18 ± 103</td>
<td>213.14 ± 108</td>
<td>192.19 ± 112</td>
<td>12.97</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean severity of depression*</td>
<td>2.2 ± 1.54</td>
<td>1.7 ± 1.37</td>
<td>1.4 ± 1.51</td>
<td>1.6 ± 1.62</td>
<td>5.23</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean severity of mania*</td>
<td>0.72 ± 0.88</td>
<td>0.59 ± 0.68</td>
<td>0.45 ± 0.57</td>
<td>0.43 ± 0.63</td>
<td>4.35</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean number of episodes (DSM IV)</td>
<td>5.4 ± 3.72</td>
<td>4.1 ± 3.43</td>
<td>2.6 ± 2.48</td>
<td>2.8 ± 3.34</td>
<td>15.78</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*1, mild; 2, low moderate; 3, high moderate; 4, severe on the NIMH-LCM.
agion and treatment of bipolar illness in adults is apparent in epidemiologic samples.

Most strikingly, even when bipolar illness is diagnosed, adults in the community are often given antidepressants without concomitant mood stabilizers, contrary to the recommendation in most treatment guidelines.

Instead of being a diagnosis of exclusion and last resort in children, as has often been the case, bipolar disorder should be actively considered and ruled in or out. This is particularly important in children at high risk due to having 1 or both parents with a diagnosis of bipolar illness (as seen in this study and in the studies of Lapalme et al and Pavuluri et al) or the presence of environmental stressors, such as the occurrence of traumatic events in childhood.

Most children with bipolar disorder also have a comorbid diagnosis of ADHD, whereas the vast majority of children with ADHD do not have bipolar disorder. Nonetheless, in patients with apparent ADHD and additional indicators of extreme mood lability and behavioral dyscontrol (especially in the presence of periods of euphoria, decreased need for sleep, increased sexual interest or acts, delusions, hallucinations, or suicidal behaviors), providers should carefully consider the possibility of bipolar disorder before initiating treatment with stimulants and antidepressants alone, because first treatment with mood stabilizers or atypical antipsychotics is the recommended approach in consensus guidelines.

Inadequate recognition, diagnosis, and treatment of adult-onset bipolar illness in clinical samples and in the community now appear to be paralleled by equal problems in recognizing and treating childhood-onset bipolar illness, particularly in the United States. Given the likely adverse consequences of long periods of untreated or inadequately treated mood-related symptomatology, as seen in this and other studies, efforts to ensure earlier diagnosis and institution of treatment are important. Whether such earlier intervention will in fact ameliorate the long-term difficulties associated with childhood-onset bipolar disorder remains to be ascertained.

Additional statistical support was provided by Sun Hwang at the Department of Biostatistics, School of Public Health, UCLA, Los Angeles, CA. We thank Chris Gavin for his editorial support.

REFERENCES


Objective  To evaluate the hypothesis that white coat hypertension (WCH) represents a prehypertensive state by correlating ambulatory blood pressure monitoring (ABPM) results with BP response to treadmill exercise (TE) and echocardiographic measurement of left ventricular mass index (LVMI) in children with high blood pressure (HBP).

Study design  We evaluated 119 consecutive children age 6 to 18 years (mean = 13.3 years; 65% male) referred for HBP. Office systolic BP (SBP) exceeded the 95th percentile for age/sex/height in all of the children; 10% also had elevated diastolic BP (DBP). WCH was defined as elevated office SBP ± elevated DBP with normal mean awake ABPM-SBP. ABPM classified 62 subjects as having WCH and 57 as having HBP.

Results  Office BP did not differ between the 2 groups. As defined, awake ABPM-SBP was lower in the WCH group (males: HBP, 142 ± 12 vs WCH, 124 ± 5; females: HBP, 137 ± 8 vs WCH, 121 ± 5). Awake and asleep DBP and asleep SBP were significantly lower in the WCH group. On TE, maximal SBP exceeded norms for age/sex/body surface area in 63% of the HBP group and 38% of the WCH group. LVMI exceeded the 95th percentile for age/sex in 59% of the males and 90% of the females in the HBP group and in 33% of the males and 36% of the females in the WCH group.

Conclusions  Exaggerated exercise BP and/or increased LVMI in 62% of those subjects with WCH suggest that this diagnosis in children may represent a prehypertensive state. (J Pediatr 2007;150:491-7)

White coat hypertension (WCH) is defined as persistent elevation of blood pressure (BP) in medical settings with normal pressures at all other times.1 Ambulatory BP monitoring (ABPM) is acknowledged to be the standard method for establishing the diagnosis of WCH.2 In adults, the prevalence of WCH is estimated at 20% to 40% of those with elevated casual BP.3,4 Long term studies document that risk for cardiovascular disease correlates with ABPM; thus, WCH is not generally associated with accelerated atherosclerosis.5-8 However, in a subset of adults, WCH is considered a prehypertensive state with progression to sustained hypertension over time.9,10

In children, WCH is less well understood, with the reported frequency varying depending on the criteria used to establish the diagnosis.11-14 Few studies have evaluated cardiac end-organ damage in children with WCH.15 A demonstration that children with WCH have an exaggerated BP response to exercise and increased left ventricular (LV) mass would support the hypothesis that when this diagnosis is made in childhood, it represents a true prehypertensive state that warrants specific follow-up.

To examine this hypothesis, we retrospectively reviewed the results of a consecutive series of children referred with a diagnosis of hypertension who were evaluated by a standard clinical protocol that included ABPM, BP response to treadmill exercise (TE) testing, and determination of LV mass index (LVMI) by echocardiography.

Increased LVMI is an established measure of end-organ effect in adults and has been shown to be a strong independent predictor of increased risk for cardiovascular morbidity.16,17 Echocardiographic estimation of LVMI has been validated anatomically in children and has been shown to be accurate and reproducible with published reference standards for children indexed to body size and sex.18-20 LVMI has been shown to be significantly increased in children with hypertension.21 Combining LVMI with BP response to exercise should allow a thorough assessment of the impact of WCH in childhood.
METHODS

Between January 1997 and January 2001, 140 consecutive children with a referral diagnosis of HBP were evaluated with a standard clinical protocol in the Pediatric Prevention Clinic at SUNY Health Science Center, Syracuse. Each child had a series of elevated BP measurements obtained by the primary care provider, which prompted referral. At the initial prevention clinic evaluation, height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg on a medical balance scale. Each child had 3 BP measurements obtained at rest using an automated oscillometric device (Dinamap model 1845X/T; Critikon, Tampa, FL), and 1 measurement obtained through a standard auscultatory technique, performed by one of the authors (R.E.K.), with cuff size determined based on recommendations of the Task Force on High Blood Pressure in Children, updated in 1996.22 If all 4 SBP measurements exceeded norms for age/sex/height, then the child was considered to have hypertension requiring evaluation.

The 4 BP results were averaged, and the result was designated the office BP. Office BP was not elevated in 9 children; results from these subjects were excluded from further evaluation. The remaining 131 children underwent ABPM, TE testing, and echocardiographic estimation of LVM.

ABPM was performed with a Suntech Accutracker II monitor (Suntech Industries, Wake Forest, NC), which uses the auscultatory technique. The BP cuff was placed on the nondominant arm, and the unit was calibrated to BP measured by auscultation in the opposite arm. The ABPM unit was programmed to measure BP every 30 minutes during traditional waking hours and every 90 minutes during sleep. Actual awake and asleep periods were established from subject diaries.

ABPM results were expressed as mean awake and asleep SBP and DBP and percent decline in BP from awake to asleep. For this study, mean awake SBP above the 95th percentile for sex- and height-specific normative data for ABPM monitoring in children was used to define HBP.23 The percent decline during sleep was calculated as the difference between mean awake and asleep SBPs divided by mean daytime SBP.

Graded TE was performed to exhaustion on a Marquette Electronics P2000 treadmill (St Louis, MO) with the standard Bruce protocol.24 The subject was not permitted to hold the hand bar during the study and was vigorously encouraged to reach a level of maximal exertion. The test was terminated when the subject refused to continue despite strong verbal encouragement. The subject was placed in a supine position immediately after exercise.

Standard electrocardiography was performed on all subjects at baseline, with leads V1, V5, and AVF monitored continuously throughout exercise and recovery using a Marquette Electronics Max 1 stress system. BP measurements were obtained with the Dinamap Critikon BP monitor with the subject in the supine position with an appropriate-sized cuff (as defined by the Task Force Report) at baseline, immediately after completion of exercise, and every 2 minutes throughout recovery.

Metabolic measurements were obtained with a Sensor-medics 2900 metabolic measurement cart in the mixing chamber mode with an appropriate-sized, low–dead space, minimal-resistance facemask (Hans-Rudolph, Kansas City, MO). Measurements included inspired/expired gas concentrations and expired flow rate with calculation of ventilatory equivalent, oxygen consumption, carbon dioxide production, and respiratory exchange ratio (RER = oxygen uptake [VO2]/carbon dioxide output [VCO2]). A RER > 1.0 was considered to represent evidence of maximal exercise effort. Combined normative data for BP response to exercise for age/sex and body surface area in childhood were used for comparison.25,26

All subjects were studied using standard M-mode echocardiographic images derived from 2-dimensional imaging. Measurement techniques were as described by the American Society of Echocardiography using leading-edge to leading-edge methodology.27 The LV end-diastolic internal dimension was measured from the leading edge of the left septal surface to the leading interface of the LV endocardium along a perpendicular line at the onset of ventricular depolarization, denoted by the beginning of the Q or R wave on a simultaneous electrocardiogram, where both anterior and posterior mitral leaflets were visible. LV posterior wall thickness was measured as the distance between the anterior surface of the endocardium and the surface of the epicardium of the LV posterior wall. Ventricular septal thickness was measured as the difference between the right ventricular septal surface and the leading edge of the LV surface of the septum. LV wall and septal thicknesses were measured during end diastole at the same position as for measurement of LV end-diastolic internal dimension.

Each measurement was made 3 times by an echocardiographer who was unaware of the BP results; the average was used to calculate LV mass based on the following formula:

\[
LV\ mass = 0.80 \times \left[1.04 \times (IVS + LVID + LVW)^3 - LVID^3\right] + 0.6
\]

To allow comparison between children of different ages and sizes, LV mass was indexed to height in meters to the 2.7 power.19 For comparison, published norms for LVMI in children were used: 36.88 g/m².7 in females and 39.36 g/m².7 in males.20 Results were also compared with the adult standard for LVH based on an LVMI > 51 g/m².7.21

Statistical analysis was performed using the StatView software program (SAS Institute, Cary, NC). Correlation between measures was made using linear regression analysis. Variables in different groups were compared using analysis of variance or Fisher’s exact test. P values ≤ .05 were considered statistically significant. All values presented are mean ± standard deviation.
RESULTS

Of the 131 children with HBP on office evaluation, 12 were eliminated because of incomplete data on the ABPM (n = 5) or for submaximal effort (RER < 1.0) on TE (n = 7). Therefore, the study group comprised 119 children with elevated BP in an office setting, complete ABPM recordings, measured BP response to maximal TE, and echocardiographic evaluation. All subjects had office SBP above the 95th percentile for age/sex/height. In 12 of 119 subjects, diastolic HBP was also present.

Based on the ambulatory mean awake SBP, subjects were classified as having HBP (n = 57) or WCH (n = 62). Characteristics of the 2 study groups are given in Table I. Obesity was common in both groups; there was a similar distribution of subjects with normal, at risk for overweight, and overweight BMI.

Ambulatory Blood Pressure Monitoring

The results of ABPM are displayed by sex in Table II. By definition, each subject in the HBP group had mean awake SBP above the 95th percentile for sex/height, although mean awake SBP for each subject in the WCH group was normal. As would be anticipated, mean awake SBP was significantly higher for the HBP group than for the WCH group.

Mean awake DBPs were elevated compared with norms for sex/height in 11 of 57 (19%) of the HBP group, but only 1 of 62 in the WCH group. When the groups were compared, mean awake DBPs were significantly higher in the HBP group.

During sleep, SBP declined in all subjects with WCH but did not decrease in 4 of the 57 subjects with HBP. Mean nocturnal decrease in SBP was similar in both groups: 12.5% for WCH and 11.9% for HBP. DBP did not decrease during sleep in 1 subject in the WCH group and in 2 subjects in the HBP group. Mean nocturnal decrease in DBP was similar in the 2 groups: 17% for WCH and 16.7% for HBP.

For the HBP group, there was a significant linear correlation between office SBP and mean awake SBP on AMBP (r = .661; P < .0001). For the WCH group, this correlation was less strong but still significant (r = .357; P = .0044).

Treadmill Exercise

In all subjects, results represented a maximal exercise effort with no difference in RER between groups (HBP RER = 1.15 vs WCH RER = 1.14; P = .861). Exercise BP results are reported in Table III. At baseline, mean SBP in both WCH and HBP subjects did not differ significantly from office SBP. In the WCH group, SBP before beginning exercise was significantly higher than ambulatory SBP (143 ± 13 vs 123 ± 6; P < .0001); this difference was less pronounced for the HBP group (148 ± 15 vs 140 ± 11; P = .006). Compared with office BP, mean baseline DBP was significantly lower in both the HBP and WCH groups, with no difference between groups when compared by sex.

We defined an exaggerated BP response to exercise as a SBP greater than both the predicted normal maximum exercise SBP for age and sex in nonobese children and the predicted maximum normal SBP for body surface area. Based on this, 61% of the males and 64% of females in the
Male the HBP subjects. Exercise with no difference from baseline. DBP was lower in comparison, SBP for the HBP group remained elevated postexercise below baseline pressures for both males and females. In comparison, SBP for the HBP group remained elevated postexercise but remained significantly higher in the HBP subjects.

Left Ventricular Mass Index

Results for LVMI calculations are summarized in Table IV. For both groups, LVMI exceeded the 95th percentile for age and sex; the mean was significantly higher for the HBP group compared with the WCH group in both males and females. Using pediatric norms, LVMI exceeded the 95th percentile for age in 59% of the HBP males and 33% of the WCH males and in 90% of the HBP females and 36% of the WCH males. Analyzing the results using the adult cutpoint for left ventricular hypertrophy (LVMI ≥ 51 g/m²) revealed that 43% of the males and 30% of the females in the HBP group were above this level, compared with 15% of the males and 14% of the females in the WCH group.

To evaluate the impact of obesity on LVMI, the subjects were grouped by BP class, BMI category, and sex. The number of subjects with BMI below the 95th percentile was small, and no significant difference in LVMI was found between those with BMI at or below the 85th percentile and those with BMI in the 86th to 94th percentile; thus, these subjects were combined as the normal BMI group for subsequent analysis. For the normal BMI subjects (BMI below the 95th percentile), mean LVMI was above the normal range in the HBP group and within the normal range in the WCH group; the difference between the groups was significant. For obese subjects with BMI at or above the 95th percentile, LVMI was abnormally increased in both males and females in both the WCH and HBP groups, with no significant difference between groups.

By simple regression, LV mass was seen to correlate significantly with height (r = .76; P < .0001), weight (r = .73; P < .0001), office SBP (r = .54; P < .0001), maximal exercise SBP (r = .61; P < .0001), ABPM awake SBP (r = .52; P < .0001) and ABPM asleep SBP (r = .47; P < .0001). Using multiple regression, maximum correlation was achieved with inclusion of height, weight, ABPM awake SBP, and TE maximal SBP (r = .835; P < .0001).

The combined findings of the echocardiographic assessment and the BP response to exercise demonstrated abnormal results for both studies in 57% of the HBP group but in only 11% of the WCH group. Abnormal results were found in 1 or both studies in 92% of the HBP group and in 62% of the WCH group. Only 38% of the WCH subjects exhibited both normal LV mass and normal BP response to exercise.

DISCUSSION

Our findings indicate that WCH, as defined for adults, is common in children referred for evaluation of hypertension. The prevalence of 52% found in this study is comparable to reports by others in varying pediatric populations. However, there were important additional findings in the WCH group, with increased LV mass in 24%, exaggerated BP response to TE in 27%, and abnormal findings on both

<table>
<thead>
<tr>
<th>Table III. BP response to TE</th>
<th>HBP</th>
<th>WCH</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
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</tr>
<tr>
<td>Baseline</td>
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<td></td>
<td></td>
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<tr>
<td>SBP 149 ± 16</td>
<td>146 ± 13</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>DBP 74 ± 10</td>
<td>70 ± 9</td>
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<td></td>
</tr>
<tr>
<td>Maximum</td>
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</tr>
<tr>
<td>SBP 212 ± 28</td>
<td>196 ± 23</td>
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</tr>
<tr>
<td>DBP 87 ± 15</td>
<td>81 ± 10</td>
<td>&lt;.05</td>
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</tr>
<tr>
<td>SBP &gt; 95th percentile for age/sex/BSA</td>
<td>61%</td>
<td>39%</td>
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<tr>
<td>Recovery</td>
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<td></td>
</tr>
<tr>
<td>SBP 149 ± 23</td>
<td>136 ± 14</td>
<td>&lt;.01</td>
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</tr>
<tr>
<td>DBP 70 ± 10</td>
<td>65 ± 7</td>
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<tr>
<td>Female</td>
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<tr>
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<tr>
<td>SBP 144 ± 14</td>
<td>137 ± 11</td>
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<tr>
<td>DBP 75 ± 10</td>
<td>71 ± 8</td>
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<tr>
<td>Maximum</td>
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<tr>
<td>SBP 201 ± 24</td>
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<tr>
<td>DBP 89 ± 18</td>
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<td>SBP &gt; 95th percentile for age/sex/BSA</td>
<td>64%</td>
<td>36%</td>
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<tr>
<td>Recovery</td>
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<tr>
<td>SBP 143 ± 17</td>
<td>132 ± 11</td>
<td>&lt;.05</td>
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<tr>
<td>DBP 72 ± 12</td>
<td>64 ± 8</td>
<td>&lt;.05</td>
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</table>

NS, not significant.

<table>
<thead>
<tr>
<th>Table IV. LVMI by BP class and by sex and BMI group</th>
<th>HBP</th>
<th>WCH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI*</td>
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</tr>
<tr>
<td>M 47.5 ± 10.5</td>
<td>40.8 ± 8.4</td>
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</tr>
<tr>
<td>F 46.7 ± 8.2</td>
<td>37.4 ± 9.8</td>
<td>.0015</td>
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</tr>
<tr>
<td>BMI &lt; 95th percentile</td>
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</tr>
<tr>
<td>M 45.3 ± 9.7</td>
<td>37.2 ± 4.2</td>
<td>.0028</td>
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</tr>
<tr>
<td>F 48.8 ± 4.2</td>
<td>32.7 ± 6.7</td>
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</tr>
<tr>
<td>BMI ≥ 95th percentile</td>
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</tr>
<tr>
<td>M 48.7 ± 11.2</td>
<td>43.4 ± 9.7</td>
<td>.0941</td>
<td></td>
</tr>
<tr>
<td>F 46.3 ± 9.2</td>
<td>40.1 ± 10.4</td>
<td>.1006</td>
<td></td>
</tr>
</tbody>
</table>

*LVMI unit = weight (g)/ht².
White Coat Hypertension in Childhood: Evidence for End-Organ Effect

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In hypertensive adults, absence of this pattern during sleep includes a decline of auscultation readings. With the elimination of mercury-based instruments, the automated device is becoming the standard in clinical settings, and BP recorded by this technique is frequently reported in studies of BP in children. In adults, LV hypertrophy is known to be an important predictor of increased risk for future cardiovascular events. In this study, LVMI was significantly greater in the HBP group than in the WCH group when compared with sex-based norms, but almost 34% of the WCH subjects also had an elevated LVMI. Of more concern, in 15% of the WCH group, LVMI exceeded 51 g/m^2.7, the level defined as severe LVH in adults and associated with a greater than fourfold increase in risk for cardiovascular events. In children, LV mass is determined primarily by lean body mass and is influenced to a lesser extent by increased fat mass and BP. A majority of our subjects in both groups were overweight. Using LV mass/m^2.5 to calculate LVMI is the method least influenced by obesity, but it is imperfect. To evaluate the impact of obesity, subjects were grouped by body size and sex. For both males and females of normal body size, mean LVMI was normal in the WCH children and abnormally increased in those with HBP; the difference was significant. In contrast, for the obese subjects, LVMI was abnormally increased for both groups, and although higher for the HBP group, there was no significant difference. Our findings are in agreement with those of other researchers who have demonstrated that although BP and body mass each contribute to development of LV mass, the combination of obesity with hypertension is a potent stimulus to the development of LV hypertrophy in children.

The present study has some limitations. Although all of the subjects were evaluated consecutively following the same protocol, the review was conducted retrospectively and thus is
subject to all of the limitations inherent in this method. All of the subjects in the HBP and WCH groups were referred to a tertiary care center for evaluation with a diagnosis of hypertension. Those children with WCH referred for evaluation may have had many elevated BP measurements in their primary care providers’ offices before referral and thus may represent a selected group trending toward a sustained hypertensive state, rather than an unselected group with high BP only in an office setting. The office BP was an average of automated oscillometric and manual auscultation readings, subject to the potential errors inherent in both techniques. However, the same method was followed in all subjects, and so measurement error should be standardized across the groups. We used reference data for ambulatory BP obtained by the oscillometric technique for comparison with our ambulatory results obtained using the auscultatory method. However, both techniques are reportedly equally accurate, particularly for SBP, and we based our interpretation of results on SBP readings.39 Most of the subjects in both groups were overweight, which makes interpretation of LVMI results difficult. Finally, obtaining accurate BP measurements on the treadmill is technically very difficult, so our results were recorded immediately postexercise in the first 30 seconds after termination. As such, they may not reflect the true maximal BP response to exercise.

In summary, evaluation for BP response to exercise and LV mass in this clinical series revealed abnormal results on 1 or both tests in 62% of the WCH group. These findings suggest that WCH in some children, particularly when associated with obesity, is not a simple elevation of BP in response to the stress of a medical setting, but may represent a prelude to sustained hypertension.

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50 Years Ago in The Journal of Pediatrics
THE UTILITY OF BLOOD OXYGENATION AS AN INDICATOR OF POSTNATAL CONDITION

Fifty years ago, pediatricians and psychologists were captivated by the thought that the future life of a child might be determined by events that occurred at the time of birth. In this study, Bettye Caldwell et al evaluated potential correlations between perinatal oxygen saturation values (assessed from umbilical cord and first-hour capillary blood samples) and the immediate postnatal clinical status of newborn infants, as well as their 24- to 48-hour neurobehavioral assessments. The authors candidly admitted that the “the results were disappointing” because only a weak correlation was found between cord blood oxygen saturation and the clinical status of the newborns, and “the relationship between oxygen and behavior was essentially random.”

Despite these negative results, this study is quite remarkable in a number of ways. First, the topic of perinatal physiological derangements and outcomes has been an active area of research for the past 50 years. Although modern methodology has been refined, the basic paradigm of correlating a physiological measure with neurobehavioral outcomes is still in use today. Today, this same study could be conducted with cerebral oximetry used as the physiological measure and amplitude integrated electroencephalograms and Brazelton examinations as the outcome measures! What is also remarkable about this study is the authors’ ruthlessly honest assessment of their study results. For example, Caldwell et al reported a statistically significant relationship between cord blood oxygen saturation and their clinical anoxia score. However, they admitted that “this relationship is so small as to be of little or no practical significance.” The article is peppered with similar comments about the results. To ensure publication of an article today, statistically significant findings are most successfully dealt with in a positive manner. Most modern authors would fear that such brutal honesty would result in unfavorable peer reviews and a rejection letter from the editor of the journal! Last, the authors of this article are remarkable for their own careers. Four of the 5 authors of this NIH-sponsored study were women, all of whom went on to have distinguished scientific careers, with PubMed citations for publications extending into 2006!

Although the results of this study now may seem quaint, the topic remains timely. Furthermore, the soundness of the experimental paradigm, the candid scientific writing, and the longevity of the authors’ scientific careers provide inspiration to current generations of women whose care for children extends to research into the most important aspects of their lives.

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Northwestern University Feinberg School of Medicine
Children’s Memorial Hospital Chicago, Illinois
10.1016/j.jpeds.2006.11.016
Objective  To investigate whether parental hypertension (HTN) affects children's body mass index (BMI) and cardiovascular reactivity (CVR) over time.

Study design  A longitudinal study of 315 students (black: 23 females, 19 males; white: 142 females, 131 males) was conducted in the public schools of Obion County, Tennessee, between 1987 and 1992. BMI and BMI z scores were calculated. The CVR task was a series of video games (taking ~10 minutes to play) given to the same students in their third-, fourth-, fifth-, seventh-, and eighth-grade years. CVR was defined as the change in blood pressure (Δ BP) or heart rate (Δ HR) between before playing and while playing the video game. Positive parental history of HTN (27.6%) was defined as at least 1 parent with HTN. Multivariable regression analyses were performed to estimate the effects of parental HTN on children's BMI and CVR over time.

Results  Children with parental HTN had significant higher BMI, BMI z score, and R_BP than did children without parental HTN (BMI: 21.6 vs 19.9, P = .001; BMI z score: 1.6 vs 1.1, P = .003; R_SBP: 112.6 vs 110.4 mm Hg, P = .01; R_DBP 62.7 vs 60.6 mm Hg, P = .003) after adjustment for covariates. Increased CVR was observed in children with parental HTN compared with children without parental HTN but was statistically significant only for SBP (Δ SBP: 17.2 vs 14.9 mm Hg; P = .01) after adjustment for covariates.

Conclusions  Parental HTN independently predicted children's BMI, BMI z score, resting BP, and BP reactivity. (J Pediatr 2007;150:498-502)

Body mass index (BMI) predicts blood pressure (BP) over time, and parental obesity predicts children's overweight and obesity. A few cross-sectional studies have reported a significant association between parental hypertension (HTN) and children's subscapular/triceps ratio1 or central fat.2 Whether parental HTN predicts children's BMI over time is unclear. In addition, longitudinal studies have identified parental history of HTN as a risk factor for HTN in children.3-5 Investigators have also reported that increased cardiovascular reactivity (CVR) to psychological stress may predict the subsequent increase in BP.6-12 Thus, if increased CVR to stress is part of the causal pathway to HTN, then family history of HTN also may be associated with CVR.

But whereas some studies have reported a significant influence of family history of HTN on increased CVR to psychological stress,13 others have reported negative findings.14 This inconsistency has led some investigators to question the role of excessive CVR to stress as a causal factor in the development of HTN.15 Others have argued that the evidence of different effects of family history of HTN on CVR warrants future clarification of its role in the causal chain leading to HTN.16 A recent meta-analysis of 48 studies of CVR associated with family history of HTN17 reported excessive CVR in the positive family history groups. In this meta-analysis, participants' age, sex, and stress-task types differed across studies; the analysis could not adjust for them. In addition, previous studies on the association between familial history of HTN and CVR to stress were cross-sectional. Few longitudinal studies have reported an association between family history of HTN and a change in CVR to psychological stress. In the present study, we assessed the effects of parental HTN on children's BMI, resting BP and HR, and CVR to video game stress in children in grades 3, 4, 5, 7, and 8.
METHODS

Study Population

In 1987, 278 third-grade students from all public schools in Obion County, Tennessee were recruited into the study. The recruitment was kept open during the follow-up years for new students joining the same grade level as that of the original participants. Each year the families were informed of the examination dates. If parents did not wish to have their child participate in the study at any time during the course of the study, they could inform the school or the investigators, but none did. However, the number of participants differed each year (278 in 1987, 297 in 1988, 315 in 1989, 280 in 1991, and 265 in 1992), because students moved in and out of the county or may have been absent on the testing days. A total of 232 students had complete records of CVR over the 5 yearly assessments and a validated parental history of HTN. Table I presents characteristics of the participants.

A passive consent procedure was used before enrollment. The study design was reviewed and approved by the institutional review boards of University of Tennessee Health Science Center and the Tennessee Department of Health and the school boards of participating schools.

Data Collection

Data were collected in 1987, 1988, 1989, 1991, and 1992. (The examination was not conducted in 1990 due to a lapse in funding.) Student age, sex, and race were recorded based on parental report at enrollment. The data on parental history of HTN and smoking status were collected through parents’ administered questionnaire at grade 5 or higher. A positive family history of HTN was defined as HTN in 1 or both parents either diagnosed by a medical practitioner or evidenced by parental use of prescribed antihypertensive medications.

Four trained nurses measured students’ height, weight, BP, and HR yearly according to a standard protocol. BMI was defined as weight (in kilograms) divided by height (in meters) squared (kg/m²). BMI z scores, which reflect the standard deviation score for the age- and sex-appropriate BMI distribution, were calculated using the same methods as used in the 2000 Centers for Disease Control Growth Charts for the United States.

CVR Task and Determinant

Measurement of students’ CVR to a video game task was done at the schools during regular school hours between January and April in each of the study years. The reactivity task involved playing 3 video games (Breakout; Atari, Sunnyvale, CA) lasting approximately a total of 10 minutes, or 3.5 minutes for each. The details of this task have been published elsewhere. In brief, the child was seated at a table on which the game controller (a rotating dial) was mounted. A 25-inch (63.5-cm) color television was located on another table, approximately 2.5 ft (76.2 cm) away. The child was instructed to operate the game controller with the dominant hand.

The child played 3 games designed to progress through 3 levels of challenge: personal challenge (“play a game and see how well you do”), experimenter challenge (“try harder and beat your score for game 1”), and challenge for financial incentive (“try your hardest to beat the average score for your classmates and win some money”). The size of the financial incentive was not specified at the time of testing. The same video game task was used each time.

BP and heat rate (HR) were measured with an appropriate-sized BP cuff connected to the children’s nondominant arm from an automated BP monitor (Dinamap; Critikon, Tampa, FL). Sitting BP was measured before (at rest) and during video game play. Three resting BP and HR measurements, taken 1 minute apart, were obtained after the child had sat quietly for at least 5 minutes. The average of the last 2 measures was used for this analysis. During each of the 3 video games, a measurement of BP and HR was started after 20 to 30 seconds of play. If the game ended before the measurement was completed, the game was reset immediately and played continuously at the same level of challenge. Extraneous speech and movement were discouraged. CVR was determined as the mean of 3 game values minus the mean of the last 2 resting values.

<table>
<thead>
<tr>
<th>Table I. Participants’ characteristics</th>
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</thead>
<tbody>
<tr>
<td>Students with CVR tests at each grade</td>
</tr>
<tr>
<td>Grade 3 (n = 278)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Whites (%)</td>
</tr>
<tr>
<td>Mother HTN (%)</td>
</tr>
<tr>
<td>Father HTN (%)</td>
</tr>
<tr>
<td>One or both parents HTN (%)</td>
</tr>
<tr>
<td>Mother smoking (%)</td>
</tr>
<tr>
<td>Father smoking (%)</td>
</tr>
</tbody>
</table>
Data Analysis

SAS 9.1 statistical software (SAS Institute, Cary, NC) was used for all analyses. Linear regression was used to estimate effects of parental HTN on the child’s resting BP, HR, and CVR to the video game task at each grade. Mixed models with repeated measures were used to estimate associations between parental HTN and child’s BMI, BMI z score, resting BP, HR, and CVR across all grades. For associations between parental HTN and resting BP or HR, BMI was included in the basic model for adjustment. For associations between parental HTN and CVR, the corresponding resting BP or HR and BMI were in the basic model. The associations of parental HTN with BMI, BMI z score, resting BP and HR, and CVR were all assessed with and without adjustment for additional covariates of race and sex. Parental smoking status was not significantly associated with children’s BMI, BP, and CVR in multivariable models, which was excluded from the final model.

The analyses were conducted separately for students with completed data in all 5 of the assessments (n = 232) and for those with missing records in some of the 5 assessments (Table I). For the estimate of association, the comparison was made between the 2 sets of analyses; the results demonstrated no significant differences. Thus, the final results reported here were based on the data with missing records at some grades.

RESULTS

During the 5-year study, the number of participants increased in the first 3 years (278 at grade 3, 297 at grade 4, and 315 at grade 5). After grade 5, the number of those lost to follow-up was greater than the number of those joining, which decreased the number of participants during grades 7 (n = 280) and 8 (n = 265) (Table I). The study group contained significantly more whites than blacks and slightly more females than males. The participants’ father was more likely to be a smoker and to have HTN. In 1989 (grade 3), the age of hypertensive parents (father, 31.3 to 64.5 years [mean, 42.2 years]; mother, 28.7 to 57.2 years [mean = 39.4 years]) were significantly higher than those of normotensive parents (father, 29.5 to 63.0 years [mean, 41.8 years]; mother, 28.8 to 56.5 years [mean, 39.7 years]) (P = .002 for hypertensive father vs normotensive father and P = .01 for hypertensive mother vs normotensive mother). Students’ mean age in grade 3 was 9.18 (8.29 to 11.13) years for those with hypertensive parents and 9.14 (8.30 to 10.99) years for those with normotensive parents. Because students’ age distribution was not significantly different by parental hypertension or significantly associated with CVR in regression analyses, the final results were not adjusted for age.

Students’ BMI z scores significantly increased over time (P = .001) from grade 3 to grade 8, except for a slight decline in grade 5 (Figure 1). At each grade, the mean BMI z score in those with hypertensive parents was significantly higher (P = .001) than in those with normotensive parents, after adjustment for race and sex. There was no interaction between grade level and parental HTN for BMI z score.

The differences in resting BP and HR, and CVR to the video game task, between students with and without parental HTN by grade levels are shown in Figure 2. Overall, the resting SBP, DBP, and HR were higher in students with hypertensive parent(s), except for the resting HR in grade 8 (Figure 2A). This difference was statistically significant for resting SBP only in grades 4, 5, and 7 and for resting DBP only in grade 5 after adjustment for BMI, race, and sex. CVR to the video game task after adjustment for corresponding resting BP or HR and covariates was also elevated in students with parental HTN in each grade (Figure 2B). However, this elevation was statistically significant for Δ SBP only in grades 3, 4, and 5 and for Δ HR only in grade 5.

Table II presents the mean values of BMI, BMI z score, resting BP and HR, and CVR by parental HTN over the 5 assessments, adjusted for other covariates. Students with hypertensive parents had significantly higher BMI (21.6 kg/m²), BMI z score (1.57), resting SBP (112.6 mm Hg), and DBP (62.7 mm Hg) compared with those with normotensive parents (BMI = 19.9 kg/m², P = .001; BMI z score = 1.12, P = .0003; SBP = 110.4 mm Hg, P = .01; DBP = 60.6 mm Hg, P = .006). Comparing the overall differences in CVR during the 5 assessments between students with and without hypertensive parents shows that the former had excessive CVR to the video game task as evidenced by greater change in SBP during the video game (Δ SBP: 17.2 vs 14.9; P = .01). DBP and HR reactivity to the video game task were not statistically significantly different between students with and without parental HTN, but the reactivity values were higher in students with parental HTN, which was in the expected direction. Race and sex differences in resting BP and HR and CVR in these study participants have been reported previously.

DISCUSSION

This 5-year study with repeated measures of BMI, BMI z score, and CVR to a video game stress task in students from grades 3 to 8 has demonstrated an association between
parental HTN and children’s BMI, BMI z score, resting BP and HR, and CVR to stress. The association seems more pronounced for BMI, BMI z score, and resting BP and HR than for CVR to stress, because parental HTN was only statistically significantly associated with SBP reactivity to the video game task. These findings are consistent with results from the Dutch Hypertension and Offspring Study.2,21

The association between parental hypertension and children’s elevated BMI, BMI z score, BP, and CVR to stress could result from both genetic makeup and shared environment. With regard to shared environment, we considered parental smoking status, an established environmental risk factor for HTN, to be a possible confounder. However, in our analysis, we found no evidence of an association between parental smoking and child’s CVR to stress or parental HTN in this sample (data not shown).

Table II. Adjusted* mean values by parental HTN over 5 assessments

<table>
<thead>
<tr>
<th></th>
<th>Parental HTN + (n = 77)</th>
<th>Parental HTN − (n = 195)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>21.6</td>
<td>19.9</td>
<td>.001</td>
</tr>
<tr>
<td>BMI z score</td>
<td>1.6</td>
<td>1.1</td>
<td>.0003</td>
</tr>
<tr>
<td>R_SBP</td>
<td>112.6</td>
<td>110.4</td>
<td>.01</td>
</tr>
<tr>
<td>R_DBP</td>
<td>62.7</td>
<td>60.6</td>
<td>.003</td>
</tr>
<tr>
<td>R_HR</td>
<td>85.2</td>
<td>83.2</td>
<td>.09</td>
</tr>
<tr>
<td>Δ_SBP</td>
<td>17.2</td>
<td>14.9</td>
<td>.01</td>
</tr>
<tr>
<td>Δ_DBP</td>
<td>12.8</td>
<td>11.6</td>
<td>.1</td>
</tr>
<tr>
<td>Δ_HR</td>
<td>14.3</td>
<td>12.9</td>
<td>.3</td>
</tr>
</tbody>
</table>

*Adjusted for the covariates of grade level, race, sex, and parental smoking status for BMI and BMI z score; adjusted for BMI and the covariates for resting BP and HR; and additional adjustment for corresponding resting BP or HR for CVR.

Figure 2. Adjusted mean values of BP and HR by parental HTN and grade level. (A) Resting BP and HR adjusted for BMI, race, and sex. (B) Difference in BP and HR between measures during video game play and measures at rest adjusted for corresponding resting BP or HR. *P < .05; **P < .01. Available in color at www.jpeds.com.
Information on other cultural or environmental factors (eg, diet, exercise, and parental body composition) also may influence the detection of associations. Because of funding limitations, those data were not collected.

The study used the same video game task over the 5 assessments. The game was more challenging when students were at lower grade levels and less challenging as they became older. Thus, theoretically, CVR may have been more excessive at lower grades than that at higher grades. To confirm this, we analyzed Δ_SBP by grade levels and quintile of resting SBP. Comparing the Δ_SBP among students in different grade levels but with the same range and a similar mean value of resting SBP showed a higher Δ_SBP in lower grades than in higher grades. For instance, in groups with the same ranges of resting SBP (108.0 to 112.5 mm Hg), Δ_SBP was 17.4 mm Hg for fourth graders (n = 60; mean resting SBP = 110.6 mm Hg), and 15.6 mm Hg for seventh graders (n = 67, mean resting SBP 110.4 mm Hg, P < .05). Because we used the same video game task over 5 assessments, we may have underestimated CVR to a video game task when students entered higher grades. However, the video game was the same for students with or without parental HTN, which was less likely to cause biased estimates of the association between parental HTN and CVR.

Information on parental HTN was collected based on parental self-report. HTN may be underreported by parents because of their lack of knowledge of their BP. This would cause an underestimation of the association between parental HTN and CVR. In addition, the existence of parental HTN and CVR. In addition, the existence of parental HTN and CVR. Information on parental HTN was collected based on parental self-report. HTN may be underreported by parents because of their lack of knowledge of their BP. This would cause an underestimation of the association between parental HTN and CVR. In addition, the existence of parental HTN and CVR. Information on parental HTN was collected based on parental self-report. HTN may be underreported by parents because of their lack of knowledge of their BP. This would cause an underestimation of the association between parental HTN and CVR. In addition, the existence of parental HTN and CVR.

In conclusion, the present study provides evidence that parental history of HTN is independently associated with children’s BMI, resting BP, and CVR to a video game task over time.

We thank the students and teachers of the participating schools and the staff at the Health Department of Obion County, Tennessee.

REFERENCES

Diastolic Filling Abnormalities in Children with Essential Hypertension

William L. Border, MBChB, Thomas R. Kimball, MD, Sandra A. Witt, RDcs, Betty J. Glascock, RDcs, Philip Khoury, MS, and Stephen R. Daniels, MD, PhD

Objective To evaluate whether essential hypertension impacts diastolic function in children.

Study design In this cross-sectional study, patients with essential hypertension (n = 50) were compared with a normotensive group (n = 53). Echocardiographic assessment of diastolic function included measures derived from transmitral, color M-mode, and tissue Doppler interrogation. Cardiac dimensions, wall thickness, geometry, and systolic function were also assessed. Multiple linear regression analysis was performed to identify predictors of altered diastolic function.

Results Diastolic filling abnormalities were found in 36% of the children with blood pressure elevation. Those subjects with concentric hypertrophy were more significantly affected. Abnormalities in indices reflective of left ventricular (LV) relaxation occurred more commonly (39%) than those of LV compliance (33%). Elevated indexed LV mass was found to be the most significant independent predictor of diastolic filling abnormalities.

Conclusions LV diastolic filling abnormalities were found in one-third of the pediatric subjects with essential hypertension. Whether these changes represent an adaptive or maladaptive response requires further study. (J Pediatr 2007;150:503-9)

Systemic hypertension is an important risk factor for cardiovascular morbidity and mortality in adults. Some of the harmful effects of systemic hypertension have been shown to occur as early as childhood. This has led to strategies to improve and refine early detection of target-organ damage in children and adolescents with essential hypertension. Pediatric investigators have detected elevated left ventricular (LV) mass in children with essential hypertension. This has clinical importance in light of studies demonstrating increased cardiovascular morbidity in adults with elevated LV mass. However, it raises the question of whether functional abnormalities may coexist with these structural indicators of target-organ changes.

LV diastolic dysfunction has been demonstrated in up to 46% of an unselected adult population with hypertension and a low prevalence (14.5%) of LV hypertrophy. In addition, LV diastolic dysfunction appears to be a significant and independent predictor of mortality and of cardiovascular events in uncomplicated hypertension in adults. Two previous pediatric studies have suggested that diastolic dysfunction may occur in hypertensive children. However, the first was not limited to essential hypertension, and the second was a retrospective study using a relatively limited non-invasive assessment of diastolic function.

The goals of this study were threefold: (1) to determine whether LV diastolic filling abnormalities are present in children and adolescents with essential hypertension, using a comprehensive Doppler evaluation; (2) to attempt to characterize the pattern of these diastolic filling abnormalities (impaired relaxation vs decreased compliance, or both); and (3) to examine the association of abnormal LV mass, cardiac geometry, and ventricular remodeling with diastolic function.

METHODS

Study Population

Study participants were children and adolescents followed in the Hypertension Clinic at Cincinnati Children’s Hospital Medical Center, Ohio, with a diagnosis of essential hypertension, and a group of healthy volunteers recruited specifically for the

From the Cardiovascular Imaging Core Research Laboratory, Division of Cardiology, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio. Supported in part by a Postdoctoral Fellowship Grant from the Ohio Valley Affiliate of the American Heart Association (AHA ID no: 0120186B) (W.L.B.). Submitted for publication Sep 6, 2006; last revision received Nov 13, 2006; accepted Jan 25, 2007. Reprint requests: William L. Border, MBChB, Pediatric Cardiology and Echocardiography Faculty, Cincinnati Children’s Hospital Medical Center, Division of Cardiology, 3333 Burnet Avenue, C-4, Cincinnati, OH 45229-3039. E-mail: william.border@cchmc.org. 0022-3476/$ - see front matter Copyright © 2007 Mosby Inc. All rights reserved.

10.1016/j.jpeds.2007.01.038

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study who served as a comparison group. Subjects were prospectively enrolled, after approval of the study protocol by the Institutional Review Board for Research in Human Subjects. Informed consent was obtained from the study subjects or their parents. Hypertensive subjects were included if they fulfilled criteria for the diagnosis of essential hypertension according to the standards of the update on the Second National Heart, Lung, and Blood Institute Task Force on Blood Pressure Control in Children. Comparison group subjects were eligible if they had no history of cardiac disease or blood pressure elevation, and if their systolic or diastolic blood pressures were recorded as being <90th percentile for age and sex on the average of two measurements before their echocardiogram. Subjects were excluded from the study for any of the following reasons: (1) evidence of a secondary cause of blood pressure elevation as determined by standard clinical and laboratory examination; (2) the presence of structural heart disease; and (3) significant chronic pulmonary disease ascertained by history. Patients on antihypertensive medication were not excluded from enrollment in the study. Obese subjects were not excluded from participating as normotensive comparisons.

Clinical Characteristics

The age, sex, race, duration of hypertension, and receipt of antihypertensive medication were determined. Subject measurements included height, weight, and body mass index (BMI, calculated as weight/height2). Heart rate was recorded at the time of the echocardiogram. Both patients with blood pressure elevation and comparison subjects had three blood pressure measurements performed in the right arm in the sitting position using a mercury manometer before the echocardiogram. The average of the second two measurements was recorded.

Echocardiography Protocol

All echocardiographic images were obtained from the left side with the patient in the partial left decubitus position. Imaging was performed with a General Electric Vivid Five (Stamford, Conn) echocardiographic system using 2.5- and 3.5-MHz sector transducers or a Phillips Sonos 5500 (Andover, Mass) system with 4.0- and 8.0-MHz transducers. All echocardiographic images were recorded on videotape and analyzed with an off-line digital analysis system (Digisonics Cardiac Analysis System, Houston, Tex). Off-line measurements of the echocardiographic indices were made with the analyst blinded to subject status.

Echocardiographic Assessment of Cardiac Structure and Geometry

Measurements of the LV internal dimension, interventricular septal thickness, and posterior wall thickness were made by M-mode during diastole, according to methods established by the American Society of Echocardiography. Relative wall thickness was calculated at end-diastole as the ratio of the posterior wall thickness plus septal thickness over the LV internal dimension. LV mass was calculated using the M-mode method described by Devereux and indexed by dividing by height in meters raised to the power of 2.7. Left atrial volume was calculated from two-dimensional images using the modified Simpson’s rule. Classification of cardiac geometric remodeling by LV mass and relative wall thickness resulted in four categories: normal, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy, as previously described.

Echocardiographic Assessment of Systolic Function, Contractility, and Afterload

Global systolic function was assessed by M-mode-derived shortening fraction and two-dimensional ejection fraction (using biplane modified Simpson’s rule). LV midwall function was assessed using midwall shortening. Meridional end-systolic stress was calculated using the standard method of Reichek et al, and circumferential end-systolic stress was calculated at the midwall. Contractility was assessed by the relation between heart-rate-corrected velocity of circumferential fiber shortening and meridional end-systolic wall stress, and expressed as the Vcf difference, as previously described.

Echocardiographic Assessment of Diastolic Function

Mitral valve inflow Doppler. Five measurements of each Doppler index were performed and averaged for data analysis. Transmitral Doppler flow signals were recorded in the same manner as described by the Canadian Consensus Panel on Measurement and Reporting of Diastolic Function by Echocardiography. The transmitral Doppler peak E-wave velocity/transmitral Doppler peak A-wave velocity (E/A) ratio and the isovolumic relaxation time (IVRT) were calculated.

Color M-mode Doppler. The M-mode cursor was placed through the center of the mitral inflow region in the apical four-chamber view. The velocity of flow propagation (Vp) was obtained by measuring the slope of the first aliasing velocity from the mitral tips to a position approximately 4 cm distally into the LV, as described by Garcia et al. E/Vp was calculated as the ratio of peak mitral E-wave velocity divided by Vp. Five measurements were averaged for data analysis.

Tissue Doppler. Myocardial velocities were obtained from the apical acoustic window to minimize the effect of cardiac translation. A 3-mm sample volume was placed at the lateral mitral annulus. The resultant myocardial velocities were recorded, and at least five satisfactory cardiac cycles were obtained. The peak velocities at the lateral annulus (Em) during early diastole were measured, as well as the lateral (Am) velocities in late diastole. The ratio of peak transmitral E velocity to early diastolic mitral annular velocity (E/Em) was calculated.
Distributions were checked for normality. Parametric (Student’s t test) and nonparametric (Mann-Whitney) tests were performed to compare values between the group with blood pressure elevation and the controls. Statistical significance required a P value < .05. Diastolic indices were adjusted for BMI Z score using analysis of covariance, when comparing the two groups. One-way analysis of variance was used to compare the mean values for diastolic function among subjects with the four different LV geometric patterns of hypertensive remodeling. Multiple stepwise forward linear regression analysis was performed to explore potential determinants of diastolic function in both groups. Eml and E/Eml were chosen as the diastolic outcome variables because they are felt to be independent of preload.23 In addition, scatter plots were created with smoothed-fit regression lines to explore potential confounding between heart rate, age, and BMI and the diastolic outcome variables of Eml and E/Eml. Reproducibility for the measurement of Vp and Eml was not performed as it has been previously studied in our echocardiography laboratory by the current investigators; the mean percentage variation for intraobserver measurements was 6.6% for Vp, and 4.6% for Eml; the mean percentage variation for interobserver measurements was 11.4% for Vp and 3.1% for Eml.24

RESULTS

Subject Clinical Characteristics

Of 103 patients enrolled, 50 had blood pressure elevation and 53 were normotensive comparison subjects (Table I). All the hypertensive patients had systolic and diastolic blood pressures persistently >90th percentile for age, sex, and height, with 45 of them (90%) persistently >95th percentile. The group with blood pressure elevation was older (mean age of 14.6 ± 4 years vs 13.0 ± 3 years, P = .01), although the distribution of race and sex was similar between the two groups. The patients with blood pressure elevation were heavier (median BMI of 29.8 vs 22.9 in the controls, P = .005) and had a higher resting heart rate (mean of 81 ± 15 vs 73 ± 12 beats per minute, P = .01). Sixteen of the 50 hypertensive subjects were on medication. The systolic blood pressure was not significantly different in those subjects on medications compared with those not on medications (137 ± 11 mm Hg vs 133 ± 18 mm Hg, respectively; P = .36). The diastolic blood pressure was also not significantly different in those subjects on medications compared with those not on medications (79 ± 11 mm Hg vs 78 ± 11 mm Hg, respectively; P = .86). The median duration of known blood pressure elevation was 10.6 months (range, 9 days to 15 years).

Cardiac Dimensions and Systolic Function

The group with blood pressure elevation had a significantly higher indexed LV mass (45 ± 15 vs 32 ± 8 g/cm², P < .001) and increased relative wall thickness (P < .001) compared with the normotensive group (Table II). Both LA dimension and LA volume were significantly larger in the group with elevated blood pressure (P < .001). There was no significant difference in indexed LA volume. Shortening fraction, ejection fraction, and midwall shortening were similar between the two groups. Meridional and circumferential wall stress were not significantly different between the two groups, nor was velocity of circumferential fiber shortening (P > .05). The Vcf difference was not significantly different between the two groups.

Diastolic Function

The measures of diastolic function are displayed in two categories—those more indicative of ventricular relaxation and those more reflective of ventricular compliance (Table III). The absolute differences between the two groups are shown, as well as the differences adjusted for BMI Z score. Both the indices of relaxation and compliance were significantly different between the two groups. In general, the adjustment for BMI did not change the significance of the differences between the groups.

To quantify the prevalence of the diastolic abnormalities in the hypertensive subjects, the proportion of diastolic indices that fell outside two standard deviations of normality in the normotensive subjects was calculated. The two indices Eml and E/Eml were selected because these two indices are felt to be most preload independent, and a large pediatric series of normal values has been published to corroborate our normotensive comparison group.25 When compared with our normotensive comparison group, 39% of the hypertensive subjects had an abnormally low Eml, and 33% had an abnormally high E/Eml. When compared with the age-stratified normal values published by Eidem et al,25 38% had abnormal Eml and 38% had abnormal E/Eml (ages 10–13 years), and

| Table I. Clinical characteristics of normotensive and hypertensive subjects |
|-----------------------------|-----------------------------|-----------------------------|-------------------------|
| Characteristic              | Normotensive (n = 53)       | Hypertensive (n = 50)       | P value*                |
| Age, y                      | 13.0 ± 3                   | 14.6 ± 4                   | .01                     |
| Sex, M/F                    | 29/24                      | 30/20                      | .59                     |
| Race, B/W                   | 7/46                       | 10/40                      | .35                     |
| Body mass index, kg/m²      | 22.9 (15-71)               | 29.8 (15-77)               | .005                    |
| Body mass index Z score     | 1.0 (-1.6-3.2)             | 2.1 (-4.2-3.6)             | .01                     |
| Systolic blood pressure, mm Hg | 111 ± 10                 | 136 ± 13                  | <.001                   |
| Diastolic blood pressure, mm Hg | 68 ± 9                   | 78 ± 11                   | <.001                   |
| Heart rate, beats per minute | 73 ± 12                   | 81 ± 15                   | .01                     |

Plus-minus values are means ±SD. Medians are provided with their ranges in parentheses. *P values were calculated by the Mann-Whitney test or Student’s t test, where appropriate.
Table II. Echocardiographic characteristics of cardiac structure, systolic function, afterload, and contractility

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac structure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic</td>
<td>4.3 ± 0.5</td>
<td>4.6 ± 0.6</td>
<td>.01</td>
</tr>
<tr>
<td>dimension, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.36 ± 0.1</td>
<td>0.50 ± 0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Indexed LV mass,</td>
<td>32 ± 8</td>
<td>45 ± 15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>g/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA dimension, cm</td>
<td>2.8 ± 0.5</td>
<td>3.3 ± 0.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LA volume, mL</td>
<td>31 ± 10</td>
<td>40 ± 12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LA volume/body surface</td>
<td>19.5 ± 3.8</td>
<td>19.3 ± 6.6</td>
<td>.84</td>
</tr>
<tr>
<td>area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardial shortening</td>
<td>42 ± 5</td>
<td>43 ± 6</td>
<td>.28</td>
</tr>
<tr>
<td>fraction, %</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ejection fraction, %</td>
<td>57 ± 6</td>
<td>55 ± 8</td>
<td>.18</td>
</tr>
<tr>
<td>Midwall shortening</td>
<td>32 ± 5</td>
<td>32 ± 4</td>
<td>.80</td>
</tr>
<tr>
<td>fraction, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCFc, circ/s</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>.49</td>
</tr>
<tr>
<td>Afterload</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Meridional end-systolic</td>
<td>42 ± 10</td>
<td>44 ± 16</td>
<td>.47</td>
</tr>
<tr>
<td>wall stress, g/cm²</td>
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</tr>
<tr>
<td>Circumferential end-systolic</td>
<td>77 ± 15</td>
<td>81 ± 22</td>
<td>.27</td>
</tr>
<tr>
<td>stress, g/cm²</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Contractility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCF difference,</td>
<td>0.26 ± 0.3</td>
<td>0.36 ± 0.3</td>
<td>.16</td>
</tr>
<tr>
<td>circ/s†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plus-minus values are means ± SD.
LA, Left atrial; VCFc, VCF corrected for heart rate; circ, circumference.
*P values were calculated by the Mann-Whitney test or Student’s t test, where appropriate. P < .05 was considered to indicate a significant difference.
†VCF difference serves as an index of contractility, and is the difference between the measured and predicted heart rate-corrected velocity of circumferential fiber shortening.

This study found that diastolic filling abnormalities occur in one-third of children and adolescents with essential hypertension. The pattern of these abnormalities suggests alteration in both LV relaxation and compliance. Among the subjects with hypertension, those with concentric hypertrophy appeared more affected. Elevated indexed LV mass was found to be a significant independent predictor of both abnormal relaxation and reduced compliance in the patients with elevated blood pressure.

**Diastolic Filling Abnormalities**

Studies have shown that diastolic dysfunction occurs commonly in adults with essential hypertension and intact systolic function. Diastolic dysfunction has been found to be more prevalent than initially expected when more comprehensive Doppler analyses are used. In one of two pediatric studies published, Snider et al found in a small group of hypertensive children that 6 out of 11 had diastolic filling abnormalities. However, transmitral Doppler alone was used, and only 7 of the 11 subjects had essential hypertension. The other study of pediatric patients reported by Johnson et al found that approximately one-third of the hypertensive subjects had diastolic dysfunction; however, assessment of diastolic function was limited to transmitral Doppler and IVRT.

A problem with establishing the prevalence of diastolic abnormalities is that there is no single measure of global diastolic function. By using transmitral, color M-mode, and tissue Doppler, we obtained a comprehensive non-invasive assessment of diastolic function. This study found that more than one-third of our hypertensive subjects had abnormal tissue Doppler indices.
of LV filling. The tissue Doppler values in our comparison group are quite consistent with the largest pediatric series of normal tissue Doppler values published by Eidem et al. This supports the external validity of our findings.

These children with elevated blood pressure exhibited cardiac functional effects in the form of diastolic filling abnormalities relatively early on in the disease process. Blood pressure elevation can lead to myocardial ultrastructural changes such as edema, interstitial fibrosis, and increased deposition of connective tissue, irrespective of more chronic adaptations. In addition, the likely pathological nature of these diastolic abnormalities is supported by studies that have shown improvement in these measures over time in adults treated with antihypertensive medication.

### Table III. Echocardiographic indices of diastolic function derived from transmitral, color M-Mode, and tissue Doppler

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (n = 53)</th>
<th>Hypertensive (n = 50)</th>
<th>P value*</th>
<th>P value of indices adjusted for BMI Z score†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relaxation indices</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.6 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>53 ± 14</td>
<td>70 ± 14</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vp, cm/s</td>
<td>112 ± 20</td>
<td>76 ± 19</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Eml, cm/s</td>
<td>19.0 ± 4</td>
<td>16.4 ± 3</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Compliance indices</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/Vp ratio</td>
<td>0.94 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>E/Eml ratio</td>
<td>5.6 ± 1.2</td>
<td>6.3 ± 1.7</td>
<td>.01</td>
<td>.02</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± SD.

A, Transmirtal Doppler peak A-wave velocity; E, transmirtal Doppler peak E-wave velocity; Eml, peak E-wave lateral mitral annular myocardial velocity; Vp, velocity of flow propagation.

*P values were calculated by the Mann-Whitney test or Student's t test, where appropriate. P < .05 was considered to indicate a significant difference.

†P value of indices adjusted for BMI Z score, using analysis of covariance.

### Table IV. Comparison of the diastolic indices among the hypertensive subjects, for the four patterns of geometric remodeling

<table>
<thead>
<tr>
<th>Diastolic index</th>
<th>Normal geometry (n = 10)</th>
<th>Concentric remodelling (n = 10)</th>
<th>Eccentric hypertrophy (n = 6)</th>
<th>Concentric hypertrophy (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relaxation indices</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.8</td>
<td>1.9</td>
<td>1.9</td>
<td>1.8</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>61</td>
<td>71</td>
<td>67</td>
<td>74*</td>
</tr>
<tr>
<td>Vp, cm/s</td>
<td>68</td>
<td>73</td>
<td>76</td>
<td>80</td>
</tr>
<tr>
<td>Eml, cm/s</td>
<td>17.2</td>
<td>17.2</td>
<td>15.9</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>Compliance indices</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/Vp ratio</td>
<td>1.5</td>
<td>1.4</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>E/Eml ratio</td>
<td>5.5</td>
<td>6.2</td>
<td>6.1</td>
<td>6.8*</td>
</tr>
</tbody>
</table>

A, Transmirtal Doppler peak A-wave velocity; E, transmirtal Doppler peak E-wave velocity; Eml, peak E-wave lateral mitral annular myocardial velocity; Vp, velocity of flow propagation.

*Indicates significant difference from normal geometry category at the 5% significance level, as determined by one-way analysis of variance.

### Table V. Multiple stepwise forward linear regression analysis explaining diastolic dysfunction in the hypertensive subjects

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Prob &gt; F for the model</th>
<th>R²</th>
<th>Variable*</th>
<th>β-coefficient</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eml</td>
<td>0.003</td>
<td>0.18</td>
<td>Indexed LVM</td>
<td>-0.098</td>
<td>0.031</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Constant</td>
<td>20.77</td>
<td>1.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>E/Eml</td>
<td>0.021</td>
<td>0.12</td>
<td>Indexed LVM</td>
<td>0.038</td>
<td>0.016</td>
<td>.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Constant</td>
<td>4.630</td>
<td>0.752</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Eml, Peak E-wave lateral mitral annular myocardial velocity; E/Eml, the ratio of transmirtal Doppler peak E-wave velocity to peak E-wave lateral mitral annular myocardial velocity; LVM, left ventricular mass.

*A significance level of 0.10 allowed entry into the model.
Characterizing the Pattern of Diastolic Abnormalities

Investigators have attempted to characterize the nature of diastolic dysfunction in adult patients with systemic hypertension. Researchers have documented both impaired ventricular relaxation and increased ventricular stiffness, and they have shown that relaxation abnormalities can be detected early after diagnosis of hypertension, before the onset of LV hypertrophy. We have previously examined the relationship between transmitral, color M-mode, and tissue Doppler in children to invasive indices of relaxation and compliance. We attempted to categorize the Doppler diastolic indices into those reflecting ventricular relaxation and those more indicative of LV compliance. This may be a somewhat simplistic approach because relaxation and compliance are potentially intertwined. However, we found alterations in both variables.

Systolic Function

We found no significant difference in systolic endocardial function between the subjects with blood pressure elevation and the controls. We also measured systolic midwall function because studies of adults have demonstrated a substantial portion of asymptomatic patients with hypertension have depressed midwall shortening, and that this is a strong, independent predictor of adverse cardiovascular events. However, we did not find systolic midwall abnormalities in our pediatric population.

Left Atrial Size

Left atrial volume and left atrial dimension were significantly increased in the children with blood pressure elevation, as has previously been reported. However, when indexed for body surface area, the difference was not statistically significant. This likely reflects an effect of obesity on ventricular preload and left atrial size. Interestingly, the group with concentric hypertrophy had the highest mean left atrial volume, which may suggest that an increase in the left atrial ejection force is required to fill a relatively stiff ventricle with concentric hypertrophy.

Cardiac Geometric Remodeling

It has been shown in hypertensive adults that abnormalities of diastolic function occur most commonly in patients with the geometric pattern of concentric hypertrophy. Our study also showed a relatively high proportion of patients with concentric hypertrophy (48%). Alterations in diastolic filling were more prominent in this group. This subset of patients may represent a group at particularly high risk for cardiac sequelae that needs to be followed closely and perhaps treated more aggressively.

Determinants of Diastolic Filling Abnormalities

In examining the potential determinants of impaired diastolic filling in the subjects with blood pressure elevation, indexed LV mass was found to be the only significant independent predictor. This is consistent with studies in adults showing a close correlation between increased LV mass and diastolic dysfunction. Elevated indexed LV mass predicted both abnormal relaxation and reduced compliance, supporting the hypothesis that cardiac hypertrophy associated with hypertension may influence both the time course of active relaxation and the passive deformation properties of the myocardium.

The Role of Obesity

A recent large, school-based study has confirmed the strong association between BMI and systolic and diastolic blood pressure in children and adolescents. In addition, children with a BMI ≥ 25 have been shown to have abnormalities in their diastolic function. Because our hypertensive group had a higher mean BMI than the comparison group, we adjusted for BMI when comparing the diastolic indices. Despite this adjustment, most of the differences in diastolic function remained significant indicating an independent effect of hypertension above and beyond an effect as a result of obesity. When exploring predictors of diastolic function in both groups combined, BMI was found to be a significant independent predictor of ventricular relaxation but not of ventricular compliance. However, this study was not designed to specifically evaluate the effects of obesity in persons without hypertension. This raises interesting questions regarding the relationship between obesity and diastolic function. Further studies should attempt to define this more clearly and evaluate potential mechanisms by which obesity may impact cardiac function.

Limitations

Limitations in this study include the fact that some of the hypertensive subjects were on antihypertensive medication. But, likely because of relatively few subjects on medication, neither the mean systolic nor diastolic blood pressures were significantly different between those subjects on medication and those not. However, medication may have affected both LV mass and measurements of diastolic function in these persons. The two groups differed with respect to age and heart rate, and this may have affected some of the diastolic indices. However, scatter plots with smoothed-fit regression lines did not unmask significant trends between age, heart rate, and the diastolic indices Eml and E/Eml. The two groups also differed in respect to median BMI. However, we did adjust for this when comparing the diastolic indices. We chose to include a number of the non-invasive diastolic Doppler indices in our subject evaluation to try to give as comprehensive an assessment of diastolic function as possible. However, we acknowledge that this may have increased the likelihood of a type I error. Casual blood pressures were used in this study. Ambulatory blood pressure measurements may provide a more detailed analysis of blood pressure and may be more predictive of diastolic dysfunction. Ambulatory blood pressure measurements were not done as part of the present study.
study. Lastly, our stated definition of what characterizes abnormal diastolic filling (greater than two standard deviations from the normal in the normotensive comparison group) is somewhat artificial.

In conclusion, we found that a significant number of children and adolescents with essential hypertension exhibit diastolic filling abnormalities. Whether these changes represent an adaptive or maladaptive response requires further study. However, we feel that a full cardiac evaluation, including determination of LV mass and diastolic function, is warranted in these patients.

REFERENCES


Validity, Reliability, and Responsiveness of a New Measure of Health-Related Quality of Life in Children with Immune Thrombocytopenic Purpura: The Kids’ ITP Tools

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Objective To refine the disease-specific health-related quality of life measure in immune (idiopathic) thrombocytopenic purpura (ITP) and to determine its validity, reliability, and responsiveness to change.

Study design The initial phase involved cognitive debriefing of 12 families, on the basis of which the measure was modified and then named Kids’ ITP Tools (KIT). The measure was administered on 2 occasions with the Pediatric Quality of Life Inventory (PedsQL) to 41 patients with acute ITP and 49 patients with chronic ITP, 2 to 18 years old, and their parents (proxy-respondents) at 6 North American centers.

Results Patients with acute ITP had lower scores when compared with patients with chronic ITP (child 64 versus 76, proxy 69 versus 77). The KIT moderately correlated with the PedsQL. Child versus proxy KIT scores showed moderate correlation, and the KIT was superior to the PedsQL. Test-retest reliability was substantial in the child report, but only moderate for the proxy report, similar to the PedsQL. The KIT showed a mean score change of 13 in the child and 15 in the proxy, which was greater than the PedsQL child’s change of 7 and proxy change of 5.

Conclusion The KIT is valid, with good distinction between acute and chronic ITP and a moderate correlation with the PedsQL. The KIT demonstrated reliability comparable with that of the PedsQL, yet it was more responsive to change. Therefore the KIT can be used as an outcome measure in future clinical trials of childhood ITP.

Immune thrombocytopenic purpura (ITP) is generally considered to be a benign disorder in children, with an incidence of 2 to 5 per 100,000 children younger than 15 years.1,2 Significant bleeding events are rare, with intracranial hemorrhage being the most feared consequence. Fortunately this occurs in <0.5% of patients during the first 6 months after diagnosis.3-5 ITP is arbitrarily divided into acute and chronic subtypes, depending on persistence of thrombocytopenia for less or more than 6 months since diagnosis.

The infrequent presentation of ITP, coupled with the rarity of serious bleeding sequelae, has made this a frustrating disorder to study in clinical trials. Treatment options include steroids, intravenous immunoglobulin, anti-Rh(D), or observation alone. Typically, the platelet count has been used as a surrogate outcome, but most patients with even

<table>
<thead>
<tr>
<th>HRQL</th>
<th>Health-related quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICC</td>
<td>Intraclass correlation coefficient</td>
</tr>
<tr>
<td>IoF</td>
<td>Impact on Family</td>
</tr>
<tr>
<td>ITP</td>
<td>Immune (idiopathic) thrombocytopenic purpura</td>
</tr>
<tr>
<td>KIT</td>
<td>Kids’ ITP Tools</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>PedsQL</td>
<td>Pediatric Quality of Life Inventory</td>
</tr>
</tbody>
</table>

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From the Department of Pediatrics, Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada (R.J.K.); Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada (V.S.B.); Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada (V.S.B.); Department of Pathology and Laboratory Medicine, IWK Health Centre, Halifax, Nova Scotia, Canada (D.B.); Department of Nursing, Hospital for Sick Children, Toronto, Ontario, Canada (C.D.W.); Community Health Systems Resource Group, Hospital for Sick Children, Toronto, Ontario, Canada (C.C., C.S.B., N.L.Y.); Department of Rehabilitation Services, Hospital for Sick Children, Toronto, Ontario, Canada (C.C., C.S.B.); Division of Hematology/Oncology, Children’s Hospital, Boston, Massachusetts (E.J.N.); University of Texas Southwestern Medical Center, Dallas, Texas (G.R.B.); Department of Pediatrics, Kingston General Hospital, Kingston, Ontario, Canada (M.P.S.); Department of Pediatrics, McMaster Children’s Hospital, Hamilton, Ontario, Canada (A.K.C.C.); Laurentian University, Sudbury, Ontario, Canada (N.L.Y.).

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severe thrombocytopenia (platelet count $<10 \times 10^9/L$) do not have serious bleeding, casting doubt on this approach.

Physicians who treat patients with ITP are aware of the impact the disease can have on the affected families. Activities are commonly restricted, and parents frequently put their children in a “protective bubble,” irrespective of medical recommendations.

One method of capturing the effect of ITP on families is to measure health–related quality of life (HRQL). A review of the literature in 2001 identified 19 generic and 24 disease-specific quality–of–life measures, but found only 3 of the generic measures and 2 of the disease–specific measures fulfilled basic psychometric criteria.\(^6\) One universally accepted and widely–used HRQL measure is the Pediatric Quality of Life Inventory (PedsQL), which consists of a generic core and a number of disease–specific modules. Unfortunately, there currently is no ITP module, and the PedsQL generic core would likely be inadequate for the detection of subtle changes in the various therapeutic approaches commonly used in the treatment of children with ITP.\(^6\)\(^–\)\(^9\) A disease–specific measure of HRQL is therefore needed to evaluate critically the impact of different treatment regimens and provide evidence–based information to aid clinical decision making in children with ITP.

Barnard et al developed a disease–specific HRQL measure, which initially consisted of 138 questions for children and 184 questions for parents. The item set was reduced to a 26–item child and proxy (identical to the child version except for replacing “I” with “my child”) questionnaire and a separate 26–item parent questionnaire.\(^9\)

The purpose of this study was to further refine the instruments developed by Barnard et al and to ensure that the refined measure was sufficiently robust for use in clinical trials. This paper describes the process by which the ITP HRQL measure was refined with input from family interviews and expert opinion (phase 1) and subsequently assessed for reliability, responsiveness, and validity (phase 2).

**METHODS**

**Recruitment of Participants**

Patients and their families were recruited from hematology clinics, emergency departments, and the inpatient units at 6 pediatric centers across North America: Hospital for Sick Children, Toronto, Ontario, Canada; Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada; Children’s Hospital Boston, Mass; Children’s Medical Center Dallas, Texas; the University of Texas Southwestern Medical Center, Dallas, Texas; McMaster Hospital, Hamilton, Ontario, Canada; and Kingston General Hospital, Kingston, Ontario, Canada. Each institution obtained approval from their local research ethics board or institutional review board before opening the study at their center.

**Phase 1: Cognitive Debriefing**

Cognitive debriefing interview sessions were conducted with 12 families according to the framework previously described by Jobe.\(^10\) The finalized version of the measure was designated the Kids’ ITP Tools (KIT), with a child version, proxy version, and parent version, each consisting of 26 questions that can be completed in <10 minutes. No separate domains were identified, and a single overall score was generated. The KIT was used for phase 2 of the study.

**Phase 2: Testing of Measurement Properties**

All 6 centers participated in this phase of the study. Eligible participants included children with either acute or chronic ITP between 2.00 and 17.99 years of age. ITP was defined as a platelet count $<150 \times 10^9/L$ with a hemoglobin level and white cell count in the reference range and no significant abnormalities on blood smear. The study group was subdivided into patients with “acute ITP,” defined as patients in whom ITP was newly diagnosed, and patients with “chronic ITP,” defined as patients who continued to fulfill the diagnostic criteria for ITP but in whom the diagnosis had been made ≥6 months earlier. Children with acute ITP were eligible for recruitment within 72 hours of diagnosis, whereas children with chronic ITP could be enrolled at any point. Children with secondary ITP, significant cognitive impairments, or inability to communicate in English were excluded.

The local research assistant approached consecutive patients with ITP fitting the inclusion criteria and explained the study in detail. Families who signed the consent form were given a baseline package to complete before leaving the hospital. All parents were instructed to complete the KIT parent and proxy measures, the PedsQL, the Impact on Family (IoF), the worry scale, and the global ratings of change. Details on these measures are provided in the section on questionnaires.

Children ≥7 years old completed the KIT child measure, the PedsQL, the worry scale, and the global ratings of change. Children <7 years old were not asked to complete any measures. Parents were encouraged not to interact with their child when completing the questionnaires. When children had questions, they were directed to the research assistant, not their parents.

All participants were requested to complete a second questionnaire package, but the timing depended on the type of ITP. Families with chronic ITP were mailed a set of the questionnaires to complete 2 weeks after enrollment. This period was chosen to allow for analysis of reliability, because it was postulated that the disease would not usually have significantly changed during that period, yet the interval was long enough for the participant to have forgotten specific responses from the first administration. Patients with chronic ITP were divided into chronic–variable and chronic–stable groups, with the latter used for analysis of reliability. Patients were considered chronic–variable when they required platelet–enhancing drug treatment in the 2 months preceding enrollment or during the study period or when both parent and child indicated a major change in the child’s health. The remaining patients with chronic ITP were designated chronic–stable.
Families with acute ITP completed the questionnaires 3 months after enrollment during a routinely scheduled clinic visit. Patients whose ITP resolved, as indicated by the attending physician, were designated acute-resolved and used for analysis of the responsiveness of the measures. Criteria for resolution included no recent therapy and a platelet count in the reference range. The remaining patients with acute ITP were designated acute-unresolved.

**Questionnaires**

The PedsQL is a well-established measure of HRQL in children. It consists of a generic core module that can be used in both healthy and ill children, with disease-specific modules. There is no disease-specific module for ITP, so the generic module was used for this study. The PedsQL has been studied in a variety of patient populations and demonstrates very good psychometric properties.\(^8,11-12\) It was included in this study to allow for validity assessment of the proxy version of the KIT.

The IoF was selected to provide a measurement of the burden of the disease on the family. Many of the items in the parent version of the KIT address this issue. The IoF has been previously shown to be reliable and valid.\(^13\) Parents were asked to complete the IoF measure to allow for validity assessment of the parent version of the KIT.

**Disease Severity, Worry Scale, and Global Rating of Health**

The attending physician was asked to complete an assessment of disease severity at the time of administration of the initial questionnaire, using a modified version of the checklist developed by Buchanan and Adix.\(^14\) The doctor, child, and parent completed a 7-point ITP “worry scale,” ranging from not at all worried to extremely worried. The families also completed a global rating of their life, health, and ITP using a visual analogue scale. The left end of the scale was anchored as “really bad” and the right end as “really good.” Also, families were asked at the time of completing the second questionnaire to rate any change in the child’s health since enrollment with another 7-point scale, ranging from “much better” to “no change” to “much worse.”

**A Priori Hypotheses**

We expected a moderate correlation (0.5-0.8) among the KIT child scores and proxy scores and the PedsQL summary scores and a fair correlation (<0.5) with the worry scale. We hypothesized that there would be only a fair correlation between the parent KIT scores and the IoF scores. We speculated that the child’s KIT scores would correlate with the proxy scores and that there would be acceptable test-retest results in the children with chronic stable ITP and their parents.

For the measure to be sufficiently reliable for use in clinical trials, the lowest level of agreement acceptable was set as substantial. Agreement is classified as recommended by Landis et al, with an intraclass correlation coefficient (ICC) <0.0 indicating poor agreement, 0.0 to 0.20 indicating slight agreement, 0.21 to 0.40 indicating fair agreement, 0.41 to 0.60 indicating moderate agreement, 0.61 to 0.80 indicating substantial agreement, and 0.81 to 1.0 indicating almost perfect agreement.\(^15\)

**Statistical Analysis**

Summary scores of all questionnaires were calculated according to the owner’s manual and represent the mean of all applicable responses. The summary score for the KIT was calculated with the equation:

\[
100 \times \left(1 - \left(\frac{\text{Sum of all scores} - \text{number of valid responses}}{\text{valid responses} \times 4}\right)\right)
\]

This yielded scores with a potential range of 0 (worst) to 100 (best). Summary scores were not calculated when >25% of the responses were not completed. Scores were calculated with the “not applicable” responses excluded. We performed a sensitivity analysis to determine how to handle the not applicable responses and determined there was no significant difference when they were excluded or coded as never. PedsQL scores have a possible range of 0 (worst) to 100 (best), and the IoF results have a potential range of 19 (least impact) to 76 (greatest impact). However, for the purposes of this report, we re-scaled the IoF to 0 (least impact) to 100 (greatest impact) to allow for comparison with the parent scores from the KIT.

The Mann-Whitney test was used to compare bleeding scores between patients with acute ITP and patients with chronic ITP, and the sign test was used to compare baseline and follow-up bleeding scores in the acute ITP group.

Different subgroups of the study sample were used to assess each of the measurement properties. The acute and chronic ITP groups were further subdivided in 4 groups: acute-resolved, acute-unresolved, chronic-stable, and chronic-variable (see Phase 2: Testing of Measurement Properties for definitions). Validity analysis was performed with a paired t test comparing the summary scores obtained at baseline on all patients. Reliability was analyzed with a single measure ICC with a random effects model. Child-proxy correlation used all baseline scores, and test-retest reliability compared the baseline and follow-up scores from only the patients in the chronic-stable group. The baseline scores from the acute-resolved patients were subtracted from the follow-up scores to determine the change in scores. The mean change in scores was compared with a paired t test. Statistical analysis was performed with STATA software version 8.

**RESULTS**

**Phase 1: Cognitive Debriefing**

The major changes to the previously published child, proxy, and parent instruments involved: 1) restricting or clarifying the not applicable (NA) responses, because the children...
often confused NA with never; and 2) rearranging the order and phrasing of the questions to allow for better flow. In the child/proxy questionnaire, 1 question, which referred to the child’s round face, was deleted, because it occurred infrequently and was encompassed by a question about changes in how the child looked. A question about being in the hospital was subdivided into a question about going to a clinic and staying overnight in the hospital, to improve precision. There were no additions or deletions in the parent instrument.

The revised questionnaires, the KIT, were used for phase 2 of the study.

Phase 2: Testing of Measurement Properties

From May 2004 to May 2005, 92 patients with ITP were enrolled at 6 centers across North America, and 90 patients successfully completed the baseline questionnaires. The mother was the proxy/parent respondent in 86% of the families, with the father being the respondent in 11% of families and another caregiver being the respondent in the remaining 3%. Forty-nine patients had chronic ITP, and 41 patients had acute ITP. When the patients with acute ITP repeated the questionnaires 3 months later, 28 (68%) had resolution of their disease. Of the chronic patients who repeated the questionnaires 2 weeks later, 30 (61%) were considered to have a stable clinical course. The patient characteristics by subgroup are shown in Table I.

The bleeding severity scores are detailed online (Table II; available at www.jpeds.com). The attending physician described significantly higher bleeding scores for the patients with acute ITP at baseline (33% moderate/severe) than both the patients with chronic ITP at baseline (4% moderate/severe) and the patients with acute ITP at follow-up (3% moderate/severe).

Validity

The summary scores from all the questionnaires administered at baseline were used for validity analysis. Patients with acute ITP had a significantly lower score when compared with patients with chronic ITP (64.0 versus 75.7 child, 68.6 versus 77.2 proxy report, respectively; all \( P < .014 \)). The child and the proxy showed moderate correlation with the PedsQL measure (child \( r = 0.53 \); proxy \( r = 0.46 \); both \( P < .001 \)). The correlation with the other measures is described in Table III.

The parent questionnaire, which focuses on the effect of the disease on the parent, was compared with the IoF total impact score. There was fair correlation at baseline (\( r = -0.28, P = .008 \)), but a moderate correlation at follow-up (\( r = -0.53, P < .001 \)). Again, the patients with acute ITP had a lower KIT score than the chronic patients (34 versus 52, \( P < .001 \)).

Reliability

Child versus proxy KIT summary scores were compared at baseline and showed moderate concordance (ICC = 0.54). Parent/child concordance was lower for the PedsQL. Test-retest reliability, analyzed with the responses from the children and parents in the chronic stable ITP group, was substantial in the child report (ICC = 0.73) and parent reports

<table>
<thead>
<tr>
<th>Table I. Sample characteristics by subgroup</th>
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<tr>
<td></td>
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<td></td>
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<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>28</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
</tr>
<tr>
<td>Number female (%)</td>
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<tr>
<td>Days after diagnosis (range)</td>
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<tr>
<td>Number of patients without follow-up data</td>
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<tr>
<td>Analysis groups</td>
</tr>
<tr>
<td>Reliability</td>
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<tr>
<td>Validity</td>
</tr>
<tr>
<td>Responsiveness</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table III. Correlation of the KIT with other measures at baseline (acute and chronic groups combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT</td>
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<tr>
<td>-----</td>
</tr>
<tr>
<td>Child</td>
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<td>Proxy</td>
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VAS, Visual analogue scale.
* \( P < .01 \).
† \( P < .001 \).

Validity, Reliability, and Responsiveness of a New Measure of Health-Related Quality of Life in Children with Immune Thrombocytopenic Purpura: The Kids’ ITP Tools
(ICC = 0.61), but only moderate in the proxy reports. The test-retest results were similar for the PedsQL child report and the IoF parent report, but were higher for the proxy report. ICC results for the various measures are summarized in Table IV.

**Responsiveness**

Twenty-eight of the 41 patients with acute ITP were reported by their attending physician as having resolution of their disease at 3 months. Their summary scores were used for analysis of responsiveness. The mean change in KIT scores was 12.7 for child report and 15.3 for proxy report. These were significantly greater than the mean change scores from the PedsQL proxy report (5.0, P < .05). The mean change in PedsQL child report scores was 7.0 (P = .23 compared with the KIT child report). Additional details are provided in Table V (available at www.jped.com). The Figure is a boxplot depiction of the responsiveness of the child KIT and PedsQL scores.

**DISCUSSION**

ITP in childhood is a relatively common disorder with a typically benign course. However, it may rarely result in significant morbidity and mortality. Therefore, families of children with ITP often live in fear that their child may be one of the unfortunate ones. Physicians treating ITP need to be acutely aware of parental anxiety and must keep this in mind when analyzing the potential risks and benefits of various treatment approaches. Simply considering changes in platelet count and the requirement for and performance of bone marrow aspiration. By measuring these disease-specific issues directly, as one would expect, the measure becomes more responsive. When used in conjunction with a generic measure such as the PedsQL, we get a com-

<table>
<thead>
<tr>
<th>Table IV. Reliability</th>
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<tbody>
<tr>
<td><strong>Intraclass correlation (95% CI)</strong></td>
</tr>
<tr>
<td><strong>Child vs proxy (n = 58)</strong></td>
</tr>
<tr>
<td>KIT</td>
</tr>
<tr>
<td>PedsQL</td>
</tr>
<tr>
<td><strong>Test-retest: chronic stable ITP</strong></td>
</tr>
<tr>
<td>KIT child report (n = 19)</td>
</tr>
<tr>
<td>KIT proxy report (n = 29)</td>
</tr>
<tr>
<td>KIT parent report (n = 30)</td>
</tr>
<tr>
<td>PedsQL child report (n = 19)</td>
</tr>
<tr>
<td>PedsQL proxy report (n = 28)</td>
</tr>
<tr>
<td>IoF parent report (n = 28)</td>
</tr>
</tbody>
</table>

Figure. Responsiveness of KIT and PedsQL scores among patients with acute ITP that resolved. Boxplots show median, quartiles, and adjacent lines (1.5 × interquartile range), with oval indicating outside values.
prehensive picture of ITP that allows comparison of diseases but that is also sensitive to change. Thus both disease-specific and generic measures are of value.

When conducting studies in ITP, we should no longer use the platelet count as the sole outcome measure. HRQL, bleeding severity, and costs and complications of treatment need to be considered as well. HRQL is arguably the most important outcome in this disease. The KIT, particularly when used in conjunction with a generic tool such as the PedsQL, provides valuable information about HRQL in ITP.

We thank Leah Adix, Pam Boardman, Joanna Hughes, Lesley MacPhail, and Sabrina Siciliano for their work with patient recruitment and data collection, and Melissa Morrison for her technical support and editorial assistance.

REFERENCES


**Table II. Bleeding severity score ratings**

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild or minor</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute ITP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, n = 40 (%)</td>
<td>1 (3)</td>
<td>26 (65)</td>
<td>12 (30)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Follow-up, n = 31 (%)*</td>
<td>24 (75)</td>
<td>6 (22)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic ITP,</strong>† n = 48 (%)*</td>
<td>27 (56)</td>
<td>19 (39)</td>
<td>2 (4)</td>
<td></td>
</tr>
</tbody>
</table>

*P < .0001 compared with baseline acute ITP.
†Bleeding severity scores were not collected at follow-up in patients with chronic ITP.

**Table V. Responsiveness**

<table>
<thead>
<tr>
<th>Measure and respondent</th>
<th>Mean change in scores (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT child report (n = 12)</td>
<td>12.7 (1.1-24.0)</td>
</tr>
<tr>
<td>KIT proxy report (n = 24)</td>
<td>15.3 (6.4-24.0)</td>
</tr>
<tr>
<td>KIT parent report (n = 24)</td>
<td>37.4 (24.5)</td>
</tr>
<tr>
<td>PedsQL child report (n = 12)</td>
<td>7.0 (0.2-10.7)*</td>
</tr>
<tr>
<td>PedsQL proxy report (n = 24)</td>
<td>5.0 (0.2-9.7)†</td>
</tr>
<tr>
<td>IoF parent report (n = 24)</td>
<td>8.2 (1.0-16.0)†</td>
</tr>
</tbody>
</table>

*P = .23, compared with KIT.
†P ≤ .05 compared with KIT.
Case Control Study of Psychosocial Morbidity in β Thalassemia Major

ARUN SAINI, MD, JAGDISH CHANDRA, MD, FIAP, UTPAL GOSWAMI, MD, DPM, VARINDER SINGH, MD, AND A. K. DUTTA, MD, FIAP

Objectives To assess the prevalence and the spectrum of psychosocial morbidity and its correlation with various social and disease-related factors in children with β thalassemia major.

Study design Sixty children with transfusion-dependent β thalassemia major were included in the study group who fulfilled these inclusion criteria: 1) age 5 to 15 years; 2) both parents alive and living together; 3) negative for human immunodeficiency virus; and 4) no family history of any chronic illness or psychological illness. The control group consisted of 60 children of matched age group and social background. A semi-structured interview and 2 preformed questionnaires (Pediatric Symptom Checklist [PSC] and Childhood Psychopathology Measurement Schedule [CPMS]) were used to assess psychosocial morbidity.

Results The mean score of the PSC was 11.63 ± 3.79 (range, 7-24) in children with thalassemia, compared with 5.78 ± 2.572 (range, 2-13) in the control group (P < .001). The mean score of the CPMS was 11.63 ± 3.6 (range, 6-25) compared with 6.08 ± 2.8 (range, 1-14) in the study and the control group, respectively (P < .001). Among the children with thalassemia, 54% had a mean CPMS score ≥10 (which is considered significant for psychopathological disorders), compared with 8.3% in the control group (P < .001).

Conclusion Children with thalassemia have significantly higher psychosocial morbidity. Psychosocial aspects need to be addressed in the overall treatment of children with thalassemia to prevent the development of clinically manifest psychological disease. (J Pediatr 2007;150:516-20)

β thalassemia major, a genetically determined disorder, primarily manifests as a progressive hemolytic anemia. India has approximately 30 million people who are carriers of the β thalassemia gene and approximately 8000 to 10,000 children are born with β thalassemia major every year.1,2 Bone marrow transplantation (BMT) is a curative treatment for thalassemia major, but most cases in India are managed with regular transfusion-chelation therapy because BMT is not available due to its high cost and non-availability of HLA-matched donors.3 Regular transfusions and iron chelation therapy have significantly increased the life expectancy of patients with thalassemia major.4,5 However, improved survival is associated with various multisystem complications primarily caused by chronic anemia, iron overload, adverse effects of chelation, and transfusion-associated infections.6-10 Thus, a disease that starts merely as hemolytic anemia attains the dimension of a chronic disease with multisystem involvement.

A few studies of children with thalassemia have shown heightened risk of developmental and behavioral problems. However, results are varied, showing mild behavioral problems to frank psychiatric disorders.11-15 There is a paucity of work on psychosocial evaluation of children with thalassemia, especially in India. We conducted this study to assess the prevalence and the spectrum of psychosocial morbidity and its correlation with various social and disease-related factors.

METHODS

The study was conducted in Thalassemia Day Care Centre, Division of Pediatric Hematology, Kalawati Saran Children’s Hospital, Lady Hardinge Medical College, New Delhi, India.

Subjects

Sixty children with transfusion-dependent β thalassemia major were included in the study group. The inclusion criteria were: 1) age between 5 and 15 years; 2) both parents
alive and living together; 3) negative for human immunodeficiency virus; and 4) no family history of any chronic or psychiatric illness. They were receiving packed red cell transfusion at 3- to 4-week intervals with an aim to maintain a pretransfusion hemoglobin level of 9.5 to 10.5 g/dL. They also were receiving an oral iron-chelating agent, deferiprone. The study group was compared with the control group of 60 children matched for age and social background who were attending our outpatient department for acute illnesses and fulfilled the inclusion criteria of age, both parents alive and living together and no family history of any chronic or psychiatric illness.

Method

A semi-structured interview that included demographic information, school performance, and family characteristics was taken. Information about disease factors (including average hemoglobin level, duration of treatment, and average serum ferritin level) of children with thalassemia was collected from medical records of the Thalassemia Day Care Centre. Physical findings, including weight, height, sexual maturity rating, hepatomegaly, and splenomegaly, were recorded. A modified socioeconomic scale for an urban Indian population was used to assess socioeconomic status.16

To assess the psychosocial morbidity in each group, both parents were simultaneously interviewed with 2 preformed questionnaires, the Pediatric Symptom Checklist (PSC)17 and the Childhood Psychopathology Measurement Schedule (CPMS).18 The PSC is a commonly used screening tool for assessing significant psychosocial morbidity in children. It is a 1-page questionnaire of children’s emotional and behavior problems that reflects parents’ impressions of their children’s psychosocial functioning. Jellinek et al have suggested a cut off score ≥28 for children aged 6 to 16 years and ≥24 for children aged 4 and 5 years, which was used in this study.17

Table I. Demographic features of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Patients with thalassemia</th>
<th>Control subjects</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>8.59 ± 2.9 (5-15)</td>
<td>8.50 ± 2.2 (5-15)</td>
<td>.57</td>
</tr>
<tr>
<td>Male: Female</td>
<td>1.7:1.0</td>
<td>2:1:0</td>
<td>.56</td>
</tr>
<tr>
<td>Type of family</td>
<td></td>
<td></td>
<td>.1</td>
</tr>
<tr>
<td>Joint</td>
<td>20</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Nuclear</td>
<td>40</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Family size</td>
<td>6.670 ± 4.047</td>
<td>6.42 ± 3.67</td>
<td>.53</td>
</tr>
<tr>
<td>Per capita income per month, Rupees</td>
<td>1316.6 ± 1119.1</td>
<td>1201.5 ± 836.0</td>
<td>.59</td>
</tr>
<tr>
<td>Socioeconomic class</td>
<td></td>
<td></td>
<td>.54</td>
</tr>
<tr>
<td>Higher middle</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>28</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Lower middle</td>
<td>25</td>
<td>31</td>
<td></td>
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</tbody>
</table>

Table II. Comparison of Pediatric Symptom Checklist and Childhood Psychopathology Measurement Schedule mean scores

<table>
<thead>
<tr>
<th></th>
<th>Patients with thalassemia</th>
<th>Control subjects</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC (range)</td>
<td>11.63 ± 3.79 (7-24)</td>
<td>5.78 ± 2.572 (2-13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CPMS (range)</td>
<td>11.63 ± 3.60 (6-25)</td>
<td>6.08 ± 2.8 (1-14)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Figures are mean ± SD.

CPMS is an Indian–adapted version of the extensively used “Child Behaviour Check List” by Achenbach and Edelbrock.19 It has an advantage of measuring overall psychopathology in the form of total score and 8 subscales divided in different symptom complexes. Therefore, it provides a profile of psychosocial problem areas and competencies. A CPMS mean score ≥10 is considered significant for psychopathological disorders; with this cutoff score, the sensitivity and the specificity rates for detecting a psychopathological disorders are 82% and 87%, respectively.20 The patients who were found to have a significant score were referred to the specialist psychiatrist for further assessment, diagnosis, and treatment.

RESULTS

As shown in Table I, demographic and social factors were comparable between the study subjects and the control group. Most of the children in both groups belonged to the middle or lower-middle class. A significant observation was made about delayed schooling (arbitrarily defined as >2-year lag in school education for age) in 22% of the children with thalassemia compared with 3% of the control group (P = .003). Four of the children with thalassemia (6.7%) had left schooling, as compared with 1 child in the control group (1.7%; P < .001).

As depicted in Table II, the mean score of both PSC and CPMS were significantly higher in the study group than in the control group. None of the children in our study had a PSC mean score greater than the recommended cutoff score (≥28 for 6-16 years, ≥24 for 4-5 years).17 However, 3 children in the study group had a score >20 (20, 24, and 24). There was no significant difference in the PSC and CPMS mean scores between boys and girls (P > .05). Of the children with thalassemia, 54% had a mean CPMS score ≥10, as compared with 8% of children in the control group (P < .001). Comparison of cutoff CPMS score with mean PSC score showed a significantly greater mean PSC score in chil-

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Case Control Study of Psychosocial Morbidity in β Thalassemia Major

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Children who had CPMS mean score ≥10 compared with children who had mean score <10 (P < .001).

Correlation of the disease and the demographic factors showed no significant correlation with PSC and CPMS mean score, as depicted in Table III, but the positive correlation with the duration of illness was statistically significant (P = .022 for PSC and P = .015 for CPMS). The CPMS mean score in the patient group was assessed versus school performance. The CPMS mean score was 13.47 ± 4.1 in children with thalassemia who had a delayed education compared with 10.98 ± 3.4 in children with thalassemia who had an age-appropriate education status (P = .033).

Psychological symptom complex was evaluated with CPMS subscales, as shown in Table IV. Comparisons were made for each subscale within and between the 2 groups. The subscale specific for “Conduct Disorder” had the highest mean score in the children with thalassemia. Stubbornness, disobedience, temper tantrums, and argumentativeness were the most common responses in this subscale. The “Behavior and Low Intelligence Scale” was the next most common finding. School underachievement, poor memory, and inability to concentrate were the most common responses in this subscale. The “Depression” subscale was the third in mean score. “Likes to be alone,” “remains sad or unhappy,” and “gets teased a lot” were the common responses in this subscale. However, none of the children with thalassemia had attempted suicide or deliberately harmed himself/herself. Fourth in the rank was the “Anxiety” subscale, which shared a common rank with the subscale for “Somatization.” Nervousness and feeling tense were the common responses. In the “Somatization” subscale, aches and pains, accident proneness, and clumsiness were the most common responses. In the “Special Symptoms” subscale, nocturnal enuresis was found to be the most common response. We found that 31% of children with thalassemia (n = 19) had enuresis, compared with 17% of children in the control group (n = 10; P < .05). However, approximately 70% of children with enuresis were younger than 8 years, and there was only 1 child older than 12 years (in both groups) who had nocturnal enuresis.

**DISCUSSION**

Children with chronic illnesses have long been shown to be at a substantial risk for psychosocial morbidity, as evidenced by various clinic-based and population-based studies. Like most chronic illnesses, thalassemia is associated with certain factors that individually or in combination predispose the patient to increased psychosocial morbidity. Factors such as early age of onset of disease, separation from parents resulting from frequent hospitalization for regular blood transfusion, or disease-related complications substantially affect the child’s overall psychosocial development. Limited mobility (particularly in children with low hemoglobin who are poorly transfused) and other disease or chelation-related complications affect children’s social interaction with peer group and recreational activities, which may adversely influence cognitive development and will probably lead to an increased tendency of withdrawal and isolation. Overprotection and gratification of demands of these children by their parents make them dependent on adults and lead to low self-esteem. Frequent school absenteeism because of regular visits to the hospital for transfusion and disease-related complications not only contribute to the child’s falling behind in studies, but also interferes with peer relationships. A constant threat of death may affect the parent-child relationship, which may increase anxiety in the child. The entire family is constantly confronted with a series of demands and stresses when faced with the diagnosis of a severe and chronic illness like thalassemia that tax the relationships both within and beyond the family unit.

Prevalence of psychosocial maladjustment has been reported in 28% to 80% of patients with thalassemia major. We observed a CPMS mean score higher than the

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**Table III. Features of disease and correlation with Pediatric Symptom Checklist and Childhood Psychopathology Measurement Schedule mean scores**

<table>
<thead>
<tr>
<th>Disease feature</th>
<th>Patients with thalasemia*</th>
<th>PSC r (P value)</th>
<th>CPMS r (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of illness, years (range)</td>
<td>6.91 ± 3.08 (1.5-14.0)</td>
<td>.295 (.022)</td>
<td>.312 (.015)</td>
</tr>
<tr>
<td>Duration of transfusion therapy, years (range)</td>
<td>6.75 ± 3.13 (1.5-14.0)</td>
<td>.236 (.070)</td>
<td>.250 (.054)</td>
</tr>
<tr>
<td>Average Hb previous year, g/dL (range)</td>
<td>8.50 ± 1.41 (4.92-10.60)</td>
<td>-.249 (.055)</td>
<td>-.179 (.172)</td>
</tr>
<tr>
<td>Duration of chelation therapy, years (range)</td>
<td>2.35 ± 1.72 (1.0-7.5)</td>
<td>.117 (.373)</td>
<td>.185 (.156)</td>
</tr>
<tr>
<td>Average serum ferritin previous year, ng/dL (range)</td>
<td>3832 ± 1796 (850-8772)</td>
<td>.321 (784)</td>
<td>.57 (.692)</td>
</tr>
</tbody>
</table>

*Figures are mean ± SD.

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**Table IV. Comparison of subscales of Childhood Psychopathology Measurement Schedule**

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Patients with thalasemia</th>
<th>Control subjects</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intelligence and behavior problems</td>
<td>0.144 ± 0.087</td>
<td>0.088 ± 0.059</td>
<td>.0001</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>0.29 ± 0.10</td>
<td>0.185 ± 0.087</td>
<td>.0001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.11 ± 0.17</td>
<td>0.030 ± 0.100</td>
<td>.004</td>
</tr>
<tr>
<td>Depression</td>
<td>0.13 ± 0.12</td>
<td>0.052 ± 0.07</td>
<td>.001</td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>0.02 ± 0.05</td>
<td>0.005 ± 0.024</td>
<td>.007</td>
</tr>
<tr>
<td>Special symptoms</td>
<td>0.08 ± 0.09</td>
<td>0.046 ± 0.085</td>
<td>.051</td>
</tr>
<tr>
<td>Physical illness with emotional problems</td>
<td>0.06 ± 0.12</td>
<td>0.008 ± 0.045</td>
<td>.001</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.11 ± 0.10</td>
<td>0.05 ± 0.08</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Figures are mean ± SD.
cutoff of $\geq 10$ in $54\%$ of children with thalassemia major in the age group of 5 to 15 years, with no difference between boys and girls. This would suggest that psychosocial morbidity might have its onset during childhood and adolescence. This morbidity is likely to increase with increasing age, as is evident from our observation of a positive correlation of CPMS mean score with duration of illness. Aydin et al observed an $80\%$ prevalence in children between 12 and 19 years, which supports this concept. Ratip et al also made a similar observation.26

We found no statistically significant correlation between maladjustment and various features of disease, except for the duration of illness. Louthrenoo et al and Pradhan et al made a similar observation.14,25 Because most of our patients were effectively transfused and their pretransfusion hemoglobin level was maintained within the expected range (9.5-10.5 g/dL), it is difficult to interpret whether the degree of anemia affects psychosocial morbidity. Effective chelation therapy may be a double-edged sword, positively influencing physical health but increasing the burden of treatment and chelation associated adverse effects. It may also serve as constant reminder to the patients about their illness. The short duration of chelation therapy received by our study group made a study of psychosocial morbidity impossible. We found no correlation between various demographic factors and psychosocial morbidity.

We observed that patients with thalassemia major have significantly disturbed school functioning, which could affect psychosocial adjustment. Various factors, such as school absenteeism, behavior or conduct disorders, overprotective nature of parents, poor self-esteem, disturbed peer relationships, and economic factors, may contribute to poor school functioning. Children with thalassemia who had poor school performance also had significantly higher psychosocial maladjustment. Beratis et al also observed that oppositional defiant disorders was associated with poor school performance.12 This would suggest that poor school performance should alarm the treating physician, calling for a thorough psychosocial examination of the child with thalassemia.

Children with thalassemia showed significantly higher maladjustment in each subscale of symptom complex individually, including conduct disorder, low intelligence and behavior problems, depression, and anxiety. Logothetis et al have reported abnormalities in character and behavior in approximately $70\%$ of patients with thalassemia, with impulsiveness and uncontrolled temper being common.25 A similar observation was made by Beratis et al.12 However, Pradhan et al reported that depression was the most prominent psychiatric disorder in patients with thalassemia.13 Ratip et al reported the entire range of psychosocial symptoms, with stigmatism and anxiety being the more common symptoms.26 The prevalence and spectrum of psychosocial morbidity among children with thalassemia is comparable with that of children with other chronic illnesses, such as bronchial asthma, diabetes mellitus, and epilepsy.33–38

The limitation of both of the questionnaire systems we used is that neither can be used to diagnose any particular psychiatric disorder. Therefore, the children who were found to have a significant CPMS mean score were referred for the diagnosis of specific morbidity and institute-appropriate treatment. A limitation of this study is that we did not correlate the results of the psychiatric evaluation with the CPMS mean score, which could have further supported our observation.

Apart from keeping children with thalassemia fit physically with regular transfusions and iron chelation, periodic psychosocial assessment, counseling, and continuous support must be provided to them and their families.22

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50 Years Ago in The Journal of Pediatrics

HYPERKINETIC BEHAVIOR SYNDROME IN CHILDREN

Laufer MW, Denhoff E. J Pediatr 1957;50:463-74

In their 1957 report, Laufer and Denhoff described their experience with children with “hyperkinetic behavior syndrome,” a condition we now call “attention deficit hyperactivity disorder” (ADHD). They described the key features of hyperactivity: decreased ability to concentrate, impulsivity, intra-patient symptom intensity variability, and poor school performance. They stated that the history is “the most valuable item in making the diagnosis.” The authors described the usually normal neurologic examination, and the variable, non-specific EEG findings. They told us that laboratory studies have no value in making the diagnosis.

Affected patients generally responded to an amphetamine—either d-amphetamine or racemic amphetamine—although one could not predict which patient would respond to which amphetamine. Patients did not become addicted to their medication. There were often associated behavior problems such as conduct disturbances (today we call these “comorbidities”), but these were, according to Lanfer and Denhoff, a reaction by the child to his unfavorable self-image.

The modern reader will note some differences, mostly minor, between the 1957 paper and what is believed today. Currently, we separate out an inattentive-hyperactive-impulsive type (80% of patients), a predominantly inattentive type (10%-15%), and a predominantly hyperactive-impulsive type (5%). We think the comorbidities, such as conduct disorder and oppositional defiant disorder, are co-occurring disorders and are not caused by the patient’s poor self-image. We currently do not think that this most common neuropsychiatric disorder of childhood disappears by age 18 years, as the 1957 article indicated. We do not use intravenous metrazol (a γ-aminobutyric acid antagonist) to induce electroencephalographic changes to make an ADHD diagnosis.

By 2007, we believe that we have learned something about the genetic factors in ADHD and anticipate that functional neuroimaging may become a diagnostic tool. What was written here 50 years ago is, by and large, true today. One might wonder whether our pediatrician-descendants, 50 years from now, will find we have made sufficient progress in clarifying the whys and wherefores of ADHD.

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Objective  To evaluate whether nasal intermittent mandatory ventilation (NIMV) compared with nasal continuous positive airway pressure (NCPAP) would decrease the requirement for endotracheal ventilation in the treatment of respiratory distress syndrome (RDS) in preterm infants <35 weeks.

Study design  Randomized, controlled, prospective, single-center study. Forty-one infants were randomized to NCPAP and 43 comparable infants to NIMV (birth weight 1533 ± 603 vs 1616 ± 494 g, gestational age 30.6 ± 3.0 vs 31.1 ± 2.3 weeks, P = .5, respectively).

Results  Infants treated with NIMV and with NCPAP had comparable cardio-respiratory status at study entry. In the total cohort, infants treated initially with NIMV needed less endotracheal ventilation than infants treated with NCPAP (25% vs 49%, P < .05) with a similar trend in infants <1500 g; 31% vs 62%, P = .06). When controlling for weight and gestational age, NIMV was more successful in preventing endotracheal ventilation (P < .05). Infants treated with NIMV had a decreased incidence of bronchopulmonary dysplasia (BPD) compared with those treated with NCPAP (2% vs 17%, P < .05, in the total cohort and 5% vs 33%, P < .05, for infants <1500 g).

Conclusions  NIMV compared with NCPAP decreased the requirement for endotracheal ventilation in premature infants with RDS. This was associated with a decreased incidence of BPD. (J Pediatr 2007;150:521-6)

Premature infants with respiratory distress syndrome (RDS) may require respiratory support. Because mechanical ventilation is associated with morbidity, mainly chronic lung disease (bronchopulmonary dysplasia [BPD]), the trend today is to minimize the use of mechanical ventilation. Nasal continuous positive airway pressure (NCPAP) was shown to be effective in treating infants with RDS and enables the avoidance of mechanical ventilation in a relatively large number of infants.1-5 Individualized intubation strategy in delivery room was found to be safe.6 Several centers administer surfactant, immediately extubate the infants and then use NCPAP,7-9 to shorten the course of mechanical ventilation. The best option for treatment of RDS with respect to gestational age and RDS severity needs to be further investigated.9 NCPAP may be used after extubation and thus decrease the incidence of reintubation.10 NCPAP is currently a common practice for the treatment of premature infants with RDS.9

Nasal intermittent mandatory ventilation (NIMV) was shown to be more effective than NCPAP immediately after extubation in the treatment of RDS11-16 and for apnea of prematurity.17,18 The rationale behind the use of NIMV is the administration of “sighs” to the infant, thus opening microatelectasis and recruiting more ventilation units.17 Moretti et al11 found that application of synchronized NIMV was associated with increased tidal volume and minute volume as compared with NCPAP. Synchronized NIMV was associated with reduction in thoracoabdominal asynchrony, and thus stabilized the chest wall, and improved lung mechanics.19 Synchronized NIMV may have advantages over NIMV. The positive pressure ventilator breath is delivered only after initiation of respiratory effort by the infants, when the glottis is likely to be open, or after an apneic interval. Synchronized NIMV also may decrease the work of breathing.17 Although NIMV was more beneficial than NCPAP after extubating infants ventilated for RDS11-16 and for apnea of prematurity,17,18 the 2 methods have not been compared yet.

BPD  Bronchopulmonary dysplasia  PDA  Patent ductus arteriosus
IVH  Intraventricular hemorrhage  PEEP  Positive end expiratory pressure
NCPAP  Nasal continuous positive airway pressure  RDS  Respiratory distress syndrome
NIMV  Nasal intermittent mandatory ventilation  VLBW  Very low birth weight

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for the initial treatment for RDS. Our study was designed to evaluate the hypothesis that NIMV would decrease the requirement for endotracheal ventilation when compared with NCPAP in the initial treatment of premature infants with RDS.

METHODS

Procedure

This was a prospective, open, controlled, single-center, clinical trial comparing the effectiveness of NCPAP and NIMV in the treatment of RDS. RDS was defined in the presence of clinical features and a positive chest x-ray film. The study was approved by the institutional review board in our center. All the parents signed informed consent before participating in the study. Endotracheal intubation was performed in the delivery room if the heart rate did not increase to >100 beats/min, or if the infant had insufficient spontaneous respiratory effort or if he showed marked and increasing dyspnea. Exogenous surfactant (100 mg/kg, 1 to 2 doses as needed, Curosurf; Chiesi Farmaceutici, Parma, Italy) was given only as rescue therapy. Early nasal respiratory support was initiated in any spontaneous breathing premature infant showing signs of respiratory distress (tachypnea, grunting, flaring of nostrils, retraction). If nasal respiratory support was indicated, the mode was randomized between NCPAP and NIMV. Crossover was not allowed between groups. The randomization was performed with a system of randomly prepared cards in sealed nontransparent envelopes containing NCPAP or NIMV group assignments. There were separate envelopes for infants weighing less than or 1500 g or more.

Subjects

Infants that were born in Bnai Zion Medical Center from September 2004 to April 2006 participated in the study. Inclusion criteria included gestational age between 24 to 34 and 6/7 weeks assessed by the obstetrical team from dating of last menstrual period or ultrasound, infants with RDS who needed nasal respiratory support, and informed consent. Infants were excluded if there was significant morbidity apart from RDS including cardiac disease (not including patent ductus arteriosus [PDA]), congenital malformation, or if they had cardiovascular or respiratory instability because of sepsis, anemia or severe intraventricular hemorrhage (IVH), parents refused consent, or the unavailability of a suitable ventilator.

Respiratory Management

Both modes of nasal respiratory support were delivered by the SLE 2000 (Specialized Laboratory Equipment Ltd., South Croydon, United Kingdom) via nasal prongs (INCA; Ackrad Labs, Berlin, Germany). NCPAP was set at 6 to 7 cm H2O, and NIMV was set at a synchronized mode, rate of 12 to 30 breaths/min (according to Pao2), inspiratory time of 0.3 seconds, positive end expiratory pressure (PEEP) of 6 to 7 cm H2O, and positive peak inspiratory pressure of 14 to 22 cm H2O according to chest excursion and the infant’s weight. Fio2 was adjusted to keep oxygen saturation by pulse oximetry between 88% to 92%.

Assessment of the Effectiveness of NIMV and NCPAP

The primary outcome measure was the percent of infants in whom nasal respiratory support failed and who needed endotracheal ventilation. The criteria for failure of nasal support were clinical deterioration (increased respiratory distress) accompanied by at least one of the following or worsening of the following: a pH <7.20 and Pco2 >60 mm Hg, a Pao2 <50 mm Hg, or arterial oxygen saturation by pulse-oximetry (Spo2) <88% on FiO2 >50%, or recurrent significant apnea requiring repeated stimulation or bag-and-mask ventilation in spite of the use of methylxanthines or adequate nasal support (proper ventilatory settings and no technical problems).

Secondary outcome measures were as follow: clinical features during treatment (hourly): blood pressure, heart rate, respiratory rate, pulse oximetry saturation, and respiratory status prior to mechanical ventilation if needed according to arterial blood gas (Pao2, Pco2, pH), and “time to stop nasal support” (only oxygen or low nasal cannula flow, <1 L/min, and allowed when infants on nasal support were on FiO2 <30%, had normal blood gases, and no respiratory distress or apnea. We also assessed neonatal clinical outcomes including incidence of intraventricular hemorrhage (IVH), duration of mechanical ventilation, incidence of BPD (oxygen at 36 weeks after conceptional age to keep saturation >92%), time until full feeds, and length of hospital stay.

Statistics

Sample size calculations for the primary outcome (need for endotracheal ventilation) were based on our rate of mechanical ventilation in previous years (55%-65%) and studies that have shown a decrease in the need for endotracheal ventilation when using NIMV as compared with NCPAP after mechanical ventilation for RDS.12,13 We estimated that there would be a more than 80% chance of detecting a 50% difference between the groups (alpha = 0.05) when sample size (n) is 40 patients for each mode of treatment. Two-sample unpaired t tests (Student’s t) were used for continuous variables with normal distribution and Wilcoxon rank-sum test was used where distribution was skewed. Differences for categorical variables were tested by use of χ2 analysis. For the primary outcome measure (need for endotracheal ventilation) we used a multivariate regression model to correct for birth weight and gestational age (MINITAB, Version 12.23, State College, Pa). For all tests the level of significance was set at P <.05. Data are presented as mean ± standard deviation or median (range).

RESULTS

Of 232 infants born <35 weeks during the study period, 10 infants were excluded (1 infant because of hydrops...
fetalis, 1 infant because of esophageal atresia and tracheoesophageal fistula, 1 infant because of unstable clinical condition caused by sepsis and disseminated intravascular coagulation, 3 infants because of no available respirator with synchronized NIMV, 2 infants because of lack of parental consent, and 2 infants who started on nasal support without prior randomization). Of the eligible infants, 24 infants underwent ventilation within 15 minutes after delivery, and 114 infants did not need respiratory support or received only oxygen treatment. Eighty-four infants were randomized to the study; 41 infants were assigned to NCPAP and 43 infants to NIMV. Two infants in the NCPAP group were switched by the medical team to NIMV in violation of the study protocol but were included in the intention-to-treat analysis according to their primary assignment (Figure 1).

The NCPAP and the NIMV groups had comparable demographic characteristics (Table I). Although there was a significant statistical difference in the 5-minute Apgar score in the infants <1500 g, this difference does not seem to be of clinical significance. The cardiorespiratory status before study entry was comparable between the infants treated with NCPAP and NIMV (Table II). Grunting or retractions occurred in 35/41 infants placed on NCPAP and in 40/43 placed on NIMV (P = .30). There was no significant difference in the number of infants placed on nasal support within the first hour of life between the 2 groups (32/41 and 29/43, P = .46 in total cohort, and 20/21 and 16/19, P = .33, in infants <1500 g, respectively).

Failure of nasal support (need for endotracheal ventilation) was higher after initial treatment with NCPAP compared with NIMV in the total cohort (P < .05), with a similar trend not reaching statistical significance in very low birth weight (VLBW) infants (P = .06) (Table III, Figure 2; available at www.jpeds.com). One of the 2 infants switched from NCPAP to NIMV was ventilated. Even when excluding these 2 infants from analysis for the primary outcome of failure of nasal support, the results were similar, P < .05 for the total cohort and P = .05 for the VLBW infants. The same findings were found when analyzing the need for mechanical ventilation within the first 72 hours from birth, which may represent mainly RDS morbidity. When checking success or failure for the primary outcome (need for endotracheal ventilation) in the total cohort, both birth weight and gestational age were significant (P < .01, and P < .05, respectively). To correct for the effects of birth weight and gestational age, we performed a multivariate regression analysis, and the nasal mode of support (NIMV or NCPAP) remained a significant factor for failure or success (P < .05). We did not find a significant difference between NCPAP and NIMV in the reasons for failure in the total cohort: oxygenation, 10 vs 6 infants; ventilation, 4 vs 3 infants; apnea, 6 vs 3 infants; and in VLBW infants: oxygenation, 5 versus 4 infants; ventilation, 2 versus 2 infants; and apnea, 6 versus 2 infants, respectively. There could be more than 1 reason for an infant to fail.

As expected, mean airway pressure on NIMV was significantly higher than on NCPAP (Table III). On the other hand, the PEEP was statistically lower on NIMV in infants <1500 g (Table III). Peak inspiratory pressure on NIMV was 19.5 ± 2.4, and 18.8 ± 1.8 cm H₂O, and the NIMV rate was 22.2 ± 5.0 and 22.7 ± 5.5 breaths/min, for the total cohort and for VLBW infants, respectively. Time to “stop nasal support” (only oxygen or low nasal flow) in case of success, or time to mechanical ventilation in case of failure were comparable between the 2 treatment groups (Table III).

While treated with nasal support, there was no difference between the 2 treatment groups in the clinical variables (mean blood pressure, heart rate, respiratory rate), oxygen-

### Table I. Demographic data

<table>
<thead>
<tr>
<th>Total cohort</th>
<th>NCPAP (n = 41)</th>
<th>NIMV (n = 43)</th>
<th>P value</th>
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<tr>
<td>Birth weight (g)</td>
<td>1533 ± 603</td>
<td>1616 ± 494</td>
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<tr>
<td>Gestational age (weeks)</td>
<td>30.6 ± 3.0</td>
<td>31.1 ± 2.3</td>
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<td>Male/female</td>
<td>25/16</td>
<td>28/15</td>
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<td>Born by cesarean section (%)</td>
<td>76%</td>
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<td>High-risk pregnancy*</td>
<td>25%</td>
<td>25%</td>
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<td>Apgar score at 1 minute</td>
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<td>8 (4-10)</td>
<td>.22</td>
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<tr>
<td>Apgar score at 5 minutes</td>
<td>9 (2-10)</td>
<td>9 (7-10)</td>
<td>.11</td>
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<td>Prenatal steroids</td>
<td>70%</td>
<td>72%</td>
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<tr>
<td>Methyloxanthine usage</td>
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<td>37%</td>
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<table>
<thead>
<tr>
<th>Infants &lt;1500 g</th>
<th>NCPAP (n = 21)</th>
<th>NIMV (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>1039 ± 238</td>
<td>1155 ± 193</td>
<td>.10</td>
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<tr>
<td>Gestational age (weeks)</td>
<td>28.2 ± 1.9</td>
<td>29.0 ± 1.4</td>
<td>.13</td>
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<tr>
<td>Male/female</td>
<td>10/11</td>
<td>12/7</td>
<td>.36</td>
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<tr>
<td>Born by cesarean section (%)</td>
<td>90%</td>
<td>79%</td>
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<tr>
<td>High-risk pregnancy*</td>
<td>33%</td>
<td>31%</td>
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<td>8 (1-10)</td>
<td>9 (6-10)</td>
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<td>Apgar score at 5 minutes</td>
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<td>Prenatal steroids</td>
<td>81%</td>
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<td>Methyloxanthine usage</td>
<td>57%</td>
<td>68%</td>
<td>.52</td>
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</table>

*High-risk pregnancy was defined as preeclampsia, maternal hypertension, and gestational diabetes.
ation (SpO₂ and PacO₂), and ventilation (PCO₂ and pH) during the 6 hours before mechanical ventilation in case of failure in the total cohort and in infants <1500 g (data not shown). Infants <1500 g in whom NIMV failed required higher initial respiratory support on mechanical ventilation (higher mean airway pressure and FiO₂ [P < .05]; Table III). However, there was no difference in the duration of mechanical ventilation between infants who failed NCPAP or NIMV (Table IV). Furthermore, the duration of mechanical ventilation tended to be shorter in the NIMV group of infants <1500 g (P = .08). The incidence of BPD was lower in infants treated with NIMV in the total cohort and in the group of VLBW infants (P < .05) (Table IV, Fig 2). One of the 2 infants switched from NCPAP to NIMV who was <1500 g had BPD. If these 2 infants are excluded from the analysis, the BPD rate decreased with NIMV in the total cohort (P < .05), and in the VLBW group this decrease did not reach statistical significance (P = .09).

Clinical outcomes during the neonatal period were similar in the 2 treatment groups (Table IV). Two infants had pneumothorax, 1 in the NCPAP group >1500 g and 1 in the NIMV group <1500 g; both occurred on mechanical ventilation. Two twin-infants had NEC in the group of infants treated with NIMV. No infant had gastric perforation on nasal support in either group during the study period. One infant in the NCPAP group <1500 g had periventricular leukomalacia, and the rate of IVH was comparable in the 2 treatment groups (in NCPAP group: 5 grade I-II, 2 grade

| Table II. Cardiorespiratory status before study entry |
|----------------|----------------|----------------|
|                | NCPAP (n = 41) | NIMV (n = 43) |
| FiO₂ (%)       | 0.37 ± 0.17    | 0.32 ± 0.14    |
| SpO₂ (%)       | 88 ± 16        | 91 ± 9         |
| PacO₂ (mm Hg)*| 78 ± 24 (n = 15)| 71 ± 22 (n = 7)|
| PCO₂ (mm Hg)   | 52 ± 7         | 51 ± 7         |
| pH             | 7.24 ± 0.05    | 7.22 ± 0.07    |
| Respiratory rate (breaths/min) | 44 ± 9 | 44 ± 13 |
| Heart rate (beats/min)          | 148 ± 12       | 151 ± 14       |
| Mean BP (mm Hg)              | 37.7 ± 7.1     | 37.1 ± 7.4     |
| Start of nasal support (min)   | 4 (3-3240)     | 17 (3-2940)    |

Infants <1500 g

|                | NCPAP (n = 21) | NIMV (n = 19) |
| FiO₂ (%)       | 0.37 ± 0.16    | 0.33 ± 0.17    |
| SpO₂ (%)       | 89 ± 13        | 90 ± 7         |
| PacO₂ (mm Hg)*| 72 ± 20 (n = 13)| 67 ± 22 (n = 5)|
| PCO₂ (mm Hg)   | 51 ± 7         | 47 ± 5         |
| pH             | 7.25 ± 0.05    | 7.26 ± 0.02    |
| Respiratory rate (breaths/min) | 44 ± 9 | 45 ± 14 |
| Heart rate (beats/min)          | 146 ± 11       | 151 ± 15       |
| Mean BP (mm Hg)              | 36.4 ± 5.9     | 35.3 ± 7.5     |
| Start of nasal support (min)   | 4 (3-140)      | 10 (3-1260)    |

BP, blood pressure.
*When arterial blood gas was available (number of infants).

| Table III. Nasal respiratory support and respiratory short-term outcome |
|----------------|----------------|----------------|
|                | NCPAP (n = 41) | NIMV (n = 43) |
| Initial MAP (cm H₂O) | 6.2 ± 0.8      | 7.6 ± 1.4      |
| Initial PEEP or CPAP (cm H₂O) | 6.2 ± 0.78 | 5.9 ± 0.99 |
| Respiratory rate (breaths/min) | 43 ± 9        | 45 ± 14        |
| Time to stop nasal support (d) | 4.9 ± 5.2     | 4.9 ± 4.3      |
| Failed nasal support (%)         | 49             | 25             |
| Time to MV (h)                   | 32 ± 33        | 44 ± 62        |
| Initial FiO₂ on MV               | 0.49 ± 0.26    | 0.55 ± 0.27    |
| Initial MAP on MV                | 7.8 ± 1.2      | 8.1 ± 1.7      |

MAP, mean airway pressure; MV, mechanical ventilation.

| Table IV. Clinical outcome |
|----------------|----------------|----------------|
|                | NCPAP (n = 41) | NIMV (n = 43) |
| Duration of MV (d) | 13.2 ± 15.8    | 10.2 ± 23.8    |
| BPD             | 17%            | 2%             |
| IVH             | 8              | 8              |
| Time to full feeds (d) | 11 ± 8     | 9 ± 4          |
| Length of stay (d)            | 53 ± 39       | 39 ± 26       |

Infants <1500 g

|                | NCPAP (n = 21) | NIMV (n = 19) |
| Duration of MV (d) | 18.3 ± 17.7    | 16.8 ± 13.0   |
| BPD             | 33%            | 5%             |
| IVH             | 7              | 6              |
| Time to full feeds (d) | 15 ± 10    | 11 ± 3        |
| Length of stay (d)            | 81 ± 36       | 63 ± 23       |

MV, mechanical ventilation; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage.
DISCUSSION

We found that NIMV was more successful than NCPAP as the initial treatment of RDS in premature infants (<1500 g) by reducing the rate of endotracheal ventilation. This was associated with a reduced incidence of BPD.

To our knowledge, there are no previous published studies that assessed whether NIMV or NCPAP is preferred in the initial treatment of RDS. However, a few studies have found that NIMV was superior to NCPAP post extubation, after mechanical ventilation and surfactant treatment, for RDS and for apnea of prematurity. The same advantages of NIMV in these situations may be the cause for its beneficial effect in the initial treatment of RDS found in our study.

Failure of nasal respiratory support was significantly associated with lower birth-weight. Other studies also correlated failure of nasal support with birth-weight or gestational age. The rate of failure of nasal support varied in previous studies, and our study failure rate is in accordance with the literature. The use of and the experience of medical teams with nasal support is increasing in recent years. Our study represents our single center experience.

We found that the level of support was comparable in the 2 modes of treatment (expressed by similar cardiorespiratory variables, as well as blood gases while being supported by NCPAP and NIMV). Previous studies also found similar PCO2 levels when the 2 methods were used for apnea of prematurity. In contrast to our study, Moretti et al found a lower TcP CO2 and respiratory rate on synchronized NIMV compared with NCPAP. As could be expected, mean airway pressure on NIMV was significantly higher than on NCPAP. On the other hand, PEEP that was set at around 6 cm H2O initially was statistically significantly lower on NIMV in the VLBW group. This difference seems to be of no clinical significance. The difference could result from a compensatory reaction of the medical team to the needs of the infants in achieving similar targeted respiratory variables according to the clinical routines, probably because of the lower mean airway pressure on NCPAP. Furthermore, the reasons for failure of nasal support were also comparable.

While others “allowed” a trial of nasal support instead of immediate intubation in small premature infants, our study demonstrates comparable safety of both methods of nasal support. It is not clear on the basis of the clinical variables and blood gases and the physiologic rationale why VLBW infants treated with NIMV required initially higher ventilatory settings (MAP, FiO2), but it was reassuring that there was no significant difference in the length of mechanical ventilation. Furthermore, the incidence of BPD was lower in infants treated initially with NIMV. This may result from the lower rate of mechanical ventilation and its associated volutrauma/barotrauma in this group. A trend toward lower rate of BPD in NIMV compared with NCPAP was reported in studies comparing the modes in the postextubation period.

Rates of IVH, or the length of hospital stay in the NCPAP and NIMV groups were comparable. There was a concern that NIMV might cause more gastrointestinal complications because of gastric distention leading to cessation of feeds or perforation. In our study there were no gastrointestinal complications, and time to full feeds was similar in the 2 methods, in accordance with other studies. Two twin-infants had NEC in the NIMV group, but the incidence of NEC was not statistically different compared with the NCPAP group.

We have used the synchronized intermittent mandatory ventilation mode for NIMV with maximal sensitivity with the ventilator (SLE 2000), and most of the time we did not get an alarm of not sensing infant’s breath. However, we can not verify that the infants got pressure-synchronized ventilation all the time because the system was open and we used the pressure sensor of the ventilator. Thus we used the term NIMV to describe our mode of nasal support. Pressure-triggering ventilation is less effective compared with airflow-triggering in ventilated premature infants. For synchronization of nasal support others have used an abdominal capsule. Nasal intermittent positive pressure ventilation and NIMV are used interchangeably in the literature, and we took the common definition from Davis et al that these are methods of augmenting NCPAP by delivering ventilator breaths via nasal prongs. We did not use the NIMV mode as an assist control, where the triggering might be of greater importance. Effectiveness of pressure-triggered ventilation and synchronization of intermittent mandatory ventilation were not evaluated previously in nasal support. Yet, whether synchronized or not, NIMV seems to be more effective than NCPAP. Future studies will need to compare the effectiveness of modes of synchronization via nasal support, and whether synchronization has an advantage over nonsynchronized ventilation delivered by nasal support in premature infants with RDS.

Our study limitations are that the mode of support assignment could not be blinded to the medical team. This could possibly explain the higher initial ventilator settings after NIMV in cases of nasal support failure in VLBW infants if we were unconsciously using a lower threshold to fail a patient in the control group. We used objective failure criteria and management protocols to reduce the possibility of such a bias. This was a clinical study that allowed the medical team to make clinical adjustments to assure that no infant would be compromised by the treatment mode. It is possible that the use of a strict PEEP of 6 cm H2O in both groups would have even strengthened the benefits of NIMV found in our study. We had only a small number of infants <1500 g, and these infants should be the target population for further studies. Our results in the VLBW infants regarding the incidence of...
endotracheal ventilation and BPD in the NIMV group should be taken with caution, because our study does not have statistical power for these outcome measures in this group of infants. Furthermore, the number of infants <1000 g in our cohort was small. The safety conclusions from our study should also be taken with caution, because our study did not have sufficient statistical power to detect differences in relatively infrequent complications such as NEC and IVH.

We conclude that NIMV was more successful than NCPAP in preventing endotracheal ventilation in the initial treatment of premature infants with RDS. This was associated with decreased incidence of BPD in infants treated with NIMV. Our study provides the basis for further, larger trials of this intervention before it can be concluded that NIMV is safe and is the preferred mode of nasal support in premature infants with RDS.

REFERENCES


Figure 2. Mechanical ventilation and bronchopulmonary dysplasia (BPD) in infants treated with NIMV and NCPAP.
Low Cortical Bone Density Measured by Computed Tomography in Children and Adolescents with Untreated Hyperthyroidism

NAWAPORN NUMBENJAPON, MD, GERTRUDE COSTIN, MD, VICENTE GILSANZ, MD, PHD, AND PISIT PITUKCHEEWAONONT, MD

Objective To determine whether increased thyroid hormones levels have an effect on various bone components (cortical vs cancellous bone).

Study design The anthropometric and 3-dimensional quantitative computed tomography (CT) bone measurements, including bone density (BD), cross-sectional area (CSA) of the lumbar spine and femur, and cortical bone area (CBA) of the femur, of 18 children and adolescents with untreated hyperthyroidism were reviewed and compared with those of age-, sex-, and ethnicity-matched historical controls.

Results No significant differences in height, weight, body mass index (BMI), or pubertal staging between patients and controls were found. Cortical BD was significantly lower \((P < .001)\) in children and adolescents with hyperthyroidism compared with historical controls. After adjusting for weight and height, no difference in femur CSA between hyperthyroid children and historical controls was evident. No significant correlations among thyroid hormone levels, antithyroid antibody levels, and cortical BD values were found.

Conclusions As determined by CT, cortical bone is the preferential site of bone loss in children and adolescents with untreated hyperthyroidism. \((J\ Pediatr\ 2007;150:527-30)\)

Thyroid hormones exert effects directly on nuclear receptors of osteoblasts to stimulate osteoclastic activity.\(^1,2\) Excessive thyroxine (T\(_4\)) and tri-iodothyronine (T\(_3\)) and subsequent increased osteoblastic activity leads to increased bone turnover and net bone resorption. In untreated adult patients with hyperthyroidism, bone resorption exceeds bone formation, leading to a negative bone balance, decreased bone mineral density (BMD),\(^3-5\) and secondary osteoporosis.\(^6\) Several studies indicate that adult patients with untreated hyperthyroidism are at increased risk for fractures,\(^3,7,8\) which occur at earlier ages.\(^9\) In addition, studies in both adults\(^5,9-12\) and children\(^13,14\) with untreated hyperthyroidism demonstrated significantly decreased spinal (cancellous) and femoral neck (cortical) BMD compared with age- and sex-matched controls. Although some studies in patients with untreated hyperthyroidism found an equal reduction in BMD in both locations,\(^7,10-13\) others reported a preferential loss at the femoral neck on the diagnosis of hyperthyroidism.\(^5,14\) These findings have raised the question of whether there is a preferential bone site affected by elevated serum concentrations of thyroid hormones.

Although the reasons for the discrepant results are unclear, one factor may be the limitations of dual-energy X-ray absorptiometry (DXA) measurements used in previous studies to evaluate BMD. Because DXA is a projection technique, it cannot distinguish between cortical and cancellous bone measurements. Moreover, DXA is not an ideal method for measuring BMD in children, because it cannot account for the changes in body and skeletal size that occur during growth.\(^15-19\) Quantitative computed tomography (CT) bone density (BD) determination is not affected by body/skeletal size.\(^19-21\) Given that CT assesses both the volume and density of axial and appendicular bone, it has a major advantage over other modalities for bone measurements in children. Although the quantitative CT radiation exposure may seem quite large compared with that of DXA

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**Table**: 

<table>
<thead>
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<tbody>
<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CBA</td>
<td>Cortical bone area</td>
</tr>
<tr>
<td>CSA</td>
<td>Cross-sectional area</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual-energy X-ray absorptiometry</td>
</tr>
<tr>
<td>FT(_4)</td>
<td>Free thyroxine</td>
</tr>
</tbody>
</table>

**Abbreviations**: 

- IGF-1 = Insulin-like growth factor 1
- IGF-BPs = Insulin-like growth factor binding proteins
- T\(_3\) = Triiodothyronine
- T\(_4\) = Thyroxine
- TSH = Thyroid-stimulating hormone
- TR Ab = TSH receptor antibody
- TG Ab = Antithyroglobulin antibody
- TPO Ab = Antithyroid peroxidase antibody

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Healthy individuals who had CT measurements performed in a previous study served as historical controls.18,20 The control subjects neither had any documented medical conditions nor took any medication known to affect bone metabolism. Their heights and weights were between the 3rd and 97th percentiles as determined from the established Centers for Disease Control (CDC) normative curves using Epi Info version 3.2.2. These values were matched with those of hyperthyroid patients based on age, sex, and ethnicity.

This retrospective review study was approved by the Childrens Hospital Los Angeles Institutional Review Board.

RESULTS

We reviewed medical records of 40 children and adolescents who had been diagnosed with TSH-independent hyperthyroidism and suppressed TSH values in our clinic between 2003 and 2005. CT bone measurements had been requested in 38 of these patients (with 2 patients excluded because they had Down syndrome in addition to hyperthyroidism), but CT bone measurements were actually performed in only 18 patients. Of the remaining 20 patients, 17 did not have authorization from insurance to undergo the test, and 3 did not undergo the test because their parents refused.

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Of the 18 patients who had bone measurements (14 females and 4 males; mean age, 13.3 ± 3.0 years; age range, 7.0 to 18.3 years), 12 were Hispanic, 4 were Caucasian, and 2 were of Asian descent. The anthropometric variables in the children and adolescents with untreated hyperthyroidism and controls are given in Table I. There were no differences in height, weight, BMI, and pubertal status between the 2 groups. Fourteen of the 18 patients with untreated hyperthyroidism had CT bone measurements performed before starting antithyroid therapy in our clinic between 2003 and 2005. CT bone measurements had been obtained before starting antithyroid therapy. The subjects were of various ethnicities and ranged in age from 5 to 19 years. The diagnosis of thyroid-stimulating hormone (TSH)-independent hyperthyroidism was based on patient symptoms, clinical findings, elevated serum thyroid hormone levels (T₄, or free thyroxine [FT₄], and/or T₃, or free T₃) and suppressed TSH level (<0.1 mU/L). In addition, a patient might have a combination of elevated serum titers of TSH receptor antibody (TR Ab), antithyroglobulin antibody (TG Ab), and/or antithyroid peroxidase antibody (TPO Ab). All participants were able to ambulate independently and were not taking any medications known to affect bone accretion. Patients with a history of previous thyroid disease, chronic illness, bone disease, or fracture were excluded.

Results are expressed as mean ± standard deviation. Two-tailed analysis with an α error of 0.05 was performed for all statistical tests. Bone area and BD values of hyperthyroid subjects were compared with those of matched controls using the paired t test. Linear regression analyses were performed to determine the correlations between anthropometric data, thyroid hormone levels, thyroid antibody levels, and bone measurements in hyperthyroid subjects.

METHODS

We reviewed medical records of children and adolescents with hyperthyroidism treated in our clinic between 2003 and 2005 who had CT bone measurements performed before starting antithyroid therapy. The subjects were of various ethnicities and ranged in age from 5 to 19 years. The diagnosis of thyroid-stimulating hormone (TSH)-independent hyperthyroidism was based on patient symptoms, clinical findings, elevated serum thyroid hormone levels (T₄, or free thyroxine [FT₄], and/or T₃, or free T₃) and suppressed TSH level (<0.1 mU/L). In addition, a patient might have a combination of elevated serum titers of TSH receptor antibody (TR Ab), antithyroglobulin antibody (TG Ab), and/or antithyroid peroxidase antibody (TPO Ab). All participants were able to ambulate independently and were not taking any medications known to affect bone accretion. Patients with a history of previous thyroid disease, chronic illness, bone disease, or fracture were excluded.

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Low Cortical Bone Density Measured by Computed Tomography in Children and Adolescents with Untreated Hyperthyroidism

Table II. Bone mineral measurements of patients with hyperthyroidism and healthy subjects*

<table>
<thead>
<tr>
<th>Bone measurements</th>
<th>Hyperthyroidism (n = 18)</th>
<th>Controls (n = 18)</th>
<th>Unadjusted P value</th>
<th>P value adjusted for height and weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral BD (mg/cm³)</td>
<td>1797.4 ± 213.7</td>
<td>2068.3 ± 141.8</td>
<td>.001</td>
<td>.003</td>
</tr>
<tr>
<td>Femoral CSA (cm²)</td>
<td>5.0 ± 1.1</td>
<td>4.6 ± 1.0</td>
<td>.029</td>
<td>.101</td>
</tr>
<tr>
<td>Femoral CBA (cm²)</td>
<td>3.9 ± 1.0</td>
<td>3.6 ± 0.9</td>
<td>.058</td>
<td>.156</td>
</tr>
<tr>
<td>Vertebral BD (mg/cm³)</td>
<td>255.8 ± 51.2</td>
<td>280.4 ± 48.7</td>
<td>.116</td>
<td>.124</td>
</tr>
<tr>
<td>Vertebral CBA (cm²)</td>
<td>8.4 ± 1.6</td>
<td>7.9 ± 1.4</td>
<td>.082</td>
<td>.182</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± standard deviation; P < .05 is considered significant.

DISCUSSION

Our study indicates that cortical, but not cancellous, BD, measured by CT, is significantly lower in children and adolescents with untreated hyperthyroidism than in age-, sex-, and ethnicity-matched healthy controls. The differences between our results and previously reported findings10-14 may be due to the limitations of DXA used in those earlier studies. Although the radiation exposure from CT is greater than that from DXA, the total body equivalent dose of radiation from CT is approximately 40 to 90 μSv; in comparison, a round-trip transcontinental flight in North America exposes a child to roughly 60 to 80 μSv of ionizing radiation.19,26 Therefore, bone measurement using CT does not expose children to amounts of ionizing radiation that deviate from the amount that constitutes part of their normal life experiences.

Several studies have demonstrated the significant impact of weight bearing (weight and BMI) on cortical bone mass and density.27,28 However, our results indicate that cortical BD in hyperthyroid patients with greater but not statistically different weight and BMI was significantly lower than in controls. This finding suggests a significant impact of thyroid hormone on cortical BD in hyperthyroid patients.

Although all of our patients had a history of weight loss at the time of diagnosis, the mean weights and BMIs were greater, but not statistically different, from those of healthy historical controls. Two of 18 patients had a BMI >30 kg/m² at the time of diagnosis, indicating that obesity should not exclude the possibility of hyperthyroidism.

The lack of significant inverse correlations between serum thyroid hormones levels and cortical BD noted in our study is similar to findings in previous studies in adults10,11 and children.14 In contrast, others reported a significant inverse correlation between serum FT4 level and spinal (r = -.42) and whole-body BD (r = -.41) at the diagnosis of hyperthyroidism.13

Several studies in animals and humans support the findings of low cortical BD in hyperthyroid patients. Although the same thyroid receptor isoform genes are expressed at cortical sites and cancellous sites,29 a significantly decreased femoral (but not vertebral) bone mass was reported in rats receiving TSH-suppressive doses of L-thyroxine.30-33 In human studies, histomorphometric analyses of iliac crest biopsy specimens in 40 untreated hyperthyroid patients demonstrated a pronounced increase in cortical osteoclastic activity, followed by a significant increase in cortical porosity.34 These findings suggest that increased cortical osteoclastic resorption is mainly responsible for bone mineral mobilization in hyperthyroidism. Furthermore, a nationwide follow-up study in Denmark of 11,776 adults with hyperthyroidism demonstrated that the incidence rate ratio of femur fractures was significantly increased compared with controls, although no difference in the incidence rate ratio of spine fractures between the 2 groups was found.3 Another prospective study demonstrated an increased risk of hip fracture in Caucasian women age 65 years or older with a history of hyperthyroidism (relative risk 1.8).8

Why thyroid hormones seem to be more detrimental to cortical bone than to cancellous bone is unclear. Potential explanations for the heterogeneous skeletal response to exces-
sive thyroid hormones include modulation of thyroid hormone action by (1) qualitative or quantitative differences in thyroid hormone receptors, (2) differential expression of vitamin D3 and retinoid receptors that form heteromeric complexes with thyroid hormone receptors in regulating thyroid hormone action in osteoblasts, (3) differences in the thyroid receptor heterodimerization pattern in femoral versus vertebral osteoblasts, and (4) postreceptor modifications in thyroid hormone action. Other regulatory factors responsible for this skeletal site-specific heterogeneity have been documented. Other studies have demonstrated that vertebral-derived marrow stromal cells had significantly greater insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding proteins (IGFBPs) gene expression than similar femoral cultures that had the same levels of IGF-1 receptors expressed in the 2 skeletal sites. The addition of T3 to the culture medium up-regulated the levels of IGFBP mRNA and caused a dose-dependent increase in IGF-1 mRNA and protein only in vertebral marrow cultures. Therefore, it is possible that the higher expression of IGF-1 in the vertebrae may account for the greater activity of osteoblasts, leading to less bone loss at the spine compared with the femur in patients with hyperthyroidism.

The results of our study indicate that cortical bone, measured by CT, is the preferential site of bone loss in children and adolescents with untreated hyperthyroidism and suggest that this loss may be due to hyperthyroxinemia. Whether correction of the hyperthyroid state will normalize cortical BD requires further investigation.

We thank Frederick Dorey, PhD for his support in the statistical analysis and Norma Castaneda for her assistance with data collection.

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Mitochondrial DNA Depletion is a Prevalent Cause of Multiple Respiratory Chain Deficiency in Childhood

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Objective  To determine the actual incidence of mitochondrial DNA (mtDNA) depletion syndrome in multiple respiratory chain deficiency.

Study design  We carried out a real-time polymerase chain reaction quantification of mtDNA in liver or muscle tissue of 100 children with unexplained multiple oxidative phosphorylation enzyme deficiency.

Results  A reduction of mtDNA copy number to <35% of control values was found in liver and/or muscle in half of the children (50/100). Most of these patients (32/50; 64%) presented with severe neonatal onset liver involvement; 7 (14%) had Alpers syndrome, and 11 (22%) exhibited various forms of neurologic involvement. Deoxyguanosine kinase or polymerase γ (POLG) mutations could be identified in 11 of 32 patients with liver involvement, and POLG mutations were consistently found in all 7 patients with Alpers syndrome. Homozygous thymidine kinase 2 and MPV17 gene mutations were found in 2 patients.

Conclusions  Our findings show that mtDNA depletion is a prevalent cause of multiple respiratory chain deficiency in infancy. (J Pediatr 2007;105:531-4)

Multiple respiratory enzyme chain enzyme deficiency is frequently observed in oxidative phosphorylation (OXPHOS) disorders and can theoretically result from various mechanisms, including (a) mitochondrial DNA (mtDNA) deletions, (b) tRNA point mutations, (c) defective mitochondrial RNA translation, (d) mtDNA depletion, (e) defects in assembly or regulation of respiratory enzyme chain subunits, and (f) abnormal import of mitochondrial proteins. The group of mtDNA depletion (MIM 251880) is a clinically and genetically heterogeneous group of autosomal recessive diseases characterized by reduced mtDNA copy number.1 Several nuclear genes have been shown to account for these severe OXPHOS disorders. Mutations in the deoxyguanosine kinase (DGUOK)2 and thymidine kinase (TK2)3 genes have been reported in the hepatocerebral and myopathic forms of mtDNA depletion, respectively, and mtDNA polymerase γ (POLG) mutations have been reported in Alpers syndrome.4 More recently, the succinyl CoA-ligase (SUCLA2)5 and MPV176 genes have been shown to account for mtDNA depletion in few pedigrees.

The aim of the present study was to evaluate the incidence of mtDNA depletion in a series of 100 children with multiple respiratory enzyme chain deficiency and to review the associated clinical features.

METHODS

Patients  Over the past 15 years, we have identified 270 patients with multiple respiratory chain deficiency. Large-scale mtDNA deletions (64/270; 24%) and MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) mutations were the most common cause of multiple respiratory enzyme chain deficiency (34/270; 12%). Liver and/or muscle DNA was available for 100 cases of unexplained multiple respiratory enzyme chain deficiency. Criteria for inclusion in the present study were multiple respiratory chain deficiency and decreased mtDNA copy number, below 35% of normal mtDNA content (or DGUOK/TK2/POLG mutation).
Respiratory Chain Analysis

Polarographic tests and/or spectrophotometric assays of respiratory chain enzymes were carried out on skeletal muscle mitochondria, muscle, and liver homogenates as described previously.7

Mitochondrial DNA Quantification

Mitochondrial DNA quantification was adapted from the method of Petit et al.8 Total DNA was extracted from liver or muscle by standard phenol/chloroform extraction and ethanol precipitation. The mitochondrial 12S rRNA and the nuclear MutL protein homolog 1 (MLH1) genes were individually amplified by real-time polymerase chain reaction (PCR) using primers 12S rRNA- F/12S rRNA-R and MLH1-F/MLH1-R, respectively (Table I; available at www.jpeds.com). For mtDNA and nuclear DNA quantification, mtDNA-A/mtDNA-B and MLH1-A hybridization probes were used. The PCR reaction mixture (10 μL) contained 200 ng of DNA, 1 × LightCycler-FastStart DNA Master hybridization probe enzyme (Roche Diagnostics, Basel, Switzerland), 300 nmol of each primer, and 200 nmol of each probe. The PCR amplification consisted of a single denaturation–enzyme activation step for 8 minutes at 95°C, followed by 50 amplification cycles of 10 seconds at 95°C, 10 seconds at 60°C, and 6 seconds at 72°C. A single fluorescence acquisition was done at the end of each annealing step, and data were analyzed using LightCycler software version 3.5.3 (Roche Diagnostics). The ratio of mtDNA copy number to nuclear DNA was used as a measure of mtDNA content in each specimen.

Mutation Screening

For haplotyping, microsatellite DNA markers of the Genethon map flanking the putative disease loci were tested in the parents and in affected and unaffected siblings. The most informative flanking microsatellites were used for chromosome 2 (D2S286-DGUOK-D2S145; D2S2247-MPV17-D2S165), chromosome 15 (D15S979-D15S1045-POLG-D15S202), and chromosome 16 (D16S503-D16S3019-TK2-D16S3107-D16S496). The exons of the DGUOK, POLG, and TK2 genes were amplified using specific primers (available on request) after initial denaturation at 96°C for 5 minutes, followed by 30 cycles of 96°C for 30 seconds, 55°C for 30 seconds, and 72°C for 30 seconds and a final extension at 72°C for 10 minutes. The coding sequences of the POLG gene were analyzed by denaturing high-performance liquid chromatography.9 Amplification products were purified by ExoSapIT (Amersham Biosciences, Piscataway, NJ) and directly sequenced using the PRISM Ready Reaction sequencing kit (PerkinElmer, Waltham, MA) on an automatic sequencer (ABI 3130xl; Applied Biosystems, Foster City, CA).

RESULTS

Incidence of mtDNA Depletion

A mtDNA depletion was identified in 50 of the 100 patients (Table II; available at www.jpeds.com) The sex ratio in this series was 1.08 (26 males and 24 females). Some patients were born to consanguineous healthy parents and others had affected siblings, suggesting an autosomal recessive mode of inheritance. Three forms could be recognized on the basis of clinical course and severity. More than half of the patients (32/50; 64%) presented with a severe neonatal-onset liver involvement (liver insufficiency or hepatocellular dysfunction, patient (P) 1 to P32). A second group of 7 patients (P33 to P40) presented with Alpers syndrome. Finally, 11 patients (22%; P41 to P50) exhibited various forms of neurologic involvement, either isolated or associated with other clinical signs. One patient (P10) presented with liver insufficiency and dysmorphic features suggestive of the CHARGE association that were subsequently ascribed to an unrelated CHD7 mutation.

The mtDNA depletions were more frequent in the liver (32/50) than in muscle (18/50). Only 4 patients carried the depletion in both tissues (P10, P11, P32, and P47). The residual mtDNA content in the depleted tissue was generally lower in liver (mean ± standard deviation, 12% ± 10%) than in muscle (mean, 24% ± 14%). All patients with severe hepatic involvement presented with multiple OXPHOS deficiency in the liver, whereas OXPHOS activity in the muscle was most often normal. Liver was the only informative tissue in Alpers syndrome; muscle was consistently normal in these patients. Conversely, apart from Alpers syndrome, most of the patients with neurologic involvement as the main symptom (P40 to P46 and P48 to P50) exhibited a respiratory enzyme chain deficiency in muscle. Cultured skin fibroblasts were normal in almost all cases (data not shown).

The mtDNA depletion resulted in various types of enzyme deficiency. Most patients presented reduced absolute activity values of mtDNA-encoded complexes (namely, complexes I, III, IV and/or V) in various combinations and abnormal activity ratios (Tables III and IV; available at www.jpeds.com). Complex II activity was consistently normal in these patients. Normal absolute activities were observed in 2 patients (P29 and P50), but complex IV/I and complex IV/V activity ratios pointed to a combined OXPHOS deficiency. In addition, single enzyme deficiency (complex I, II, or IV) was found in 2 patients whose activity ratios indicated a combined deficiency (liver of P24 and P48). Surprisingly, several patients exhibited a severe deficiency of complex II, citrate synthase, and/or fumarase with low activity of other respiratory enzyme chain complexes (liver of P19, P21, P28). Finally, a generalized reduction of all respiratory enzyme chain activities, including complex II, citrate synthase, and/or fumarase, was detected in 9 patients (liver of P7, P10, P12, P16, and P26 and muscle of P31, P41, P42, P46, and P48). To rule out a nonspecific effect of liver dysfunction on OXPHOS, we studied OXPHOS activities in the liver of 5
infants with hepatic failure from other causes and found no enzyme deficiency (data not shown).

**Mutation Analyses**

Direct sequencing of exons and exon–intron boundaries of the *DGUOK* gene identified mutations in 9 of the 50 patients (18%) (Table II). Various types of mutations were found, including missense (6/9), non-sense (1/9), splice mutations (2/9), 2-bp deletion (1/9), and 4-bp insertion (1/9) (Table II). Several mutations have been already reported, but 2 of them are novel: the *DGUOK* mutation presented with neonatal-onset liver involvement.

**POLG mutations** were identified in 9 of the 50 patients (19%; Table II). Two patients presented with neonatal onset liver involvement, and 5 presented with typical Alpers syndrome. Compound heterozygosity was found in all 9 children carrying **POLG** mutations; genotyping of the parents showed primary or secondary to an as-yet unknown event also causing OXPHOS deficiency;11 however, the residual mtDNA levels that among those patients, mtDNA depletion was a frequent cause of hepatocellular insufficiency or hepatic failure, detected in 32 of the 36 children with multiple respiratory enzyme chain deficiency with severe liver involvement that we tested (89%), a much higher prevalence than reported previously.10 Previously reported *DGUOK*, *POLG*, and *MPV17* mutations were found in 12 of these 32 children with severe liver involvement. They all presented with hypoglycemia, jaundice, hepatocellular insufficiency, and liver failure, but no specific genotype–phenotype correlation could be established. Because no mutations in the *DGUOK*, *POLG*, and *MPV17* genes were found in 20 of the 32 patients, we suggest that other genes causing mtDNA depletion remain to be identified.

Here we report on the high incidence of mtDNA depletion (18%) in children with multiple respiratory enzyme chain deficiency. In our series of 270 patients with multiple respiratory enzyme chain deficiency, 24% exhibited large-scale mtDNA rearrangements (64/270 patients) and 12% exhibited a MELAS mutation (34/270 patients). Therefore, mtDNA depletion represents the second most common cause of multiple respiratory enzyme chain deficiency in our series. This incidence is certainly an underestimate, however, because liver or muscle was available for only 1/3 of the patients with multiple respiratory enzyme chain deficiency. Based on our finding of mtDNA depletion in 50% of the patients tested, it is likely that mtDNA depletion is in fact the most common cause of multiple respiratory enzyme chain deficiency in childhood.

In our experience, half of the patients with liver insufficiency suspected of mitochondrial disorder were indeed diagnosed as having respiratory enzyme chain deficiency (52 patients), and 18% of multiple respiratory enzyme chain deficiencies are associated with liver insufficiency. It is noteworthy that several children were found to have hypoglycemia, jaundice, hepatocellular insufficiency, and liver failure, but no specific genotype–phenotype correlation could be established.

**DISCUSSION**

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We have previously identified a neonatal form (before 3 days of age) and a delayed-onset form of liver failure in OXPHOS deficiency;11 however, the residual mtDNA levels were similar regardless of the age at onset, and either *DGUOK* or *POLG* mutations were found in the 2 groups, precluding any genotype–phenotype correlations in our series. It is also noteworthy that several children were found to have an associated complex II deficiency. Whether mtDNA depletion is primary or secondary to an as-yet unknown event also causing complex II deficiency remains questionable. Identification of POLG mutations in some of these patients (ie, P10 and P35) suggests that primary mtDNA depletion may secondarily trigger complex II deficiency. Along these lines, reduced complex II activity has been reported in patients with mtDNA deletion, again suggesting a secondary event.12

We have identified 2 novel missense POLG mutations (C224Y and L428P) modifying amino acid residues that are...
conserved across species and located in the vicinity of previously described mutations. The substituting tyrosine and proline are expected to induce hydrophobic interactions and to modify protein folding. In 2 patients (P36 and P39), only 1 heterozygous POLG pathogenic mutation could be identified. Most likely, the second mutation was overlooked and lies in noncoding sequences. Finally, we found a G517V mutation in a patient with psychomotor retardation who died from Leigh syndrome (P43). This mutation has been previously reported to cause dominant ataxia and neuropathy in adults.\(^{15}\) Heterozygosity for this mutation in our patient and her healthy father suggests that it could be a polymorphism. Taken together, our results support the view that DGUOK and POLG genes should be considered in hepatocerebral forms of mtDNA depletion.\(^{13-16}\) Thus, the clinical presentation of DGUOK mutations seems to be restricted to infantile liver failure, whereas POLG mutations are associated with a wide spectrum of clinical presentations, including dominant and recessive progressive external ophthalmoplegia,\(^{17}\) ataxia,\(^{18}\) sensory ataxic neuropathy, dystarthish, and ophthalmoparesis syndrome,\(^{19}\) Parkinsonism,\(^{20}\) and male infertility.\(^{21}\)

We also detected mtDNA depletion in patients with encephalopathy, leukodystrophy, or Leigh syndrome. Encephalopathy and Leigh syndrome have seldom been reported in association with mtDNA depletion.\(^{22,23}\) Moreover, several patients also developed uncommon clinical symptoms, including cardiomyopathy, tubulopathy, and villous atrophy. Therefore, although mtDNA depletion is the major cause of liver insufficiency in our series, we suggest that mtDNA depletion should be considered in all patients with combined respiratory enzyme chain deficiency, regardless of the presenting symptom.

Up to now, only 5 nuclear genes involved in mtDNA maintenance have been reported to cause mtDNA depletion.\(^{2-6}\) The large number of genes encoding proteins known to interact with mtDNA and the clinical heterogeneity of those conditions will make elucidation of the molecular bases of mtDNA deletions particularly tedious. Nonetheless, the study of consanguineous/multiplex families should help identify other disease genes in the near future.

REFERENCES

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Table IV. Respiratory chain activities in muscle homogenate and muscle mitochondria
**Truncal Distribution of Fat Mass, Metabolic Profile and Hypothalamic-Pituitary Adrenal Axis Activity in Prepubertal Obese Children**

**Pascal Barat, MD, PhD, Michelle Gayard-Cros, MD, Ruth Andrew, PhD, Jean-Benoît Corcuff, MD, PhD, Béatrice Jouret, MD, Nicole Barthe, MD, Paul Perez, MD, PhD, Christine Germain, MSC, Mathé Tauber, MD, PhD, Brian R. Walker, MD, Pierre Morhède, PhD, and Martine Duclos, MD, PhD**

**Objective**  To investigate whether truncal distribution of fat mass (TDFM) is associated with variations of the hypothalamic-pituitary-adrenocortical (HPA) axis activity in prepubertal obese children.

**Study design**  TDFM, assessed with dual energy X-ray absorptiometry and a comprehensive set of measures of HPA axis activity and reactivity have been studied in 45 prepubertal obese children aged 6 to 11 years (girls) and 6 to 13 years (boys).

**Results**  After adjustment for whole body fat mass (%) (WBFM), TDFM correlated positively with insulin ($r = 0.50, 95\% CI [0.23; 0.70]$) and homeostasis model assessment of insulin resistance ($r = 0.52, 95\% CI [0.25; 0.71]$). When adjusted for WBFM, TDFM correlated positively with morning plasma cortisol ($r = 0.38, 95\% CI [0.15; 0.64]$) in the total population. TDFM correlated negatively with the rise of salivary cortisol after a standard meal ($r = -0.43, 95\% CI [-0.71; -0.02]$), obviously in girls. When adjusted for WBFM and TDFM, morning plasma cortisol correlated positively with total cholesterol ($r = 0.41, 95\% CI [0.11; 0.65]$) and triglyceride ($r = 0.44, 95\% CI [0.14; 0.67]$). The rise of salivary cortisol after a standard meal was negatively ($r = -0.56, 95\% CI [-0.85; -0.01]$) and positively ($r = 0.74, 95\% CI [0.16; 0.94]$) correlated with homeostasis model assessment of insulin resistance in boys and girls, respectively.

**Conclusions**  Association exists in prepubertal obese children between TDFM and markers of HPA axis activity. These data suggest that HPA axis could be involved early in life in obesity associated with pejorative metabolic profile. (J Pediatr 2007;150:535-9)

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Excess of trunk fat in obesity is most closely associated with the metabolic syndrome. This led many authors to look for factors involved in the accumulation of visceral adipose tissue. Because of the prevalence of abdominal obesity in Cushing's syndrome, the hypothalamic-pituitary-adrenal (HPA) axis has been extensively studied in adult obesity. On the one hand, abdominal obesity has been linked with stress-related cortisol secretion and hyperactivity of the HPA axis. On the other hand, changes in peripheral glucocorticoid metabolism have been shown in human obesity, perhaps stimulating excess production. Nevertheless, whether cortisol changes are primary causes or secondary effects in abdominal obesity is still debated.

Studying abdominal obesity early in life could contribute to our understanding. Even in prepubertal children, visceral fat accumulation is related to metabolic risk factors, independently of obesity, which are in turn implicated in cardiovascular morbidity and death later in life. However, little is known about the factors involved in fat mass distribution in prepubertal children, and, particularly, the HPA axis has been inadequately studied in this population. The objective of this study was to investigate whether truncal distribution of fat mass (TDFM), assessed with dual-energy X-ray absorptiometry (DEXA), is associated with metabolic profile and HPA axis activity and reactivity in prepubertal obese children, independently of percent fat mass.

---

**ACTH**  Adrenocorticotropic hormone  **HPA**  Hypothalamic-pituitary-adrenocortical

**BMI**  Body mass index  **QUICKI**  Quantitative insulin sensitivity check index

**CBG**  Corticosteroid binding globulin  **TDFM**  Truncal distribution of fat mass

**DEXA**  Dual energy-X ray absorptiometry  **THE**  Tetrahydrocortisone

**DXM**  Dexamethasone  **THF**  Tetrahydrocortisol

**HOMA**  Homeostasis model assessment of insulin resistance  **WBFM**  Whole body fat mass

---

From the Departments of Pediatric Endocrinology (P.B.) and Nuclear Medicine (B.J.C., N.B.) and the Clinical Epidemiology Unit (P.P., C.G.), Centre Hospitalier Universitaire de Bordeaux, the Laboratoire Neuro-régénétique et Stress, University of Bordeaux (P.M., M.D.), France; and the Department of Pediatric Endocrinology (M.G.C., B.J., M.T.), Centre Hospitalier Universitaire de Toulouse, France, and the Endocrinology Unit, Centre of Cardiovascular Science, University of Edinburgh (R.A., B.R.W.), United Kingdom.

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10.1016/j.jpeds.2007.01.029
METHODS

Inclusion Criteria

Children were recruited in the Departments of Paediatrics of Bordeaux and Toulouse from obesity clinics before their participation in a program of care coordination. Inclusion criteria were ages 6 to 11 years for girls and 6 to 13 years for boys, prepubertal stage with breast, genital, and pubic hair stage 1 according to Marshall and Tanner and obesity defined by body mass index (BMI) as proposed by the International Obesity Task Force13; subjects had BMI above international cutoff points defined to pass through BMI of 30 kg/m² at age 18. Exclusion criteria were oral or inhaled steroids in the last 6 months, bulimia, dieting for at least 3 months before the study (>30% variation of caloric intake), hypothyroidism, Cushing syndrome and, for girls, hyperandrogenia. The study had the approval of the local ethics committee. Informed consent was obtained from the children and from the parents of each study participant.

Clinical Protocol

Forty-five obese children (n = 29 in Bordeaux; n = 16 in Toulouse) were included in this study. The average BMI was 27.8 ± 5.9 kg/m² for fathers and 27.5 ± 5.4 kg/m² for mothers. All children had normal physical examination results apart from obesity. In the Bordeaux and Toulouse hospitals, children were admitted in the evening of day 0. On day 1 at 0800 hours after an overnight fast, blood pressure was measured with the patient in the supine position, and 11 mL of blood was drawn to determine plasma cortisol, adrenocorticotropic hormone (ACTH), glucose, insulin, lipid profile, corticosteroid binding globulin (CBG), and leptin levels. Then, body weight and height and waist and hip circumferences were measured to the nearest 0.1 kg or cm, respectively. On the same morning, total fat mass and truncal distribution of fat mass were determined with DEXA.

In addition, children in Bordeaux had further exploration of HPA axis activity and reactivity. Twenty-four hour urine collection was started at 2000 hours on day 0. On day 1, saliva samples were collected at 0800 hours before blood sample and at 1130 and 1200 hours. A standardized meal (950 Kcal; 55% carbohydrate, 15% protein, 30% fat) was served at noon, and saliva samples were repeated every 30 minutes for 2 hours. The highest value of saliva cortisol after the meal was used to determine the increment of saliva cortisol after a meal as follows: Δ meal Cortisol saliva (%) = 100 × (highest Cortisol saliva − 1200 h Cortisol saliva)/1200 h Cortisol saliva. On day 2 at 2000 hours, urine collections stopped and urine aliquots were stored without preservative at −20°C until assayed for free urinary cortisol and total glucocorticoid metabolites. On day 1 at 2300 hours, oral dexamethasone (DXM) was given (0.25 mg). On day 2 at 0800 hours, blood samples were collected for cortisol measurements. We measured the decrease of plasma cortisol after DXM (0.25 mg) as followed: ratio DXM × (0.25 mg) Cortisol plasma = day 2 Cortisol plasma/day 1 Cortisol plasma.

Laboratory Methods

Cortisol, ACTH, insulin, CBG, and leptin measurements were measured by the centralized laboratories in Bordeaux. Blood glucose was measured at the bedside with a glucose dehydrogenase oxidation technique (Olympus Diagnostica GmbH, Lismeehan, O’Callaghan/Mills Co. Clare, Ireland). Serum insulin was analyzed with a commercial IRMA (Dia Sorin, Saluggia, Italy). Homeostasis model assessment of insulin resistance (HOMA-IR = [fasting insulin × fasting glucose]/22.5) and quantitative insulin sensitivity check index (QUICKI = 1/[log(fasting insulin) + log(fasting glucose)]) were calculated as previously described. Commercial colorimetric method was used for blood cholesterol (Olympus Diagnostica GmbH) and triglycerides (Olympus Diagnostica GmbH). Serum leptin was assayed with commercial RIA (Mediagnost,Tuebingen, Germany). Blood was collected in serum separator tubes for cortisol determination and serum was stored at −20°C until assayed with a commercial RIA (Dia Sorin, Stillwater, MN). Samples for ACTH determination were taken in prechilled EDTA test tubes and spun in a centrifuge immediately, and plasma was stored at −70°C until assayed with a commercial IRMA (Nichols Institute Diagnostics, San Clemente, Calif). The binding capacity of CBG (Bmax) and its affinity (Kd) for cortisol were measured at 4°C by a solid phase assay with Concanavalin A-Sepharose.15 Salivary cortisol was then extracted into dichloromethane (cortisol recovery >95%) and assayed after evaporation and resuspension of the dried extract in human disteroidized serum with a commercial RIA Coat-A-Count (DPC, Los
Table II. Correlations between fat mass, truncal distribution of fat mass, and metabolic data in total population

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<th></th>
<th>Truncal distribution of fat mass</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>r</td>
<td>95% CI</td>
<td>n</td>
</tr>
<tr>
<td>Leptin</td>
<td>36</td>
<td>0.67*</td>
<td>[0.43; 0.82]</td>
<td>36</td>
</tr>
<tr>
<td>Glucose</td>
<td>43</td>
<td>0.18</td>
<td>[−0.03; 0.46]</td>
<td>45</td>
</tr>
<tr>
<td>Insulin</td>
<td>41</td>
<td>0.21</td>
<td>[−0.10; 0.49]</td>
<td>43</td>
</tr>
<tr>
<td>HOMA</td>
<td>41</td>
<td>0.25</td>
<td>[−0.06; 0.52]</td>
<td>43</td>
</tr>
<tr>
<td>QUICKI</td>
<td>41</td>
<td>−0.10</td>
<td>[−0.40; 0.22]</td>
<td>43</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>43</td>
<td>0.02</td>
<td>[−0.29; 0.32]</td>
<td>45</td>
</tr>
<tr>
<td>LDL-C</td>
<td>43</td>
<td>0.14</td>
<td>[−0.17; 0.42]</td>
<td>45</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>43</td>
<td>0.13</td>
<td>[−0.18; 0.42]</td>
<td>45</td>
</tr>
</tbody>
</table>

r, Pearson correlation coefficient.
*The r is significantly different from 0 (P < .05).

RESULTS

Forty-five obese children (26 boys, 19 girls) were recruited. Table I (available at www.jpeds.com) shows the clinical and metabolic characteristics, as well as HPA axis activity and reactivity variables in boys and girls. None of them had abnormal blood pressure, plasma glucose, total and LDL-cholesterol, or triglycerides values.

WBFM (%) was not different between boys and girls. When adjusted for WBFM (%), ACTH and morning plasma cortisol were higher in boys than in girls. No other statistically significant difference was seen between boys and girls for other HPA axis data.

In boys, TDFM was correlated significantly with BMI (r = 0.47; 95% CI [0.09; 0.73]), waist circumference (r = 0.48; 95% CI [0.07; 0.75]), and waist-to-hip ratio (r = 0.71; 95% CI [0.41; 0.87]) but not with WBFM (%) (r = 0.34; 95% CI [−0.08; 0.66]). In girls, TDFM was correlated significantly with waist circumference (r = 0.64; 95% CI [0.25; 0.85]), and waist-to-hip ratio (r = 0.64; 95% CI [0.24; 0.85]) but not with BMI (r = 0.34; 95% CI [−0.15; 0.70]) nor WBFM (%) (r = 0.25; 95% CI [−0.24; 0.64]). Because there is no sex difference for correlations between fat mass, truncal distribution of fat mass, and metabolic data, all data are presented for the total population (Table II). Serum leptin was significantly correlated with WBFM (%) but not with fat distribution when adjusted for WBFM (%). No significant correlation was found between WBFM (%) and glucose, insulin, insulin sensitivity indexes or lipid measures. By contrast, TDFM adjusted for WBFM (%) was significantly correlated with insulin and HOMA.

No significant correlation was found between WBFM (%) and any of the HPA axis activity and reactivity variables in the total population (Table III). On the other hand, when adjusted for WBFM (%), TDFM was positively correlated with morning plasma cortisol in the total population but not in boys and in girls studied separately. TDFM was negatively correlated with salivary cortisol response to lunch in the total population with significant correlation in girls but not in boys. In Angeles, Calif). Free urinary cortisol was assayed in Bordeaux using a commercial kit: CORT-CT2 (Cis Bio International, Gif sur Yvette, France). Glucocorticoid metabolites were measured by gas chromatography and electron impact mass spectrometry after Sep-Pak C18 extraction, hydrolysis with β-glucuronidase, and formation of methoxime trimethylsilyl derivative, as previously described.16 Epi-cortisol and epi-tetrahydrocortisol were used as internal standards, which were added to samples before extraction. Total cortisol metabolite excretion was calculated as tetrahydrocortisol (α and β THFs) + tetrahydrocortisone (THE) + cortols + cortolones. Relative metabolism by 5α and 5β-reductases were inferred from the 5α-THF/5β-THF ratio. A-ring reduction of cortisol was inferred from the ratios of THFs/cortisol and 5α-reductase activity from the ratio of THE/cortisone. Whole-body equilibrium between cortisol and cortisone, determined by the balance of tissue-specific activities of 11β-reductase and 11β-dehydrogenase activities, was inferred from the ratio of THFs/THE. Renal 11β-dehydrogenase activity was inferred from the urinary cortisol/cortisone ratio.17

Statistical Analysis

Statistical analysis was performed by using SAS system software (version 8.2, SAS Institute, Inc., Cary, NC). Patients’ characteristics were described by mean and standard deviation (SD) and compared between boys and girls by a Student t test except for HPA axis activity, which was compared by an analysis of variance, adjusted for fat mass percentage. Associations between fat mass, TDFM, anthropometric and metabolic data and HPA axis were evaluated with Pearson correlation coefficients. Ninety-five percent confidence intervals (95% CI) were estimated with Gaussian assumption after Fisher transformation. A correlation coefficient was considered as significantly different from 0 if its 95% CI did not include 0. Correlations were adjusted for the fat mass percentage, with partial Pearson correlations.

Truncal Distribution of Fat Mass, Metabolic Profile and Hypothalamic-Pituitary Adrenal Axis Activity in Prepubertal Obese Children 5371
**Table III. Correlations between fat mass, truncal distribution of fat mass and HPA axis**

<table>
<thead>
<tr>
<th>Body fat mass (%)</th>
<th>Truncal distribution of fat mass adjusted for body fat mass (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total population</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>0800 h Cortisol(_{\text{plasma}})</td>
<td>39</td>
</tr>
<tr>
<td>0800 h Cortisol(_{\text{saliva}})</td>
<td>19</td>
</tr>
<tr>
<td>0800 h ACTH</td>
<td>39</td>
</tr>
<tr>
<td>B max(_{\text{CBG}}) (nM)</td>
<td>32</td>
</tr>
<tr>
<td>K(_{\text{CBG}})</td>
<td>32</td>
</tr>
<tr>
<td>Δ meal Cortisol(_{\text{saliva}}) (%)</td>
<td>23</td>
</tr>
<tr>
<td>DMX (0.25 mg) Cortisol(_{\text{plasma}})</td>
<td>24</td>
</tr>
<tr>
<td>Free urinary cortisol</td>
<td>28</td>
</tr>
<tr>
<td>Total glucocorticoid metabolites</td>
<td>22</td>
</tr>
<tr>
<td>Cortisol/Cortisone</td>
<td>22</td>
</tr>
<tr>
<td>(5α-THF + 5β-THF)/THE</td>
<td>22</td>
</tr>
<tr>
<td>5α-THF/5β-THF</td>
<td>22</td>
</tr>
</tbody>
</table>

r, Pearson correlation coefficient.
*The r is significantly different from 0 (P < .05).

Girls, TDFM was negatively correlated with the ratio of plasma cortisol after DMX (0.25 mg) (day 2)/cortisol day 1 (r = −0.77; 95% CI [−0.96; −0.03]) and positively correlated with total glucocorticoid metabolites (r = 0.92; 95% CI [0.62; 0.99]).

Because of the number of potential variables to analyze, we limited our study to morning plasma cortisol and salivary cortisol response to lunch because of their association with trunk fat distribution in the total population. When adjusted for WBFM (%) and TDFM, morning plasma cortisol was positively correlated with total cholesterol (r = 0.49, 95% CI [0.01; 0.78]) in girls and total cholesterol (r = 0.41, 95% CI [0.11; 0.65]) and triglyceride values (r = 0.44, 95% CI [0.14; 0.67]) in the total population. When adjusted for WBFM (%) and TDFM, no significant correlation was found between salivary cortisol response to lunch and metabolic data in the total population (data not shown). However, we found inverse correlations when comparing boys (n = 17) and girls (n = 9). Salivary cortisol response to lunch (%) was negatively correlated with HOMA (r = −0.56, 95% CI [−0.85; −0.01]) and positively correlated with QUICKI (r = 0.58, 95% CI [0.04; 0.86]) in boys and positively correlated with HOMA (r = 0.74, 95% CI [0.16; 0.94]) and negatively correlated with QUICKI (r = −0.71, 95% CI [−0.93; −0.08]) in girls.

**DISCUSSION**

Our results demonstrate that TDFM is positively associated with insulin resistance and morning plasma cortisol and negatively associated with the increase of saliva cortisol after lunch in obese prepubertal children, and that this effect is independent of the percentage of WBFM. DEXA, taking into account subcutaneous and visceral truncal fat together, has already been used in children and adolescents aged 9 to 17 years, demonstrating that TDFM is a more important independent correlate of cardiovascular risk factors than percent body fat. Here, we used the same method to evaluate TDFM in strictly prepubertal obese children and confirmed the independent association between TDFM and plasma insulin levels and insulin resistance estimated with HOMA in this population.

We made the choice not to include non-obese control subjects because we were more interested in changes of HPA axis activity and reactivity with body fat distribution in obese children than changes of HPA axis with obesity. The associations we found between morning plasma cortisol and TDFM but also between morning plasma cortisol and some lipid profile measures, independently of TDFM, suggest that HPA axis is involved early in life in truncal obesity, even in prepubertal children. However, because our results were independent of the percentage of fat mass, it would be of interest to perform the same study in non-obese children.

Saliva cortisol closely reflects the free/active plasma cortisol. In spite of positive correlation with morning plasma cortisol, we found no significant correlation between morning salivary cortisol and trunk fat distribution. However, salivary cortisol was not obtained for all children because children have more difficulty than adults spitting saliva early in the morning and having fasted. To complete the assessment of extracellular cortisol availability, we studied CBG level and its affinity for cortisol. Serum CBG levels measured by RIA are known to correlate negatively with BMI, waist-to-hip ratio, and HOMA in adults. Here, cortisol and ACTH were reduced in girls, independently of the percentage of fat mass. Moreover, we found strong relationships between TDFM and urinary total...
glucocorticoid metabolites, sensitivity to DXM or cortisol responsiveness after lunch in girls but not in boys. We also found opposite relationships in boys and girls between salivary cortisol response to lunch and indexes of insulin resistance.

The urinary cortisol metabolites provide insights into activities of cortisol metabolizing enzymes. 11β-HSD1 activity is increased in adipose tissue of obese adults and is preferentially increased in omental than subcutaneous adipose stroma cells which may explain the specific action of glucocorticoids on different adipose tissue deposits. However, 11β-HSD1 activity in the liver is decreased in obese human beings and rodents, perhaps as a compensation to reduce the local intrahepatic load of glucocorticoids. The ratio of (5α-THF + 5β-THF)/THF indicates the balance of 11β-HSD1 and 11β-HSD2 in all tissues but is also influenced by the activities of A-ring reductases. Hence, correlations between the values and degree of obesity have been inconsistent. In this study we found a trend for a negative correlation between (5α-THF + 5β-THF)/THF ratio and the percentage of WBFM. This tendency disappeared when correlating with TDFM.

HPA axis reactivity after a meal is known to be higher at lunch time. In premenopausal obese women, cortisol response after lunch has been shown to be the same or enhanced in women with abdominal fat distribution compared with women with peripheral obesity. This response of salivary cortisol after lunch is the same between non-obese and obese children. Interestingly, salivary cortisol responsiveness to a standardized lunch was negatively correlated with TDFM in the total population but more clearly in girls. This result is the opposite of what we have reported in premenopausal women. If this difference as compared with adults is confirmed in a larger population, this suggests that HPA axis reactivity after a meal evolves in accordance with age, at least in females.

Our study confirms that, in prepubertal obese children, an association exists between some markers of HPA axis activity and TDFM, independently of WBFM. Morning plasma cortisol is associated with the lipid profile, independently of fat mass and fat mass distribution. Moreover, salivary cortisol response to lunch is associated with insulin resistance. Both truncal distribution of fat mass and lipid profile are criteria defining the metabolic syndrome in adults. Therefore our data suggest that HPA axis could be involved early in life in an obesity associated with pejorative metabolic profile. To gain better insight into this relationship between HPA axis and abdominal obesity, both the sexual dimorphism of the HPA axis activity in prepubertal obese children and the evolution of the HPA axis reactivity after a meal from childhood to adulthood need to be investigated.

REFERENCES

Table I. Subject characteristics, DEXA, biochemical and hormonal data in boys and girls

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
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<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (y)</td>
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</tr>
<tr>
<td>Weight (kg)</td>
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</tr>
<tr>
<td>Height (cm)</td>
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<td>QUICKI</td>
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<tr>
<td>Leptin (ng/mL)</td>
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<td>0800 h Cortisolplasma (nmol/L)</td>
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<td>DMX (0.25 mg) Cortisolplasma</td>
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<td>0.59</td>
</tr>
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NS, Nonsignificant difference between boys and girls.
Adenotonsillectomy Improves Sleep, Breathing, and Quality of Life But Not Behavior

EVELYN CONSTANTIN, MD, ANDREA KERMACK, BSC, GILLIAN M. NIXON, MD, LEE TIDMARSH, MD, FRANCINE M. DUCHARME, MD, AND ROBERT T. BROUILLETTE, MD

Objective To obtain parental perspectives on changes in sleep, breathing, quality of life (QOL), and neurobehavioral measures after adenotonsillectomy.

Study design This retrospective cohort study comprised otherwise healthy children evaluated for obstructive sleep apnea syndrome (OSAS) from 1993 to 2001. We compared those children who underwent adenotonsillectomy with those children who did not. The parents of 473 children (292 boys) 2 years of age and older were sent questionnaires to evaluate QOL and clinical and behavioral changes. For 94 children 3 years of age and older, behavioral changes were evaluated using the Conners’ Parent Rating Scale-Revised (CPRS-R) for three different periods: pre-operatively/pre-polysomnography, postoperatively/postpolysomnography, and recently.

Results One hundred and sixty-six questionnaires were returned (35%), 138 of which were complete with written consent provided. Compared with parents of unoperated children, parents of children who had adenotonsillectomy were more likely to report improvements in sleep, breathing, and QOL but not improvements in concentration, school performance, and intellectual or developmental progress. Both short and long term, there were no significant effects of adenotonsillectomy on any of the CPRS-R behavior subscales.

Conclusion From a parental perspective, adenotonsillectomy frequently improves sleep, breathing, and QOL but does not often improve neurobehavioral outcomes. (J Pediatr 2007;150:540-6)

Obstructive sleep apnea syndrome (OSAS) is a relatively common problem in childhood, having a prevalence of 0.7% to 3%.1-2 OSAS in children is a disorder of breathing during sleep characterized by upper airway obstruction that disturbs sleep and disrupts normal respiratory gas exchange.3-5 Adenotonsillar hypertrophy is the most common etiology of OSAS in children. For most children, complete resolution of OSAS is achieved with adenotonsillectomy. When a diagnosis of OSAS is not recognized or remains untreated, serious sequelae may ensue, including cor pulmonale and failure to thrive.4-6

Over the past 10 years a number of studies have reported adverse behavioral and developmental consequences of OSAS. Several studies have reported a relationship between sleep disordered breathing and neurobehavioral and cognitive deficits.9-19 A few studies have evaluated neurobehavioral outcomes20-23 and quality of life (QOL)24-28 in the months following adenotonsillectomy. As parents have the opportunity to observe their child’s behavior and development over prolonged periods, it is important to understand what parents can tell us about responses to medical and surgical interventions.

We hypothesized that, several years after adenotonsillectomy, parents would report improved sleep, breathing, QOL, and neurobehavioral and cognitive deficits in children with OSAS, as compared with children who did not have adenotonsillectomy. Furthermore, we expected that the improvement would be sustained and that the greatest improvements would be in the children with the most severe OSAS. To test these hypotheses, we sent questionnaires to parents of children who were evaluated for possible OSAS with subsequent treatment with adenotonsillectomy (the intervention group) and to parents of those who did not have adenotonsillectomy (the comparison group).
METHODS

Study Population

The study cohort consisted of children between 2 and 17 years of age at the time of polysomnography who were evaluated for possible OSAS between January 1993 and December 2001. Subjects with asthma were included, but we excluded children with other significant lung diseases, and those with neuromuscular, cardiac, craniofacial, or genetic disorders. We also excluded children evaluated in the sleep laboratory for reasons other than diagnosis of OSAS (ie, neuromuscular weakness, Continuous Positive Airway Pressure (CPAP) titration, or central hypoventilation). Our Institutional Review Board granted ethical approval for the study.

Questionnaires and informed consent forms were sent to each child’s parent or legal guardian in the spring of 2002. We sent reminders and follow-up questionnaires to those parents who had not returned the questionnaires. We did not include in our study any questionnaire responses that were returned after June 1, 2002. We collected the following for each patient: (1) cardiorespiratory data from nocturnal polysomnography; (2) pre-polysomnography parental questionnaire; and (3) follow-up parental questionnaire designed for the current study.

Polysomnography

Overnight polysomnography was conducted either in our sleep laboratory or at the subject’s home using our home polysomnography montage.29-31 Our home polysomnography system, which includes calibrated respiratory inductive plethysmography, pulse oximetry, and audiovisual recordings, has been shown to give results equivalent to those from laboratory polysomnography for mixed/obstructive apnea/hypopnea index, desaturation index, and respiratory arousal index. Sleep efficiency and the total sleep time were slightly higher in the home compared with the laboratory.29 Laboratory polysomnography followed the 1996 American Thoracic Society standards.3 Scoring of polysomnography was performed manually by 30-second epochs.12 An obstructive apnea was defined as a reduction in the sum signal on calibrated respiratory inductance plethysmography to <20% of baseline for ≥3 seconds, paired with paradoxical movements of the ribcage and abdomen. Obstructive hypopnea was scored as a reduction in the sum signal to 20% to 50% of baseline for ≥3 seconds, associated with a drop in SaO2 of ≥4%. The desaturation index was defined as the number of drops in SaO2 of ≥4% per hour. The respiratory arousal index was defined as the number of respiratory-related arousals per hour of total sleep time. The mixed obstructive apnea/hypopnea index (MOAHI), calculated as the number of mixed obstructive apneas and hypopneas per hour of total sleep time, was used to define OSAS when there was at least one event per hour.13,14

Pre-polysomnography Questionnaire

At the time of the initial clinical referral to the Sleep Laboratory, each parent or guardian had completed a validated sleep laboratory questionnaire.8 In this first questionnaire, parents were asked to provide demographic data and information about their child’s past medical and surgical history, as well as information regarding snoring frequency and loudness, difficulties breathing awake or asleep, and excessive daytime sleepiness. Parents were also asked to report any problems with behavior and/or development. Based on information about snoring, difficulty breathing during sleep, and apneas, an OSA score was calculated.8

Follow-up Questionnaire (OSAS Outcomes and Neurobehavioral Assessment)

The questionnaire mailed to the parents consisted of two parts: one focusing on OSAS outcomes and the other addressing neurobehavioral outcomes, using the Conners’ Parent Rating Scale-Revised (CPRS-R).35,36

Sleep, Breathing, and Quality of Life Outcomes. In the first part of the follow-up questionnaire, parents provided demographic details and information about what treatment, if any, their child received following the initial assessment. Because our primary hypothesis concerned outcomes after treatment, we divided our subjects into two groups: those who had undergone adenotonsillectomy and those who had not. We asked before-after questions to assess for changes in the months following adenotonsillectomy, or following the polysomnography if no surgery had been performed. The questions covered several dimensions: QOL, daytime and sleep breathing, loudness of snoring, asthma, bedwetting, excessive daytime sleepiness, and neurobehavioral/cognitive functioning. The parental responses were based on a 4-point scale: “improved,” “no change,” “worsened,” and “not sure.” We recoded the latter three responses into one group (“not improved”), for comparison with the “improved” group. We asked parents to inform us if their child has been diagnosed with attention deficit hyperactivity disorder (ADHD) by a physician and, if so, if the child was on any treatment for ADHD (medication, behavioral treatment, psychological treatment, or no treatment).

 Neurobehavioral Outcomes. For children 3 years of age or older at the time of initial polysomnography, we asked parents to complete a questionnaire based on the CPRS-R, a widely used, validated measure of child behavior for children 3 to 17 years of age. Twenty-seven questions were used to evaluate behavior in three time periods: (1) “In the months before sleep study/surgery”; (2) “In the months after sleep study/surgery”; and (3) “In the past few months.” The 27 questions were reported by parents/guardians using a 4-point scale (“not true at all,” “just a little true,” “pretty much true,” and “very much true”). The CPRS-R permits evaluation of four subscales: Oppositional, Cognitive/Inattention, Hyperactivity, and ADHD index. The scores were tabulated and...
converted to age- and sex-adjusted standardized \( t \) scores. All calculations were conducted in duplicate by two different co-authors (EC and AK), who were blinded to the rest of the patient information and questionnaire results. \( T \) scores have an average of 50, a standard deviation of 10, and a range of 0 to 100. A \( t \) score \( \geq 60 \) for each subscale has been reported to be correlated with a diagnosis of ADHD. A difference of 10 points (1 standard deviation) in the \( t \) score has been suggested as a clinically significant change. The parent-reported short-term and long-term CPRS-R scores for each of the four subscales were compared with the baseline scores, using repeated-measure analysis of variance (ANOVA).

**Statistical Analysis**

We compared the “No adenotonsillectomy group” with the “Adenotonsillectomy group.” We analyzed our nominal data using \( \chi^2 \) and Fisher’s exact tests; continuous data were analyzed using unpaired \( t \) tests and Wilcoxon’s rank sum tests, as indicated.

Our primary hypotheses were that adenotonsillectomy would improve sleep, breathing, QOL, and neurobehavioral and cognitive deficits in the months after adenotonsillectomy, and that the improvement would be sustained. The 10 OSA outcomes measured in the follow-up questionnaire were analyzed using binary backward logistic regression for improvement or non-improvement. The primary intervention of interest was adenotonsillectomy or not; other covariates for the analyses included OSAS or not, MOAHI as a continuous variable (to assess for severity of OSAS), age, and sex. To evaluate whether parents recognized neurobehavioral improvement in children after adenotonsillectomy, analyses were conducted for each of the CPRS-R subscales, to compare changes in two time periods compared with baseline: “In the months after sleep study/surgery” and “In the past few months.” The four CPRS-R subscales provided continuous data allowing analysis using three-way repeated measures ANOVA; adenotonsillectomy and a polysomnographic diagnosis of OSAS were independent factors and time period was the repeated measure.

A \( P \) value \( \leq 0.05 \) was considered to be statistically significant for all analyses, with the exception of the logistic regression analysis, where we applied the Bonferroni correction for multiple comparisons and considered a \( P \) value of \( 0.005 \) as statistically significant. The Statistical Package for the Social Sciences (SPSS), version 12 for Windows (SPSS Inc., Chicago, Ill) was used for data analysis.

**RESULTS**

**Description of the Cohort**

The recruitment pathway is schematically shown in Figure 1 (available at www.jpeds.com). No difference was found between responders and the nonresponders for age at time of polysomnography, sex, OSA score, MOAHI, and mean saturation or minimum saturation during sleep. Complete data were available for 138 (31%) eligible subjects for the first part of the questionnaire on sleep, breathing, and QOL outcomes; 94 of 109 subjects who were 3 years of age or older had complete data for the neurobehavioral outcome (CPRS-R) section of the questionnaire (Figure 1). Of the 138 subjects, 75 had a diagnosis of OSAS, and 63 did not meet the criteria for OSAS. Adenotonsillectomy was performed on 87% (65/75) of subjects with OSAS and 33% (21/63) of subjects without OSAS. As this was a retrospective cohort study, we have no information on the reasons why the parents and otolaryngologists decided to go forward with adenotonsillectomy in children without polysomnography-documented OSAS or why they decided not to operate on children with polysomnography-documented OSAS.

The cohort included a wide range of sleep-related airway obstruction from normal to severe OSAS (MOAHI range, 0 to 55.1). The age and sex distribution of the subjects evaluated for possible OSAS were characteristic of those usually reported for children with OSAS secondary to adenotonsillar hypertrophy (Table I). The adenotonsillectomy group was younger than the group that did not have surgery, but it had similar sex distribution. As expected, the adenotonsillectomy group had a higher OSA score and more severe OSAS as determined by polysomnography (Table I).

**Sleep, Breathing and Quality of Life Outcomes**

Compared with children who had not undergone adenotonsillectomy, parents of the adenotonsillectomy group more frequently reported improvement in breathing, snoring, excessive daytime sleepiness, and QOL postoperatively (Table II). Parental reporting of asthma, bedwetting, concentration, school performance, and intellectual or developmental progress were not statistically different between the two groups. Including age and sex as covariates in the logistic regression analysis did not affect these findings.

Surprisingly, sleep, breathing, and QOL also improved following adenotonsillectomy in children who did not have OSAS at baseline (n = 21). In addition, severity of OSAS, using MOAHI as a continuous variable in the logistic regression model, did not influence the likelihood of improvement after adenotonsillectomy on any medical or neurobehavioral measure.

We conducted post hoc analyses to evaluate the effect of early versus late parental recall for the OSA outcomes. The mean time between questionnaire date and surgery date (or questionnaire and polysomnography date, if no surgery was done) was approximately 3.5 years. We chose this midpoint of 3.5 years to designate recall time as early (<3.5 years) versus late (\( \geq 3.5 \) years). Using the Fisher’s Exact Test, there was no statistically significant effect on all OSA outcomes (with the exception of bedwetting) for early versus late recall groups.

**Neurobehavioral Outcomes**

Table III shows the four Conners’ Parent Rating Scale-Revised subscale scores at baseline, short-term follow-up, and
long-term follow-up by adenotonsillectomy status. At baseline, the scores were similar for children with and without OSAS (data not shown) and for those who subsequently had or did not have adenotonsillectomy.

Figure 2 (available at www.jpeds.com) shows the short-term changes in one of the Conners' subscales, the Hyperactivity Index, by adenotonsillectomy status; only two subjects had a decrease of at least 10 points after treatment. Other subscale analyses were similar in showing very few subjects improved with or without adenotonsillectomy. Figure 3 shows the long-term changes in the Hyperactivity Index by adenotonsillectomy status; a total of eight subjects had a

### Table I. Descriptive data for the total study group and the two subgroups (no adenotonsillectomy and adenotonsillectomy groups)

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 138)</th>
<th>No adenotonsillectomy Group (n = 52)</th>
<th>Adenotonsillectomy Group (n = 86)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (n (%))</td>
<td>65 (47.1)</td>
<td>26 (50.0)</td>
<td>39 (45.3)</td>
<td>.72</td>
</tr>
<tr>
<td>Age in years at time of PSG</td>
<td>5.5 (3.0)</td>
<td>7.4 (3.5)</td>
<td>4.6 (2.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age in years at time of T&amp;A</td>
<td>N/A</td>
<td>N/A</td>
<td>5.0 (2.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Age in years at time of follow-up questionnaire response</td>
<td>9.6 (3.8)</td>
<td>10.9 (4.2)</td>
<td>8.8 (3.2)</td>
<td>.001</td>
</tr>
<tr>
<td>OSA score</td>
<td>1.3 (2.5)</td>
<td>0.2 (2.6)</td>
<td>1.9 (2.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>8.3 (1.3)</td>
<td>8.1 (1.3)</td>
<td>8.4 (1.4)</td>
<td>.22</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>90.1 (7.7)</td>
<td>91.4 (6.1)</td>
<td>89.4 (8.4)</td>
<td>.12</td>
</tr>
<tr>
<td>MOAHI (#/h)</td>
<td>5.5 (9.7)</td>
<td>1.5 (3.7)</td>
<td>7.9 (11.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory Arousal Index (#/h)</td>
<td>3.0 (5.0)</td>
<td>1.1 (2.1)</td>
<td>4.2 (5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean SaO₂ (%)</td>
<td>97.6 (1.3)</td>
<td>97.8 (1.3)</td>
<td>97.5 (1.4)</td>
<td>.18</td>
</tr>
<tr>
<td>Minimum SaO₂ (%)</td>
<td>88.0 (8.3)</td>
<td>91.5 (4.0)</td>
<td>86.0 (9.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Desaturation Index (#/h)</td>
<td>4.3 (7.6)</td>
<td>2.0 (4.8)</td>
<td>5.6 (8.6)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Values are expressed as mean (standard deviation). P values determined comparing no adenotonsillectomy and adenotonsillectomy groups.

MOAHI, mixed/obstructive apnea/hypopnea index; PSG, polysomnography; T&A, adenotonsillectomy.

### Table II. Percentage of subjects improving by parental report

<table>
<thead>
<tr>
<th></th>
<th>No adenotonsillectomy group</th>
<th>Adenotonsillectomy group</th>
<th>P value</th>
<th>OR*</th>
<th>CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>10.2</td>
<td>74.1</td>
<td>&lt;.001</td>
<td>25.1</td>
<td>8.8, 71.8</td>
</tr>
<tr>
<td>Daytime breathing</td>
<td>10.0</td>
<td>61.4</td>
<td>&lt;.001</td>
<td>14.3</td>
<td>5.2, 39.9</td>
</tr>
<tr>
<td>Sleep breathing</td>
<td>20.0</td>
<td>91.7</td>
<td>&lt;.001</td>
<td>44.0</td>
<td>15.6, 124.3</td>
</tr>
<tr>
<td>Loudness of snoring</td>
<td>25.0</td>
<td>90.7</td>
<td>&lt;.001</td>
<td>29.1</td>
<td>10.1, 83.9</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>18.0</td>
<td>47.5</td>
<td>.001</td>
<td>4.1</td>
<td>1.8, 9.6</td>
</tr>
<tr>
<td>Asthma</td>
<td>11.6</td>
<td>25.7</td>
<td>.08</td>
<td>2.6</td>
<td>0.9, 7.6</td>
</tr>
<tr>
<td>Bedwetting</td>
<td>5.6</td>
<td>15.6</td>
<td>.15</td>
<td>3.1</td>
<td>0.7, 15.2</td>
</tr>
<tr>
<td>Concentration</td>
<td>10.2</td>
<td>20.0</td>
<td>.15</td>
<td>2.2</td>
<td>0.7, 6.5</td>
</tr>
<tr>
<td>School performance</td>
<td>18.0</td>
<td>24.4</td>
<td>.40</td>
<td>1.5</td>
<td>0.6, 3.6</td>
</tr>
<tr>
<td>Intellectual or developmental progress</td>
<td>22.4</td>
<td>24.7</td>
<td>.78</td>
<td>1.1</td>
<td>0.5, 2.6</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

*Adjusted for age and gender.

### Table III. Conners' Parent Rating Scale-Revised (CPRS-R) subscales*

<table>
<thead>
<tr>
<th>CPRS-R subscales</th>
<th>No adenotonsillectomy group (n = 40)</th>
<th>Adenotonsillectomy group (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Short-term</td>
<td>Long-term</td>
</tr>
<tr>
<td>Opposition</td>
<td>52.0 ± 15.1</td>
<td>52.4 ± 15.9</td>
</tr>
<tr>
<td>Cognitive/Inattention</td>
<td>54.0 ± 11.5</td>
<td>54.3 ± 11.7</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>52.0 ± 12.4</td>
<td>51.7 ± 12.1</td>
</tr>
<tr>
<td>ADHD Index</td>
<td>52.0 ± 9.9</td>
<td>52.1 ± 9.6</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation.

*Short-term and long-term CPRS-R scores for the each of the four subscales were compared with baseline scores. There were no significant differences found in the four subscales across time, treatment group (the no adenotonsillectomy and the adenotonsillectomy groups), or apnea status (OSA, no OSA).
children in each group had a decrease of 10 or more.

Hyperactivity Index, irrespective of whether or not they had surgery. Four
time. Note that the majority of children had minimal difference in the
dashed line at zero indicates no change in the Hyperactivity Index over
be consistent with a diagnosis of hyperactivity or ADHD. The horizontal
sillectomy on any of these outcomes, and even children who
not influence the likelihood of improvement after adenoton-
instrument, the CPRS-R. Notably, the severity of OSAS did
improvements in behavior as assessed by a validated
improvements in sleep, breathing, and QOL but rarely re-
who had adenotonsillectomy for OSAS frequently described
Figure 3. Long-term changes in the CPRS-R Hyperactivity Index from
baseline to the past few months are plotted against baseline Hyperactivity
Index. A Hyperactivity Index >60 (vertical dashed line) is considered to
be consistent with a diagnosis of hyperactivity or ADHD. The horizontal
dashed line at zero indicates no change in the Hyperactivity Index over
time. Note that the majority of children had minimal difference in the
Hyperactivity Index, irrespective of whether or not they had surgery. Four
children in each group had a decrease of 10 or more.

decrease of at least 10 points: four subjects who had adenotonsillectomy and four subjects who had not had adenotonsillectomy. Other subscale analyses were similar in showing that over the long-term, only a few patients in both groups (the Adenotonsillectomy and No Adenotonsillectomy groups) had decreases in the CPRS-R score of >10. There were no statistically significant changes from baseline to both short-term and long-term changes within any of the four CPRS-R subscales in either the adenotonsillectomy group or the unoperated group (Table III).

As for the OSA outcomes, we also conducted post hoc analyses evaluating the effect of early versus late parental recall for the CPRS-R subscales. We performed two-way repeated measures ANOVA with recall time (early versus late) as an independent factor and time period (baseline, short-term, and long-term) as a repeated measure. There was no statistically significant effect on the outcomes of the four CPRS-R subscales for early versus late recall groups.

**DISCUSSION**

In this retrospective cohort study, parents of children who had adenotonsillectomy for OSAS frequently described improvements in sleep, breathing, and QOL but rarely reported improvements in behavior as assessed by a validated instrument, the CPRS-R. Notably, the severity of OSAS did not influence the likelihood of improvement after adenotonsillectomy on any of these outcomes, and even children who did not have OSAS on polysomnographic recording showed improvements in sleep, breathing, and QOL, by parental report.

A number of studies have reported an association between OSAS and neurobehavioral and cognitive deficits. Several groups have found improved neurobehavioral outcomes in children after adenotonsillectomy. Ali and his group evaluated 33 children before and after adenotonsillectomy (12 with sleep disordered breathing, 11 snorers, 10 controls). Their study concluded that following surgery, relief of mild to moderate sleep-disordered breathing improves behavior and functioning. Chervin et al and Goldstein et al conducted prospective before-after studies evaluating children’s neurobehavioral outcomes following adenotonsillectomy. Parent rating scales showed improvement of behavior, inattention, hyperactivity, ADHD, and excessive daytime sleepiness. By contrast to these studies, we found that several years after surgery, parents did not report that their children had improved neurobehavioral outcomes following adenotonsillectomy, either in the period immediately following surgery or in the long term. Moreover, our study included a relatively large sample size of children referred to a pediatric sleep laboratory for evaluation of OSAS; clinical and polysomnographic data were available for all study patients and the follow-up period averaged 5 1/2 years.

It is possible that recall, observer, information, or selection biases could explain the discrepancy between our results and those of previous investigators. For this retrospective cohort study, the long follow-up can be seen as a disadvantage as well as an advantage. We cannot exclude the possibility that parents had difficulty remembering changes in their child’s behavior and development after adenotonsillectomy but had no such difficulty recalling significant improvements in sleep, breathing, and QOL at the same time. However, our analyses revealed no effect of duration of follow-up on OSA outcomes (with the exception of bedwetting) and no effect on outcomes for the CPRS-R subscales.

Most previous studies that have evaluated neurobehavioral outcomes after adenotonsillectomy have used psychometric tests measuring such domains as attention and executive function. It may be that parents overlook small changes in such specific domains (observer bias), instead focusing on global development and behavior. Alternatively, in many children, the improvements in cognitive/behavioral functioning after adenotonsillectomy may be too small to be noticed by parents, in the face of all the other impacts on a child’s cognition and behavior over time.

Numerous tests exist to measure behavior in children. We chose the CPRS-R as our measurement tool for neurobehavioral outcomes because it is a validated, brief, comprehensive and age- and sex-specific measure. However, some of the discordance could be due to test-to-test differences (information bias). More studies are needed to determine the best tests to evaluate neurobehavioral outcomes in children when assessing the impact of interventions to improve sleep quality.

Although our study has a relatively large sample size in
comparison with most other studies of behavior in OSAS, our response rate was lower than optimal. To explain our results by selection bias would require the parents of children who had neurobehavioral improvement after adenotonsillectomy to selectively choose not to respond to our follow-up questionnaire. Responders and nonresponders were similar in demographic profiles and polysomnographic metrics, and such a scenario seems unlikely.

It is interesting that several children had marked neurobehavioral improvement after evaluation for OSAS. However, these children included both those who had adenotonsillectomy and those who did not. Thus, it remains possible that adenotonsillectomy results in dramatic neurobehavioral improvement in a small percentage of children treated for OSAS, and/or that subgroups, such as children with concurrent ADHD or severe learning problems, may improve. In our study, only 18 of 94 children had a CPRS-R baseline Hyperactivity Index >60, 11 of whom had adenotonsillectomy. Only seven of these 11 children had an improvement in the CPRS-R Hyperactivity Index (four of 7 having a change in their index of more than 10 units). Thus, it will be important both to study such subgroups but also to avoid the temptation to generalize results from such studies to the general population of children with OSAS.

Of interest, parents reported improvements of sleep, breathing, and QOL in children who had adenotonsillectomy but who did not have OSAS by polysomnography. Several investigators have found a relation between snoring and behavioral and neurodevelopmental outcomes. It is possible that polysomnography does not detect all children who will benefit from adenotonsillectomy. One possible explanation is that those children who had a normal polysomnogram but improved after adenotonsillectomy had upper airway resistance syndrome. However, this possibility seems unlikely because our monitoring included calibrated respiratory inductive plethysmography with audiovisual observation, and because our definition of OSAS included patients with a MOAHI as low as one event per hour. Children who were not diagnosed with OSAS rarely showed any increased work of breathing, paradox, snoring-associated arousals, or other evidence of difficulty in breathing during sleep.

Several studies have now shown that sleep, breathing, and QOL are likely to improve following adenotonsillectomy for children with OSAS. To the extent that parents’ memories are accurate and that our questions measure the appropriate outcomes, adenotonsillectomy frequently improved sleep, breathing, and QOL but not neurobehavioral outcomes. Thus, pediatricians and otolaryngologists should advise parents that adenotonsillectomy most likely results in these clinical improvements, but physicians should be guarded in promising improvement in behavior and development.

We would like to thank the following collaborators for all their hard work and dedication to this project: Sebastien Dube, MS: (Clinical Research Coordinator, Montreal Children's Hospital/McGill University Research Institute), for his much-appreciated guidance and assistance in our statistical analysis; Vanessa Bonneau and Daron Creighton, for their enthusiasm and assistance in data collection and database entry; and our sleep laboratory technicians: Angela Morielli, Lois Earle, Melodie Mograss, Sylvia Ladan, Severina Luciano, Jacinthe Lavergne, and Christine McGregor, for obtaining initial questionnaire data and for performing and analyzing the polysomnographic data.
Figure 1. Recruitment pathway. See text for description.

Figure 2. Short-term changes in the months after adenotonsillectomy or polysomnography in the Conners' Parent Rating Scale-Revised (CPRS-R) Hyperactivity Index are plotted against baseline Hyperactivity Index. Data for 94 subjects ≥3 years of age are shown. Note that only two subjects had a decrease of 10 or more after adenotonsillectomy; a change in the CPRS-R score of 10 is usually considered significant (improvement or worsening).
Objective  To assess pediatric resident and preceptor environmental tobacco smoke (ETS)-reduction practices and attitudes to inform the development of resident tobacco intervention training.

Study design  Pediatricians in a teaching hospital anonymously completed a 65-item survey.

Results  Residents’ and preceptors’ (n = 93) ETS actions were generally similar. Pediatricians inconsistently intervened across treatment settings and when treating different ETS-related illnesses (eg, 60% “always” assessed during asthma visits, 13% during otitis visits). Less than 50% “always” explained ETS risks to smoking parents and less than 33% “always” advised about creating smoke-free homes. Most pediatricians reported negative attitudes toward smoking parents; however, attitudes were not related to actions. Most frequently cited barriers to ETS action were lack of time and low confidence in effectiveness.

Conclusion  Understanding barriers to ETS intervention could promote transdisciplinary (TD) training and intervention approaches that effectively promote pediatrician advice while offloading the time burden of intensive smoking intervention. ETS intervention training should foster pediatrician confidence and TD relationships with affiliated health professionals who could facilitate intervention, referral, and follow-up necessary to sustain smoking behavior change. (J Pediatr 2007;150:547-52)

A lmost 60% of US children 3 to 11 years of age (approximately 22 million children) are exposed to environmental tobacco smoke (ETS) daily—with urban children suffering the highest rates of exposure.1,2 Although research suggests slightly lower rates of exposure when considering broader child age ranges,3 younger children are more susceptible to ETS-related consequences than older age groups.4,5 Children exposed to ETS have higher rates of lower respiratory infections, asthma, middle ear effusions, behavior problems, and sudden infant death syndrome.6-8 Moreover, a child with a parent who smokes has a threefold higher risk of becoming a smoker.9 ETS exposure is a leading cause of childhood morbidity and mortality, and an estimated $4.6 billion in direct medical costs are expensed annually to treat children with ETS-related illnesses and disease.10 Recent evidence suggests that complete development of the lungs continues through 6 to 8 years of age.11 Exposure to ETS during infancy can modify the formation, structure, and maturity of the lungs—an important factor in the development of asthma, to which researchers attribute 40% to 60% of the cases to ETS exposure.12,13 Children exposed to environmental toxins (eg, ETS) may accrue half of their total lifetime cancer risk because of this exposure by 6 years of age.14 ETS also significantly increases cardiovascular disease risk as much as 20%.15,16 Pediatricians recognize the harmful effects of children’s exposure to ETS and have been encouraged by the American Academy of Pediatrics and the US Surgeon General to directly address ETS with parents and provide guidance on smoking cessation.1,6,17 Moreover, numerous studies indicate that even brief advice about smoking and reducing ETS facilitates parent action toward smoking behavior change.18 For example, a recent meta-analysis showed that brief physician advice provided in primary care, hospital wards, and outpatient clinics significantly increased the odds of quitting smoking by approximately 2.5% compared with no advice.19

A broad, multidisciplinary literature suggests that a combination of physician and healthcare worker advice, referrals to behavioral counseling programs with or without pharmacotherapies, and ongoing follow-up are necessary components to motivate smok-
ing behavior change and sustain long-term abstinence.20–21 However, pediatricians have yet to embrace fully their role in ETS reduction and in helping parents quit smoking, even when patients present with diagnoses directly affected by ETS and despite parental interest in the topic.22,23

We developed the present assessment to determine physician training needs to improve ETS-reduction efforts. As such, we wanted to explore the extent to which pediatric residents and their primary care preceptors currently addressed ETS. We also sought to determine the frequency of resident intervention with smoking parents across different settings (eg, emergency department [ED] and inpatient units). Finally, we wanted to explore pediatrician attitudes about ETS intervention and their role in helping parents change their smoking behavior. Knowledge of these attitudes and how they relate to physician practices would serve as a guide for our ETS training approach.

**METHODS**

We conducted a cross-sectional study of pediatric residents and primary care preceptors at Children’s Hospital of Philadelphia using an anonymous, self-report questionnaire. The survey was distributed to all pediatric residents’ and primary care preceptors’ mail boxes, during one grand rounds presentation and a routine primary care training session. Respondents voluntarily completed the survey in approximately 10 minutes based on observations during pilot testing of the instrument. Then, residents returned the surveys to an investigator’s (KPL) office mail box. E-mail reminders encouraged participation. Duplicate responses were possible, but very unlikely, given the length of the survey and the lack of any monetary or other incentive for completion. The survey consisted of 65 items assessing pediatrician tobacco intervention practices and attitudes. Item selection blended previous published research, primary care practice guidelines for smoking cessation,22,24 and our goal of determining ETS intervention training issues at Children’s Hospital of Philadelphia. The survey included 40 forced-choice questions about pediatrician ETS practices for different patient visit types (eg, well child vs asthma or lower respiratory tract infection [LRTI]) and different treatment settings, (eg, primary care vs inpatient). Forced-choice questions used a 4-point Likert-type response scale (“none,” “occasionally,” “often,” and “always”) for assessing (1) how often pediatricians ask about ETS exposure for different visit types and settings; (2) how often they advise and assist parents to create a smoke-free home; and (3) how often they assess parents’ willingness to quit, advise them to quit, assist them in their quit attempt, and monitor their smoking behavior through follow-up. Ten open-ended questions were included to assess pediatrician attitudes about ETS intervention, for example: “Think about the last time you walked into an exam room and smelled tobacco smoke on a parent. What were your thoughts and feelings? What did you say to the parent? If you said nothing, what were your reasons?” To classify open-ended responses, a panel of three, study-blind tobacco researchers independent of the coding investigators created response codes into these subsequent categories: (1) visceral negative reactions (eg, “disgusted,” “Yuck!”); (2) frustration, anger, or disappointment with a parent; (3) helplessness; and (4) motivation to actively address ETS. Coders achieved an average intra-item agreement of 87%. Responses coded with <75% reliability were recoded as (5) “other” for analyses. Primary analyses were descriptive and included χ² tests to assess differences in frequencies of behaviors between residents and preceptors in primary care, across ETS-related visits, and across settings. Pearson correlations were used to assess attitude-behavior relationships. A priori significance was set at P < .05. Results were entered and analyzed using the Statistical Package for the Social Sciences version 11.0 (SPSS Inc., Chicago, Ill). Surveys with incomplete answers were included in the analyses and denominators were adjusted accordingly.

**RESULTS**

Sixty-six residents across all years of training (approximately 60% of all pediatric residents) and 27 preceptors (70% of all preceptors) responded to the survey. Almost all respondents (93%) reported that they received <2 hours of smoking cessation training during residency.

**ETS-Related Practice in Primary Care Clinics**

Preceptor and resident reports of ETS practices in clinic visits were similar across assessment and advice behaviors except for two items. Chi square analyses indicated differences between groups in frequency of ETS exposure assessment during clinic visits for asthma or LRTI (χ² = 12.41, P < .05). For example, 70% of residents versus 42% of preceptors “always” asked about ETS during these visits. Conversely, for clinic visits in general, there were group differences in advising smoking parents about creating a smoke-free home (χ² = 23.25, P < .01) with 69% of preceptors versus 19% of residents stating they “always” advise smoking parents to create a smoke-free home. Otherwise, group differences across action categories were not significant, thus, we collapsed data between groups to illustrate in Figure 1 the specific ETS practices of all pediatricians in primary care.

Respondents most frequently engaged in four ETS action categories based on the frequencies of “always” or “often” asking about ETS during well child visits and sick visits for asthma or LRTI as well as advising smoking parents about creating a smoke-free home or quitting smoking. However, these frequencies are far below the recommended consistent courses of action. Even when parents were interested in smoking cessation, nearly all respondents reported that they neglected to provide standard advice, (eg, identifying triggers, establishing quit-dates, providing referrals, and arranging follow-up to monitor parents’ smoking behavior). Respondents also reported infrequently asking about ETS during otitis visits.
Resident Practices across Clinical Settings

Figure 2 shows residents’ tobacco intervention behaviors across clinical settings (assessing attending physician actions across settings was beyond the scope of this study). Residents “often” or “always” explained hazards of ETS to smoking parents more frequently in primary care versus inpatient ($\chi^2 = 28.94, P < .01$) and ED units ($\chi^2 = 23.77, P < .001$). Similarly, albeit much less frequently, residents “always” provided smoke-free home advice more often in primary care and inpatient units than in the ED (clinic vs ED, $\chi^2 = 16.48, P < .001$). Respondents also advised smoking parents to quit smoking more frequently in primary care versus inpatient settings ($\chi^2 = 37.62, P < .001$) and the ED ($\chi^2 = 29.85, P < .001$).

Beliefs and Attitudes

More than 75% of respondents agreed that ETS is “one of the most important health hazards for children,” and 95% believed it is an “extremely serious concern for patients with asthma.” Yet, only 55% agreed that they were “very comfortable” with their “knowledge about the effects of ETS.” Many respondents (51%) also reported believing they were ineffective in reducing their patients’ ETS exposure, in providing advice about how to quit (61%), and in positively influencing a parent’s smoking behavior (54%). None believed they were “very effective” in any of these activities.

Pediatricians also reported a perceived conflict about their role in advising smoking parents about smoking cessation. Most pediatricians (82%) agreed they should “help parents quit smoking;” however, most stated they do not have enough “time” (69%) or “training” (79%) to talk about tobacco issues. Almost all (89%) stated they were “not familiar with the resources available for parents interested in quitting.” Most pediatricians (53%) also believed that “parents are not interested in hearing about smoking cessation from pediatricians.” Pediatricians’ open-ended responses about their thoughts and feelings when entering a room and smelling tobacco smoke fell into four categories: 33% reported visceral negative responses (eg, “Yuck, I can’t breathe”); 37% reported feeling annoyance or anger toward the parent (eg, “I can’t believe that the parent smoked right before coming here”); 9% reported helplessness and dismay (eg, “Wish they would quit . . . I can’t do anything about it”); and 16% reported actions to intervene (eg, “I need to do something about this . . . .”).
Bivariate Pearson $r$ correlations indicated that differences in attitudes toward parental smoking did not relate to a number of tobacco intervention-related behaviors. For example, residents with greater negative attitudes toward parent smokers were not less likely to ask about ETS, advise parents to establish a smoke-free household or to quit smoking, assess willingness to quit smoking, or provide advice on how to quit than residents with less negative attitudes toward parent smokers. However, there was a relationship between intervention-oriented attitudes and reported confidence in helping parents create smoke-free homes ($r = .31, P < .01$). Pediatrics were less likely to assess readiness to quit smoking if they believed a handout about ETS ($r = .27, P < .01$) or literature on how to quit ($r = -.22, P < .05$) would be helpful to smoking parents. Also, the belief that ETS is “one of the most serious health hazards for children,” was related to interest in learning more about how to help parents quit smoking ($r = .31, P < .01$). This belief also correlated with beliefs that “it is a pediatrician’s role to help parents quit smoking” ($r = .24, P < .05$), that “a handout on ETS would be very helpful” ($r = .31, P < .01$); and that “lack of proper documentation is a big problem in helping parents quit smoking” ($r = .26, P = .01$). Finally, the concern that one does not have enough training in advising parents to quit smoking was related to feeling uninformed about ETS resources ($r = .33, P < .01$).

**Practice and Tobacco Training—Behavior Relationships**

Among all respondents, years of practice ranged from 1 to 25 years (mean = 4.80, SD = 5.61), with mean tobacco training in residency = 1.37 hours (SD = .63). Years of practice was significantly related to frequency of providing smoke-free home advice ($r = .22, P = .03$); cessation advice ($r = .33, P = .002$); cessation referrals ($r = .33, P = .002$); and explanation of ETS hazards ($r = .26, P = .04$). Years of practice also related to the following attitudes: “It is my role to help smoking parents quit” ($r = .33, P = .001$); “I am comfortable helping parents create a smoke-free home” ($r = .21, P = .04$); and “I am familiar with smoking cessation resources” ($r = .22, P = .02$). No significant correlations emerged between tobacco training and either actions or attitudes, perhaps because of the restricted range of training hours. However, trends emerged between tobacco training and frequency of assessing parent readiness to quit ($r = .20, P = .07$) and explaining ETS dangers in the ED ($r = .22, P = .08$).

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**Figure 2.** Percent of pediatric residents performing each ETS action “often” or “always” in different settings when learning that a parent smokes. Statistically significant differences among settings ($\chi^2, P < .01$). [Often], [Always].

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DISCUSSION

This study provides a distinct view of pediatrician attitudes and actions associated with parent smoking and child ETS exposure. These data suggest an opportunity to improve pediatrician ETS intervention behavior given that too few pediatricians are following best practice guidelines for addressing parental smoking. For example, only 75% of pediatricians in this sample agreed that ETS is one of the most important health hazards for children, and when pediatricians identified a parent smoker, they rarely intervened beyond brief advice to eliminate children’s ETS exposure or to quit smoking—they typically did not assess willingness to quit, provide advice about how to quit, or arrange follow-up. Such omissions occurred across treatment settings. Pediatricians were more likely to assess ETS for patients with asthma or LRTI than for other ETS-related illnesses, as expected. However, it is concerning that only 13% of respondents “always” asked about ETS during otitis visits when ETS is one of the leading causes of otitis.25

Among respondents’ primary reasons for inconsistent ETS intervention was lack of training. This reason suggests that the average of 1.4 hours of tobacco training reported in this sample may be grossly insufficient to promote routine smoking intervention. Even though practice years influenced some specific actions, data indicated that general pediatric experience is not sufficient to promote full adherence to tobacco guidelines. Thus, it appears that preceptors as well as residents would benefit from more thorough tobacco intervention training. Other key barriers to ETS intervention included lack of time, lack of knowledge about appropriate, intensive tobacco intervention resources, and lack of confidence in their tobacco intervention skills. To a degree not documented previously, pediatricians appeared very frustrated with parents who smoke and were pessimistic about their ability to help them change. However, our analyses suggest that negative attitudes toward parent smokers did not significantly affect physician practices.

All barriers described herein can be addressed through comprehensive training. Previous research suggests that training directly relates to physicians’ smoking cessation counseling self-efficacy and effectiveness,26,27 and that self-efficacy can improve pediatrician tobacco guideline adherence.26 Our data support the assertion that tobacco intervention self-confidence may improve the frequency of ETS-related actions. In our sample, pediatricians expressed general interest in learning more about strategies to reduce patients’ ETS exposure and in being able to provide smoking parents with useful information.

Transdisciplinary Training

The multi-determined nature of chronic behavioral health problems, such as smoking, requires that practitioners promote the implementation of broad, comprehensive treatments that blend disciplinary perspectives. Previous articles have described training for transdisciplinary (TD) scientists in approaching public health problems.28 The theses of these articles can be extended to training for practitioners who address public health problems at an idiographic level. Specific to pediatrician ETS training, recent research supports this assertion.29 In a recent study by Collins and colleagues,27 pediatric residents were provided multidimensional training including didactics, problem-solving, patient education materials, and clinical reminders for guideline adherence. Residents who were trained with this approach compared with nontrained residents were more likely to ask parents about their patients’ ETS exposure, to advise parents to cut down or to quit smoking, to help set a quit-date, and to provide ETS-specific follow-up. Moreover, follow-up was facilitated because trained residents were more likely to record history of passive tobacco exposure in the medical record.27 A TD training approach integrating disciplinary approaches could address barriers to effective, brief ETS intervention by suggesting ways to offload the burden of intensive intervention components to specialists and by boosting pediatrician confidence in the effectiveness using brief behavioral advice and follow-up.

Limitations of this study include the lack of respondent demographic data collected through the anonymous survey process. We opted not to include these items in favor of maximizing response validity by protecting the identity of residents, many of whom felt their responses might be evaluated as part of their training program. As a consequence, it is impossible to assess potential biases in resident versus preceptor behaviors. We also were unable to obtain information on nonrespondents. Without these data, it is difficult to determine the generalizability of our results; however, we feel that the issues identified in the survey parallel similar issues that can shape training at other academic pediatric health systems.30 Furthermore, respondents’ recall rates across different settings may be influenced by training status or even by the other questions on the survey in ways that this study could not measure, and our results were vulnerable to respondent bias toward inflating socially desirable responses.20,31 Future studies can address these limitations and better elucidate how pediatricians’ attitudes and behaviors could be influenced by pediatrician versus patient demographic characteristics. Other measurement-related limitations included the typical challenges with open-ended response coding. However, the investigators employed standard coding procedures with high reliability, and these results can inform the construction of future instruments to better ascertain physician attitude–behavior relationships.

Another limitation was that we only collected data related to acute illnesses known to be related to or exacerbated by ETS. Aside from asthma, we did not query actions with ETS-related chronic illness or behavioral presentations (eg, cancers, heart disease, attention deficit hyperactivity disorder), nor did we collect data from pediatric specialty clinics (eg, oncology, otolaryngology, cardiology, etc). To our knowledge, no study has examined such pediatrician tobacco intervention practices, therefore leaving that area open for study. We also did not assess nursing staff adherence, as this information was
beyond the scope of the study. Future studies should examine this issue and whether a clinic-team approach to ETS exposure enhances guideline adherence.

A large body of research points to pediatricians’ influence on smoking parents, particularly in helping them seriously consider smoking behavior change. This study demonstrated key areas where pediatricians can improve their tobacco intervention actions with parents, and the results delineated opportunities for training strategies that could maximize pediatricians' effectiveness with reducing ETS. It is likely that just improving ETS knowledge and intervention skills with smoking parents will not guarantee improved adherence to tobacco intervention guidelines when barriers to action, such as time constraints, exist. However, given the deficits in pediatricians’ ETS knowledge and ETS-reduction actions suggested in this study, improving training to enhance knowledge and tobacco intervention skills is a good starting point that in the end could have a wide, pediatrician-lead public health impact.

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Sulfonylurea-Responsive Diabetes in Childhood

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We describe a family in which 3/6 siblings had transient, relapsing neonatal diabetes. The father and another sibling had diabetes diagnosed at 20 and 9 years old, respectively. All affected individuals carried the same KCNJ11 gene mutation. In all, sulfonylurea treatment permitted cessation of insulin treatment, with improved glycemic control. (J Pediatr 2007;150:553-5)

Neonatal diabetes mellitus, defined as insulin-requiring hyperglycemia within the first month of life, is rare (incidence ~1/400,000 neonates). In about half, diabetes is transient (TNDM, OMIM 601410), resolving within several months. In most of these, alterations in chromosome 6q24 were found, although activating mutations in KCNJ11 and ABCC8 were reported in some. Most patients with TNDM will relapse during childhood or adolescence.

KCNJ11 encodes Kir6.2, the pore-forming subunit of the adenosine triphosphate–sensitive potassium channel (KATP), which plays a critical role regulating glucose-stimulated insulin secretion. A broad spectrum of phenotypes has been ascribed to KCNJ11 mutations. Inactivating mutations cause hyperinsulinemic hypoglycemia of infancy. The common polymorphism E23K is associated with increased risk of type 2 diabetes. Activating mutations cause TNDM, relapsing TNDM, permanent neonatal diabetes mellitus and DEND syndrome (developmental delay, epilepsy, neonatal diabetes).

More than 20 KCNJ11 activating mutations have been described. Most patients carry de novo mutations; only a few multiplex families were reported. Identification of KCNJ11 mutations has important therapeutic implications because most mutant channels can be closed by sulfonylurea and glinide, insulin secretagogues in common clinical use.

We report on an Arab-Muslim family with 5 diabetic individuals, all initially treated with insulin. An activating KCNJ11 mutation was identified, and all were transferred to oral hypoglycemic agents, with markedly improved glycemic control.

CASE REPORTS

The clinical characteristics of the patients with diabetes are shown in Figure 1. The proband (sibling 1) was born at term, appropriate for gestational age. Insulin treatment was initiated immediately on diagnosis of diabetes mellitus at age 9 years. The proband's parents are second-degree cousins. The father had development of diabetes at age 20 years. Currently he is overweight (body mass index: 29.4 kg/m²), having gained considerable weight over the previous 5 years.

Three of the proband's siblings (siblings 2 to 4) were diagnosed with diabetes during the first 10 days of life. They all were appropriate for gestational age. Insulin treatment was started immediately but could be withdrawn at ~4 months of age. Diabetes recurred at 12 and 9 years of age in siblings 2 and 4, respectively, and insulin treatment was reinstated. In sibling 3, transient episodes of hyperglycemia were noted from age 6 years during intercurrent illnesses or systemic glucocorticoid treatment, and, since the age of 10, intermittent insulin therapy was given for symptomatic hyperglycemia.

None had documented diabetic ketoacidosis. The proband's mother and 2 other siblings (sib-5 and sib-6) never had any documented or suspected hyperglycemia. The maternal grandfather was reported to have insulin-treated diabetes, diagnosed at age 45 years.

RESULTS

Direct sequencing of KCNJ11 revealed a heterozygous mutation, E227K, in the proband. Polymerase chain reactionrestriction fragment length polymorphism (PCR-
RFLP) analysis of DNA from the rest of the family confirmed that the father and siblings 2 to 4 are also heterozygous for the same mutation; whereas the proband’s mother and unaffected siblings (III-5, 6) were mutation negative (Figure 1). All diabetic family members tested negative for all autoantibodies tested (anti-glutamic acid decarboxylase, anti-islet cell, anti-thyroid peroxidase, anti-thyroglobulin, anti-endomysial, and anti-gliadin), although these were tested at the time of this study and not at diagnosis.

Basal c-peptide levels were in the low-normal range in 3 of 4 diabetic siblings (Figure 1). In sibling 2, a standard mixed meal (1 kcal/kg Nutren; Nestlé, Glendale, CA) test was performed. Pretreatment with a single dose of repaglinide 1 mg resulted in decreased glucose and increased C-peptide levels 2 hours after meals (287 vs 328 mg/dL glucose; 4.0 vs 1.8 ng/mL C-peptide, in treatment and control test, respectively).

Glycemic control was markedly improved in all affected individuals after substitution of glyburide for insulin treatment (Figure 1). HbA1c levels decreased from 10.4 ± 2.4 to 6.1 ± 0.6 (mean ± SD, P = .01, paired Student’s t test). Continuous glucose monitoring (Medtronic, Northridge, CA) was performed on sibling 4, confirming markedly improved glycemic control on glyburide when compared with insulin (Figure 2).

**DISCUSSION**

We describe a family with 5 individuals with diabetes diagnosed between the ages of <10 days and 20 years. A single, previously described, KCNJ11 missense mutation gene co-segregated with disease. The possibility that the father or proband had undiagnosed hyperglycemia in the neonatal period cannot be entirely excluded, but this appears very unlikely, since infants with neonatal diabetes are critically ill, with severe dehydration, weight loss, and failure to thrive.

The clinical severity of the diabetes was also variable. The insulin and glyburide dose requirement was remarkably similar in 4 patients; however, 1 patient (sib-3) had particularly mild disease, requiring very low doses of either drug. Contrary to previous reports, none of our patients were small for gestational age at birth, perhaps because of the relatively mild effect that this mutation appears to have on insulin secretion.

Yorifuji et al recently reported a family with 4 diabetic patients in 3 generations with a single KCNJ11 mutation, C42R, which was shown to increase the channel’s open probability but also to decrease its membrane expression, thus limiting its effect. Three of these patients had disease onset after the neonatal period (3, 22, and 26 years of age).
The family reported here confirms this previous report that activating KCNJ11 mutations can present as a maturity onset diabetes of the young (MODY) phenotype: autosomal dominantly inherited, sulfonylurea-responsive diabetes mellitus. The cause of the marked variability in clinical severity seen in our patients and those reported by Yorifuji et al is not clear, and genetic or environmental factors may contribute.

Oral sulfonylurea can replace insulin in most patients with activating KCNJ11 mutations. Our finding that a single dose of repaglinide, a short-acting specific KATP channel inhibitor, increased insulin secretion suggests that this class of drugs may also be effective for long-term treatment in these patients. In our patients, transfer from insulin to sulfonylurea treatment resulted in marked improvement in diabetes control. In the family reported here, the father failed to adequately respond to sulfonylurea treatment alone. This is likely to be due to his central obesity and presumed insulin resistance. The addition of the insulin sensitizer, metformin, resulted in markedly improved glycemic control.

The change to oral sulfonylurea treatment dramatically improved our patients’ quality of life and glycemic control. Therefore it is of utmost importance to identify patients with KCNJ11 mutations as early as possible. Clearly, all patients with transient or permanent diabetes appearing before 6 months of age should undergo genetic evaluation. What about patients diagnosed later? Although Flanagan et al report that none of their patients with disease onset after 26 weeks of age had a KCNJ11 mutation, we show that this can occur in the rare patient. Large-scale studies are needed to define the cost and benefit of screening all antibody-negative new-onset diabetics for KCNJ11 mutations. Until these studies become available, it seems prudent to consider genetic evaluation for young patients with new-onset, antibody-negative diabetes.

We thank the Wolfson Hospital Diabetes Unit nursing staff for their excellent patient care and other assistance.

REFERENCES
Mutations in Bile Salt Export Pump (ABCB11) in Two Children with Progressive Familial Intrahepatic Cholestasis and Cholangiocarcinoma

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Fatal peripheral cholangiocarcinoma developed in 2 girls with progressive familial intrahepatic cholestasis, ABCB11 mutations, and absent bile salt export pump (BSEP) expression. BSEP deficiency may cause cholangiocarcinoma through bile-composition shifts or bile-acid damage within cells capable of hepatocytic/cholangiocytic differentiation. This observation suggests the need for hepatobiliary-malignancy surveillance and early consideration for liver transplantation. (J Pediatr 2007;150:556-9)

We report 2 non-related girls with chronic cholestasis caused by mutations in ABCB11, encoding bile salt export pump (BSEP), who lacked immunohistochemically demonstrable BSEP. Both died of peripheral cholangiocarcinoma arising against a background of intrahepatic cholestasis, inflammation, and fibrosis. Our findings identify a novel risk for biliary-tract epithelial malignancy and indicate the need for close monitoring of children with severe BSEP deficiency and early intervention with liver transplantation.

CASE REPORTS

Patient A, a Hispanic girl, had hyperbilirubinemia (conjugated bilirubin level, 4.0 mg/dL; expected, <0.1 mg/dL) and low serum concentrations of gamma-glutamyl transpeptidase activity (S$_{/}^{\gamma}$GT) (65 IU/L; expected, 10-160) in infancy. Parental consanguinity and a family history of hepatobiliary disease were denied. Urinary bile-acid analysis via fast atom bombardment ionization-mass spectrometry (FAB-MS; Prof KDR Setchell) excluded inborn errors in cholesterol or bile-acid synthesis. Percutaneous liver biopsy (2 months) revealed giant-cell hepatitis and mild portal-tract fibrosis (Figure 1A). Intractable pruritus developed; with follow-up liver biopsies, persistent cholestasis and bridging fibrosis (2 years) and transition to biliary cirrhosis (3 years) were identified. Partial external biliary diversion (3 years), with short-term relief of pruritus, was complicated by recurrent intussusceptions, bowel obstruction, and fluctuating stomal drainage. During evaluation of fever and gastrointestinal bleeding (4 6/12 years), multiple intrahepatic lesions were revealed with ultrasound scanning. Serum concentrations of CA 19-9 and alpha-fetoprotein were 132 U/mL (expected, <33) and 61.5 ng/mL (expected, <10), respectively. Biopsy found cholangiocarcinoma (Figure 1B). Chemotherapy was discontinued because of hepatic decompensation. The parents declined autopsy (4 11/12 years).

Patient B, a non-Hispanic Caucasian girl, exhibited icterus and pruritus in infancy. Her home was approximately 150 miles away from that of patient A. Parental consanguinity and a family history of hepatobiliary disease were denied. The pruritus responded to neither phenobarbital nor cholestyramine. S$_{/}^{\gamma}$GT was not measured; urine was not screened for abnormal bile acid species. Initial liver biopsies (at age 2 and 8 months) found giant-cell hepatitis. Further biopsies revealed bland intralobular cholestasis with minimal chronic inflammation and paucity of intrahepatic bile ducts (11 months–5 years; Figure 1C). Fibrosis progressed from centrilobular involvement to portal-central bridging, with clinical splenomegaly (20 months). Imaging studies suggested a left hepatic lobe lesion (7 9/12 years). Serum tumor-marker concentrations were not determined. Hepatic re-
lymphatics. H&E, original magnification 160×. Confirmed at necropsy (8 2/12 years), infiltrates connective tissue within D, Patient B, left hepatic lobectomy (7 9/12 years). Cholangiocarcinoma, and minimal inflammation are seen. H&E, original magnification 200×. Bile duct; intralobular cholestasis, pseudoacinar dilatation of bile canaliculi, Patient B, liver biopsy (11 months). A small portal tract (arrow) lacks a bile duct; intralobular cholestasis, pseudoacinar dilatation of bile canaliculi, and minimal inflammation are seen. H&E, original magnification 200×. D, Patient B, left hepatic lobectomy (7 9/12 years). Cholangiocarcinoma, confirmed at necropsy (8 2/12 years), infiltrates connective tissue within lymphatics. H&E, original magnification 160×. Figure 1. Histologic stages toward cholangiocarcinoma. A, Patient A, initial liver biopsy (2 months). Note extensive giant-cell transformation of hepatocytes with portal tract expansion by proliferating ductules, a mixed inflammatory infiltrate, and fibroplasia. Hematoxylin/eosin (H&E), original magnification 250×. B, Patient A, biopsy of liver lesion (4 6/12 years). Neoplastic bile duct growth (cholangiocarcinoma) in a dense, fibrous, desmoplastic background. Giant-cell change of hepatocytes no longer is seen, but cholestasis persists. H&E, original magnification 125×. C, Patient B, liver biopsy (11 months). A small portal tract (arrow) lacks a bile duct; intralobular cholestasis, pseudoacinar dilatation of bile canaliculi, and minimal inflammation are seen. H&E, original magnification 200×. D, Patient B, left hepatic lobectomy (7 9/12 years). Cholangiocarcinoma, confirmed at necropsy (8 2/12 years), infiltrates connective tissue within lymphatics. H&E, original magnification 160×.

The brother of patient B also had chronic cholestasis. “Neonatal hepatitis” without coarsely granular bile (“Byler bile”) was found by means of a liver biopsy (8 months) with ultrastructural study. Analysis of urine excluded a disorder of cholesterol or bile-acid synthesis. Treatment for seizures after a head injury included phenytoin; SyGT with phenytoin therapy was 30 IU/L, despite conjugated hyperbilirubinemia (3.2 mg/dL). Malignancy was not identified before loss to follow-up (19 years).

Specialty immunohistologic and genetic studies were conducted under an institutionally approved protocol. Blood for DNA analysis was collected from patient A and her parents and from the brother of patient B. Mutational analysis, with microsatellite typing for both intragenic and flanking microsatellite marker loci, was performed as described. 1 BSEP and multidrug resistance-associated protein 2 (MRP2) expression was evaluated, as described, in archival formalin-fixed, paraffin-embedded liver samples of patients A and B and of the brother of patient B, using a rabbit polyclonal anti-BSEP antibody and a mouse monoclonal anti-MRP2 antibody. 1 Archival liver samples of both patients also were evaluated immunohistochemically, using routine techniques, for expression of cytokeratin 7 and of hepatocyte-associated antigen OCH1E5.

Molecular analysis in patient A and her parents identified the ABCB11 mutation c.1723C>T; p.Arg575X, previously described, 2 in apparently homozygous state in patient A and in heterozygous state in her mother. The father of patient A did not carry the c.1723C>T mutation, and non-paternity was not suspected; hemizygosity was postulated in patient A. This was confirmed by linkage analysis using microsatellite markers within and adjacent to the ABCB11 locus. A deletion of at least 12.5 Mb (outermost markers, D2S156 and D2S326) was identified in 1 copy of chromosome 2 in both patient A and her father. The exact breakpoints were not determined; however, they lay well beyond the coding region and promoter of ABCB11. These changes were predicted to cause total absence of functional BSEP in patient A.

Because peripheral-blood DNA from patient B was not available, blood was obtained from her brother, who had low-SyGT intrahepatic cholestasis without hepatobiliary malignancy. Compound hemizygosity was found for the ABCB11 mutations c.890A>G; p.Gln297Gly, previously described, 2 and c.2343+1 G>T, a novel splice-site change. These were predicted to cause marked deficiency of functional BSEP in patient B and her brother.

Immunohistochemical study found no expression of BSEP in non-tumoral liver from patient A (not shown), patient B (Figure 2A), or the brother of patient B (not shown). The structurally related canalicular transporter MRP2, assessed to evaluate tissue preservation and the specificity of any abnormalities in BSEP immunoreactivity, was normally expressed in liver of patients A (not shown) and B (Figure 2B) as well as in liver of the brother of patient B (not...
shown). Controls marked appropriately (Figures 2A and B, insets). These findings supported the diagnosis of severe BSEP deficiency.

At necropsy, non-neoplastic liver of patient A contained many cells which co-expressed cytokeratin 7 and OCH1E5. Rare such cells were seen among cholangiolar epithelium in liver obtained at biopsy from patient B the year before death. Neither cholangiocarcinoma specimen expressed these antigens.

**DISCUSSION**

Hepatocyte canalicular-membrane transporters include BSEP for amidated bile acids, MRP2 for sulfated and glucuronidated anions, multidrug resistance protein 1 for organic cations, multidrug resistance protein 3 for phosphatidylcholine, and anion-exchanger 2, a bicarbonate/chloride exchanger. Anion-exchanger 2 and MRP2 drive bile-acid independent bile flow; BSEP drives bile-acid dependent flow. Although in mice the loss of the BSEP orthologue Bsep reduces bile-acid secretion to 30% of reference range values, complete loss of BSEP in humans results in negligible bile-salt concentrations (<1% of reference range). Patients with severe BSEP deficiency have progressive intrahepatic cholestasis with low SγGT and high serum bile-acid concentrations and are at risk of hepatocellular carcinoma.

We describe 2 children with peripheral cholangiocarcinoma arising against a background of intrahepatic cholestasis caused by BSEP deficiency. Cholangiocarcinoma is rare in childhood. Its incidence is higher in adults, in whom it is associated with choledochal cysts, Caroli’s disease, primary sclerosing cholangitis, and infestation with *Clonorchis sinensis* or *Opisthorchis viverrini*. Children with cholangiocarcinoma and biliary-tract anomalies reported include a 15-year-old girl with multiple intrahepatic and extrahepatic biliary cysts and a 3-year-old boy and an 11-year-old girl with extrahepatic biliary atresia. Children with X-linked immunodeficiency and hyperimmunoglobulinemia M also are at risk for cholangiopathy and cholangiocarcinoma, hypothesized to arise from chronic opportunistic cholangitis caused by organisms such as cryptosporidium. Association of cholangiocarcinoma with defective hepatocellular bile-acid secretion has not been recognized.

Chronic inflammation of the biliary tract has been thought to underlie increased susceptibility to cholangiocarcinoma in various conditions, including biliary-tract anomalies. Bile acids are corrosive, but biliary epithelium obviously resists modest concentrations of bile acids. How loss of functional BSEP, with decreased biliary bile-acid concentrations, might predispose patients to cholangiocarcinoma via inflammation is not evident. Although bile acids stimulate cholangiocellular proliferation, this may not pertain to patients with BSEP deficiency.

Loss of functional BSEP results in intrahepatic accumulation of bile acids, however, with injury to cellular constituents, including DNA. Bile acids induce mutation via reactive oxygen and nitrogen species generated from detergent effects on membrane enzymes. Damage induced by intrahepatic accumulation of bile acids is hypothesized to lead to hepatocellular carcinoma. It also may induce disorderly proliferation of stem-cell elements that can differentiate along biliary-epithelium lines. Cells with immunophenotypic features associated with, but not diagnostic of, such elements were found in non-malignant liver of both children.

Alternatively, bile acids may have no direct role in causing cholangiocarcinoma in these patients. The incidence of cholangiocarcinoma is rising in many adult populations perhaps because of environmental factors. Many environmental noxa are excreted in bile. With deficiency of BSEP, decreased biliary flow may both increase concentrations of potential carcinogens in bile and prolong transit time of bile between canaliculus and duodenum, potentiating cholangiocarcinogenesis. Reporting only 2 children who did not live near each other and presented >10 years apart, however, we can suggest no particular exposure.

We conclude that evaluation in low-SγGT cholestasis, after exclusion of errors of bile-acid synthesis, should include histologic and immunohistochemical studies, followed by genetic analysis. Children with BSEP deficiency require close surveillance for hepatobiliary malignancy to permit salvage by liver transplantation.

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50 Years Ago in The Journal of Pediatrics

THE COMMUNITY RESPONSIBILITY FOR THE CARE OF THE MENTALLY RETARDED

Yannet H. J Pediatr 1957;50:397-403

In the late 50s and for several subsequent decades, many, if not most, mentally retarded children and adults were housed in large state institutions often referred to as “training schools.” Indeed, it was not uncommon for pediatricians to recommend to families of infants with conditions known to be associated with mental retardation that their infants be institutionalized immediately after birth. In this article, Yannet points out that the “training schools” so prevalent at the time were rarely fulfilling the objectives implied in their titles but were instead simply segregating the moderately and severely retarded from their families and communities. He proposed a system of community-based programs for the care of the mentally retarded to include day-care centers or specialized kindergartens, specialized classes and facilities in the public schools, and sheltered workshops. For the most severely retarded and handicapped patients, those who required residential care, he recommended the development of a network of smaller decentralized facilities that would allow patients to be cared for closer to their families. Yannet recognized that this blueprint of a comprehensive program for the community care of mentally retarded children would not be achieved in a short time in most of the country but would require an enlightened public concern, a well-oriented parent group, and the interested, public-spirited, and enthusiastic participation of professional colleagues.

Fortunately, 50 years later, much of Yannet’s vision has become a reality. The vast majority of mentally retarded children are cared for, at least through childhood, at home and receive an education through the public school system in their home community. Early intervention programs and developmental preschools prepare mentally retarded children for entry into special education in the public school system. Sheltered workshops and groups homes do exist in many communities for adults with mental retardation, although many more such facilities are needed. There remains a shortage of decentralized care facilities for the most severely handicapped infants and children who require specialized care that cannot reasonably be provided in the home, but some such facilities can be found. No doubt there is more to be done. But we have come a long way—and life is better for us all because of it.

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Mutations in Bile Salt Export Pump (ABCB11) in Two Children with Progressive Familial Intrahepatic Cholestasis and Cholangiocarcinoma

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Morphea (Localized Scleroderma)

A 6-year-old girl presented with an 8-month history of swelling and progressive redness underneath her left eye. Previous treatment with antibiotics and topical corticosteroids had no effect. Examination revealed an erythematous skin lesion extending from the lower eyelid to the cheek. The affected skin felt slightly thickened and was shiny in some areas. Most notably, most of the lower eyelashes were gone (Figure 1). Ophthalmologic examination was normal. Histopathologic examination of a skin biopsy specimen revealed dermal edema with a perivascular and interstitial mixed inflammatory cell infiltrate and degeneration of collagen fibrils, consistent with the clinical diagnosis of early-stage morphea (localized scleroderma).1 Thermography showed a “hot” lesion, consistent with active inflammation (Figure 2).2

Within 6 weeks of treatment with pulsed intravenous methylprednisolone, followed by oral prednisolone on a reducing regimen and weekly methotrexate, the skin lesion had completely resolved. Three months later, eyelash regrowth had occurred, and thermography revealed a cooling of the lesion. The patient will continue on weekly methotrexate for at least 2 years.3 If untreated, this condition would progress and ultimately cause disfiguring facial asymmetry.

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Figure 1. Erythematous, slightly shiny skin lesion with mild swelling extending from the left lower eyelid to the cheek.

Figure 2. Thermal image showing the “hot” affected area, consistent with active inflammation.
Physical activity program for preschool children fails to reduce body mass index


**Question** Among young children, does a physical activity intervention reduce body mass index?

**Design** Cluster randomized, controlled, single-blinded trial over 12 months.

**Setting** 36 nurseries in Glasgow, Scotland.

**Participants** 545 preschool children, mean age 4.2 years at baseline.

**Intervention** Enhanced physical activity program in nursery (three 30-minute sessions a week over 24 weeks) plus home-based health education aimed at increasing physical activity through play and reducing sedentary behavior.

**Outcomes** Body mass index, expressed as a standard deviation score relative to UK 1990 reference data. Secondary measures were objectively measured physical activity and sedentary behavior, fundamental movement skills, and evaluation of the process.

**Results** Group allocation had no significant effect on the primary outcome measure at 6 and 12 months or on measures of physical activity and sedentary behavior by accelerometry. Children in the intervention group had significantly higher performance in movement skills tests than control children at 6 month follow-up ($P = .0027$; 95% confidence interval 0.3-1.3) after adjustment for sex and baseline performance.

**Conclusions** Physical activity can significantly improve motor skills but did not reduce body mass index in young children in this trial.

**Comment** The obesity pandemic is threatening the current generation of children with shorter life expectancies than those of their parents. There is a paucity of published data evaluating the effectiveness of local school-based programmatic and policy change interventions. Even fewer studies have addressed nutrition and physical activity improvements in preschool and child care settings. This study, by Reilly and colleagues, was rigorously designed to try to address this critical gap in the literature. However, the study's findings of a failure of the intervention to influence body mass index and, especially, physical activity levels seem contrary to much of the recent scholarship in this field. Several methodological weaknesses may explain the null findings, for example, insufficient intervention dose, less-than-ideal outcome measure selection, compromises to the fidelity of the intervention implementation to enhance generalizability and exportability, and inadequate power to detect modest effects in subsamples (sex and/or overweight status).

However, let's not miss the forest for the trees. These findings represent yet another demonstration of the weak and, at best, transient salutary behavioral effects of self-limited programmatic and primarily individual-level interventions, especially in the absence of anchoring structural or systemic changes. Widespread and comprehensive changes in social norms and values supporting physical activity engagement, and undermining prolonged sitting, must ultimately permeate school, family, and community settings. That said, early evidence provides reason for optimism that preschool settings can be useful as part of a comprehensive obesity prevention strategy. Their captive audiences represent an important segment of the youth population, worthy of continuing investment and investigation to identify successful intervention models.

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Antibiotics are effective in acute otitis media in children younger than 2 years with bilateral disease and in children with both otorrhea and acute otitis media


Question Are there subgroups of children who would or would not benefit more than others from treatment with antibiotics?

Design Meta-analysis of data from six randomized trials of the effects of antibiotics in acute otitis media.

Study Selection and Assessment Following a systematic search of the Cochrane library, PubMed database, EMBASE, and the proceedings of the international symposia on recent advances in otitis media, six trials were identified. All trials were assessed rigorously for quality.

Outcomes The primary outcome was an extended course of acute otitis media, which was defined as pain, fever, or both at 3 to 7 days.

Results Individual patient data from 1643 children from 6 months to 12 years of age were validated and reanalyzed. Significant effect modifications were noted for otorrhea, and for age and bilateral acute otitis media. In children <2 years of age with bilateral acute otitis media, 55% of controls and 30% on antibiotics still had pain, fever, or both at 3 to 7 days, with a rate difference between these groups of −25% (95% CI −36% to −14%), resulting in a number-needed-to-treat (NNT) of four children. We identified no significant differences for age alone. In children with otorrhea, the rate difference and NNT, respectively, were −36% (−53% to −19%) and three, whereas in children without otorrhea, the equivalent values were −14% (−23% to −5%) and eight.

Conclusions Antibiotics seem to be most beneficial in children <2 years of age with bilateral acute otitis media, and in children with both acute otitis media and otorrhea. For most other children with mild disease, an observational policy seems justified.

Comment Acute otitis media is usually a bacterial infection that is preceded by a viral upper respiratory tract infection. Evidence from systematic reviews, however, suggests that antibiotics provide only marginal benefit.1 Reliable identification of subgroups of children who do, and do not, benefit from treatment with antibiotics has not been straightforward because individual trials have been too small for valid and reliable subgroup analyses. This study is so far the best attempt to identify such subgroups of children by pooling the original data from several randomized trials and performing a meta-analysis of the individual patient data. Despite the large number of patients in the meta-analysis, only a limited number of subgroups were analyzed: age (<2 vs ≥2 years), bilateral acute otitis media (yes vs no), and concurrent otorrhea (yes vs no). Data were not provided for subgroups dichotomized on the basis of pain severity, amount of nasal discharge, cough, or fever. Indeed, the original trials included studies that had excluded children on the basis of severe symptoms, the child being too unwell, or recurrent acute otitis media. Thus, treatment of children without antibiotics should presumably be reserved for those with a mild general illness.2 This study shows that antibiotics are effective in acute otitis media in children <2 years of age with bilateral disease and in children with both otorrhea and acute otitis media.

REFERENCES

Hot air is an effective treatment for head lice


Question Among children with head lice, how effective is hot air at eradicating the lice and their eggs?

Design Observational trial.

Setting University of Utah.

Participants 169 elementary school children (>6 years of age) with head lice infestation.

Intervention Six different hot air treatment methods were tested. Follow-up inspections were performed on 11 subjects to evaluate whether the most successful method resulted in cure of the head louse infestation.

Outcomes Egg and louse mortality.

Results All 6 methods resulted in high egg mortality (>88%), but they showed more-variable success in killing hatched lice. The most successful method, which used a custom-built machine called the LouseBuster™, resulted in nearly 100% mortality of eggs and 80% mortality of hatched lice. The LouseBuster™ was effective in killing lice and their eggs when operated at a comfortable temperature, slightly cooler than a standard blow-dryer. Ten of 11 subjects were cured of head lice when examined 1 week after treatment with the LouseBuster™. There were no adverse effects of treatment.

Conclusions One 30-minute application of hot air is an effective, safe treatment for head lice, and one to which lice are unlikely to evolve resistance.

Comment Head lice is a common problem in children that is frequently seen in any pediatric practice and school. Head lice can be effectively treated with chemical shampoos such as pyrethrins or lindane, but developing resistance makes these
methods less effective. Based on observations made more than 60 years ago that hot air can effectively kill body lice, the investigators have tested six different methods of using hot air to eradicate head lice and their eggs. They used different techniques with a bonnet-style hairdryer, a handheld blow dryer, a wall-mounted dryer, and a custom-built high-volume, hot-air dryer named the LouseBuster™ (developed by study authors). A protocol was developed to standardize removal of head lice and eggs before and after the treatments on different sides of the head, and statistical power (>0.80 to detect a medium effect size \(d = 0.50\)) was calculated for each method. Each method effectively killed lice eggs (all >88%), but the effect on head lice (range, 10%-80%) and the reported discomfort (range, 11%-50%) varied widely. The LouseBuster™ with a specially designed hand-piece was the most effective (80% louse mortality, 98% egg mortality) and well-tolerated (11% reported discomfort) method. There are some caveats to these results. First, the study was small, and the participants were not randomized. In addition, no direct comparison was made to standard chemical shampoos, which have been previously reported to cause 60% mortality of eggs in situ. Thus, it is difficult to determine if this new method offers any advantage, although the egg mortality is higher in the present study. Although the LouseBuster™ seems to be very effective and could be used by trained personnel in a variety of clinical settings (office, school, or day care), the 30-minute treatment time makes this method less practical, and potentially costly. Further randomized studies with shorter treatment times and comparisons with standard therapies will be useful as we decide whether this innovative treatment should be implemented more widely.

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Duct tape may not be superior to placebo in the treatment of common warts


Question Among children with verruca vulgaris infection, is duct tape more likely than placebo to eradicate the wart?

Design Randomized placebo-controlled trial.

Setting Three primary schools in Maastricht, the Netherlands.

Participants 103 children 4 to 12 years of age with verruca vulgaris.

Intervention Duct tape applied to the wart or placebo (a corn pad [protection ring for clavi]), applied around the wart for 1 night a week. Both treatments were applied for a period of 6 weeks. Patients were blinded to the hypothesis of the study.

Outcomes Complete resolution of the treated wart.

Results After 6 weeks, the wart had disappeared in 16% of the children in the duct tape group compared with 6% in the placebo group \((P = .12)\). The estimated effect of duct tape compared with placebo on diameter reduction of the treated wart was 1.0 mm \((P = .02, 95\% \text{ confidence interval}, -1.7 \text{ to } -0.1)\). After 6 weeks, in seven children (21%) in the duct tape group, a surrounding wart had disappeared compared with nine children (27%) in the placebo group \((P = .79)\). Fifteen percent of the children in the duct tape group reported adverse effects such as erythema, eczema, and wounds compared with 0 in the placebo group \((P = .14)\).

Conclusions In a 6-week trial, duct tape had a modest, but nonsignificant, effect on wart resolution and diameter reduction when compared with placebo in a cohort of primary school children.

Comment Warts are common problem in primary care, and a quick, well proven, inexpensive treatment is not available. An earlier randomized, controlled trial compared duct tape with cryotherapy, showing duct tape to be beneficial.1 In contrast, the present study reports no significant difference in complete resolution of warts between the two groups. Coupled with complications of duct tape (15% developed skin reactions), the authors concluded that duct tape was ineffective in treating warts.

Several limitations in the study lead us to question this conclusion. First, considering epidemiological data showing that 30% of warts resolve without treatment by 32 weeks,2 the mean length of time that subjects had had their warts was quite long—34.2 weeks for the experimental group and 38.5 weeks for the control group. Also, many subjects had already tried another treatment. Therefore, subjects’ warts may be particularly resistant not only to spontaneous resolution but also to any treatment, and the subjects may not be representative of those who would likely consider the treatment in question. Second, the analysis included all subjects, even those who did not complete treatment. This intention-to-treat analysis was designed to produce conclusions that are more applicable to real-life situations. However, including in the analysis those who did not finish the treatment could dilute a positive effect. Third, the investigators had determined that a 30% effect size would be clinically meaningful, and they adjusted the sample size accordingly. Yet, some clinicians and wart-sufferers may feel that an even smaller effect size is clinically meaningful, given the feasibility of duct tape therapy. Thus, when 16% of the warts in the treatment group resolved, compared with 6% in the placebo group, the study was not powered to detect this smaller difference. Finally, subjects were followed for 6 weeks, which may have been too short a time to see the full effect of duct tape. At 6 weeks, the mean decrease in diameter of the treatment group warts was greater than that of the placebo group. If subjects had been followed for longer, a greater difference between the two groups might have been detected. Although the authors suggest that duct tape therapy is ineffective, further studies
that address the above limitations are needed before such definitive conclusions can be drawn.

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REFERENCES

ALSO NOTED

The purpose of this study was to evaluate the effectiveness of different vaccination schedules for the seven-valent pneumococcal conjugate vaccine. During the shortage of this vaccine in the US, large numbers of children received fewer than the three-shot primary series, and many did not receive the booster dose. Using a case-control design, these authors were able to show that the effectiveness of the vaccine against one or more serotypes among children who had received one or more doses of the vaccine was 96% for healthy children and 81% for children with underlying chronic conditions. They also documented that three doses plus the booster was more effective than the three primary doses alone (P = .032).


The goal of this study was to evaluate the utility of prolonged (>2 seconds) capillary refill time (pCRT) as a prognostic factor for mortality from malaria in endemic areas. The authors studied 2446 children who presented with severe malaria to a tertiary referral center in Ghana, West Africa. They examined 12 clinical and laboratory signs. Among this group of high-risk patients, pCRT had a sensitivity of 85% and a specificity of 28%, yielding likelihood ratios of 1.90 for the presence of pCRT and 0.84 for its absence. In addition, pCRT was found to be an independent risk factor for death, along with acidosis, coma, and respiratory distress. pCRT can be used as a marker for those children with more severe disease and those who could benefit from rapid administration of intravenous fluids.
In the article “Efficacy and Safety of Fluticasone Propionate Hydrofluoroalkane Inhalation Aerosol in Pre-school-age Children with Asthma: A Randomized, Double-blind, Placebo-controlled Study,” by Qaqundah et al, which appeared in the November 2006 issue of *The Journal* (J Pediatr 2006;149:663-70), on page 668, 2nd column, 2nd full paragraph, the sentence “For the children in the UC population, a plot of change in UC versus FP AUC_{last} revealed a $\chi^2$ value of 0.00928” should read “For the children in the UC population, a plot of change in UC versus FP AUC_{last} revealed a $r^2$ value of 0.00928 ($\chi^2$ should read $r^2$).

In the piece within the Current Best Evidence section, “A preparticipation screening program can decrease the incidence of sudden cardiac death among young athletes,” which appeared in the March 2007 issue of *The Journal* (J Pediatr 2007;150:319-20), the author is given as “Benjamin D. Levine, MD, University of Texas Southwestern Medical Center, Dallas, TX” and should read “John G. Frohna, MD, MPH, University of Michigan, Ann Arbor, MI.”
Selection bias and vitamin E status in cystic fibrosis

To the Editor:

We read with interest the report by Huang et al1 in which they evaluated vitamin E status and its determinants in a selected population of 69 children with cystic fibrosis (CF) at 13 CF centers in the United States. The authors described a relatively high frequency (48%) of elevated serum α-tocopherol and an even higher frequency (83%) of elevated ratio of serum α-tocopherol to serum cholesterol (E/Chol), with a very low frequency (4%) of low levels. Of these patients with CF, 91% had been routinely receiving vitamin E supplements (as recommended by the CF Foundation),2 with an average daily intake of 224 mg of total vitamin E per day. The authors conclude that most children with CF and current standards of care had normal or high vitamin E levels and few had low levels, and that the risks and benefits of high vitamin E levels are unknown and require attention. This cross-sectional study provides useful information about the specific population of children studied, but should not be generalized to the CF population at large for several important reasons.

The 69 patients in this study all underwent extensive dietary analysis and a fecal fat collection in the 13 centers. Thus, on average, only slightly more than 5 patients were evaluated at each center, hardly a representative sample of patients with CF for determining the nutritional status of the larger population of patients followed at these 13 centers. It can be presumed that these highly selected patients were chosen for this study because of their willingness to participate in research and their ability to conform to the requirements of the study, including fecal fat collection. Thus, it can be reasonably assumed that these patients adhered to their treatment regimens and represent the “best case” scenario for outcomes in CF. The authors failed to cite a previous prospective analysis of vitamin E status in patients with CF that we believe that supplementation to prevent vitamin E deficiency is essential in CF.

Finally, the higher percentage of patients with elevated vitamin E:cholesterol ratios in the report of Huang et al1 merits comment. Because patients with CF have low serum cholesterol levels for as-yet unknown reasons, it is possible that this ratio may not accurately reflect vitamin E status in CF. For example, in children with chronic cholestasis, the serum E:total serum lipid ratio outperforms the E:cholesterol ratio in identifying children with clinically proven vitamin E deficiency.3 Clearly, vitamin E:lipid ratios that incorporate more of the species of circulating lipids (either total lipids or cholesterol plus triglycerides) are more effective indices of vitamin E status than ratios that include only 1 lipid species. Thus, the significance of the elevated E:cholesterol ratios in CF remains to be determined.

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10.1016/j.jpeds.2007.01.010

REFERENCES

Reply

To the Editor:

We appreciate Dr Sokol’s comments in response to our recent article regarding vitamin E status in preadolescent children with cystic fibrosis, pancreatic insufficiency (PI), and with other recommended therapies. Thus, a more representative sample of patients with CF may show a considerably higher frequency of low vitamin E levels than that reported by Huang et al. In our study, we also observed that approximately 10% to 40% of patients at different ages had serum vitamin E above the NHANES 95th percentile for children. Although the clinical significance of mildly elevated serum levels of vitamin E are unknown, the devastating neurologic effects of chronic vitamin E deficiency have been well described in children with CF and other conditions.4 Thus, we believe that supplementation to prevent vitamin E deficiency is essential in CF.

Recently, the higher percentage of patients with elevated vitamin E:cholesterol ratios in the report of Huang et al1 merits comment. Because patients with CF have low serum cholesterol levels for as-yet unknown reasons, it is possible that this ratio may not accurately reflect vitamin E status in CF. For example, in children with chronic cholestasis, the serum E:total serum lipid ratio outperforms the E:cholesterol ratio in identifying children with clinically proven vitamin E deficiency.3 Clearly, vitamin E:lipid ratios that incorporate more of the species of circulating lipids (either total lipids or cholesterol plus triglycerides) are more effective indices of vitamin E status than ratios that include only 1 lipid species.

Thus, the significance of the elevated E:cholesterol ratios in CF remains to be determined.

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REFERENCES

Reply

To the Editor:

We appreciate Dr Sokol’s comments in response to our recent article regarding vitamin E status in preadolescent children with cystic fibrosis, pancreatic insufficiency (PI), and
mild-to-moderate lung disease. To address vitamin E status, we presented data using both serum vitamin E level and vitamin E:cholesterol ratio in 7- to 10-year-old children compared with healthy children of the same age from NHANES III. We agree with Dr Sokol that vitamin E supplementation to prevent deficiency is essential in CF care and is the reason for the low incidence of vitamin E deficiency seen in our preadolescent sample. We found that an unexpectedly high proportion of our subjects had high vitamin E levels on currently routine supplementation. We suggested that future dose and response studies are warranted to determine a more optimal level of vitamin E supplementation in children with CF.

Here we address the 3 issues that Dr Sokol raised: (1) the generalizability of the data and concern for selection bias, (2) differences between our findings and those of Feranchak et al., and (3) the strengths and weakness of various vitamin E biomarkers. We suggest that the data presented are generalizable to school-age preadolescent children with CF, PI, and mild to moderate lung disease. Subjects within the inclusion/exclusion criteria from each center were sorted into a random order and approached to join the 2-year study of nutrition and lung function. Although we recruited a limited number of subjects from each center, for many of the 13 centers, these children represent a substantial proportion of children within this age range. Feranchak et al. presented important prospective, longitudinal data from 1 state/1 center with 113 subjects in our age range of interest. The findings in the 2 studies are remarkably similar.

The data of Feranchak et al. for children age 7 to 10 years show that the same proportion (4%) of children were deficient in their sample using the cut point from the 1978 data of Farrell et al. as in our sample using the 5th percentile cut point from NHANES. In addition, 7% of the children in the study of Feranchak et al. had low vitamin E:lipid ratios, and a comparable 4% to 13% of children in our study had low vitamin E:cholesterol ratios, depending on the cut point used. Thus, similar rates of deficiency were documented by both groups of investigators using various approaches. Moreover, in children age 7 to 10 years, 48% in our study and up to 40% in the Feranchak et al study had serum vitamin E levels above the NHANES 95th percentile for healthy children. Again, the 2 data sets appear to be comparable using the approaches that we reported.

The issue of the optimal vitamin E biomarker for clinical care remains a challenge. The vitamin E:total lipids ratio may be preferable, but this is rarely available in the clinical setting. We were interested in examining vitamin E status with measures that are widely clinically available. One of the strengths of our study is the presentation of vitamin E status, using both serum vitamin E and the vitamin E:cholesterol ratio, in children with CF compared with healthy children of the same age from the NHANES nationally representative reference set. This provides appropriate comparison values for children in our age group. We suggest that our approaches have merit in routine CF clinical care and should be investigated further.

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New rotavirus vaccines: Renewed optimism and reason for caution

To the Editor:

We read with interest the report by O’Ryan et al regarding the renewed optimism on rotavirus vaccines. Encouraging results of 2 large phase III trials testing the new rotavirus vaccines have been published. Both vaccines were demonstrated to be highly effective in protecting infants against severe rotavirus gastroenteritis and were not associated with an increased risk of intussusception.

Undoubtedly, these vaccines may improve child health and survival considerably. Nevertheless, premarketing randomized clinical trials, even if conducted on thousands of individuals, may fail to reveal rare adverse events to vaccines; the brief life of Rotashield is an illuminating example of this. Concerns regarding the safety of attenuated human rotavirus (HRV) vaccine may arise, considering the potential imbalance of deaths due to pneumonia.

The primary cause of death was related to pneumonia in a significantly higher proportion of vaccinated children (16 vaccine recipients vs 6 placebo recipients; P = .05). Further analysis failed to demonstrate any significant difference in the distribution of pneumonia-related deaths within the first 31 days after vaccination, but this may be due to the low number of cases (7 children in the vaccine group and 3 in the placebo group). An additional analysis showed no difference in number of serious adverse events related to pneumonia and pneumonia-related hospitalizations.

Temporal association is not synonymous with causal association, and obviously a biological explanation is lacking for the increased mortality for pneumonia with no increased
number of other pneumonia-related serious adverse events. Nevertheless, it must be considered that in the event that the higher fatal pneumonia rate is not coincidental, considering a cohort of 4,000,000 children born in the United States each year, 2020 children (vs 760) would die from pneumonia—an extra 1260 deaths per year. Given these figures, we suggest that aggressive postlicensure monitoring of attenuated HRV should include surveillance for pneumonia-related severe adverse events.

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REFERENCES

Reply

To the Editor:

Ciappani et al rightfully point out that in the study of the attenuated human rotavirus (HRV) vaccine, there was a marginally significant imbalance of pneumonia-associated deaths in the vaccine group compared with the placebo group—an issue that was discussed in the article.6 Sixteen vaccine recipients and 6 placebo recipients had a primary cause of death related to pneumonia (P = .054). The distribution of cases in the first 31 days postvaccination was 7 cases in the vaccine group versus 3 in the placebo group, including 2 and 2 cases, respectively, in week 1, 2 and 0 cases in weeks 2 and 3, and 1 and 1 case in week 4. Further evaluation of all pneumonia-associated events indicated no other imbalances, including significant adverse events relating to pneumonia (280 in the vaccine group vs 276 in the placebo group), overall hospitalizations related to pneumonia (277 in the vaccine group vs 273 in the placebo group), hospitalizations related to pneumonia within 31 days after the first dose (99 in the vaccine group vs 94 in the placebo group), and hospitalizations within 31 days after the second dose or at any other time point (49 in the vaccine group vs 56 in the placebo group). Moreover, no specific clinical pattern or etiologic agent was identified.

A relationship between vaccination and death from pneumonia seems implausible in the absence of any increase in vaccine-attributable risk of hospitalization for pneumonia. Moreover, in none of the other studies with the live attenuated HRV vaccine, alone or pooled, was there any suggestion of increased morbidity or mortality related to pneumonia. The association is most probably a chance association due to the multiple comparisons performed to detect any signal of a possible vaccine-associated significant adverse event. Nevertheless, as with any new medical product, fatalities among HRV vaccine recipients must be evaluated during postmarketing surveillance. Such surveillance is currently ongoing.

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REFERENCE