Anomalies associated with gastroschisis and omphalocele: Analysis of 2825 cases from the Texas Birth Defects Registry

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A R T I C L E   I N F O

Article history:
Received 7 June 2013
Received in revised form 8 November 2013
Accepted 9 November 2013

Key words:
Gastroschisis
Omphalocele
Multiple congenital anomalies
Prenatal diagnosis
Surgical management

A B S T R A C T

Background/Purpose: The increasing prevalence of abdominal wall defects prompted analysis of anomalies associated with gastroschisis and omphalocele in the Texas Birth Defects Registry (TDBR).

Methods: Cases of gastroschisis (ICD9 code 756.71), omphalocele (756.70), and/or unspecified abdominal wall defects plus 9680 associated anomalies that were classified according to system. The overall prevalence of abdominal wall defects among 3,806,299 Texas births from 1999 to 2008 was 7.4 per 10,000 with 4.8 per 10,000 for gastroschisis and 2.1 for omphalocele. After excluding ambiguous cases (8.5%), independent associated malformations were noted for 25%, and early embryonic origin [35] that imply mechanisms other than vascular disruption [36–38].

1. Methods

The Texas Birth Defect Registry (TBDR) employs active surveillance (outreach) on the major structural birth defects among all pregnancy outcomes, including live births, spontaneous fetal deaths, and induced pregnancy terminations at any gestational age. Trained personnel identify potential cases by review of logbooks from delivery and tertiary care hospitals, birthing centers, and midwives throughout Texas, registering demographic and diagnostic information for birth defects of natal Texans that were documented prenatally or within one year of delivery. Epidemiologists and clinical geneticists review the collected data for accuracy with over 75% of AWD cases being diagnosed according to system.

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Gastroschisis has shown an epidemic-like increase in prevalence to 4-5 per 10,000 births [1–16], affecting 1300–1500 American children each year with $200–240 million dollars spent for an average 40 days of hospitalization [17]. The expense reflects remarkable surgical advances that allow 90%–96% of patients to be discharged with normal feeding and development [17–28], especially for cases without associated anomalies that have a traditionally underemphasized 5%–10% frequency [3–5]. Omphalocele has half this impact (prevalence around 2 per 10,000 births [14,16,27]) with similar surgical success in isolated cases [19,25] if its higher proportion of genetic disorders and 60%–70% frequency of associated anomalies are recognized [8,9,14,29,30]. Other authors have noted gastroschisis association with younger, primagravid mothers, drug-exposures, or social disorganization [12,31] and emphasized vascular disruption as a primary mechanism, exemplified by associated limb reduction defects [5–9]. Co-existing bowel atresias that occasion the term “complex gastroschisis” [24,32], have also been explained by vascular disruption or by action of hyperosmolar amniotic fluid on exposed bowel [42].

During study of gastroschisis prevalence and geographic distribution [1], Benjamin observed an unexpected number of cases with associated anomalies. In order to test this observation and supporting data from recent articles [2–16], detailed analysis of anomalies associated with gastroschisis was undertaken using a system- and severity-based classification for cases in the Texas Birth Defect Registry (TDBR). Our analysis supports recent data suggesting that gastroschisis, like omphalocele, has significant genetic predisposition [33,34], independent associated malformations [3–5], and early embryonic origin [35] that imply mechanisms other than vascular disruption [36–38].

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0022-3468/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jpedsurg.2013.11.052
anomalies of the abdominal wall (UAAW) were provided by TBDR in a Microsoft Access® database after IRB approval. Data columns contained 9-digit case numbers (the only patient identifier), ICD9 codes (e.g., 747.00), and anomaly descriptions (e.g., moderate PDA), in 12,599 rows (cases with defects in addition to the AWD would occupy several rows, one for each anomaly or suggested diagnosis like Beckwith syndrome).

First, AWD descriptors considered to be true gastrochisis or omphalocele were identified for analysis, eliminating duplicate descriptions (e.g., gastrochisis plus UAAW) and those qualified as possible or atypical like 2 cases of left gastrochisis. Cases with isolated AWD are referred to as single, those with associated defects as multiple. Associated anomalies were classified by system and region [39] using standard codes that also included TBDR qualifiers like mild/trivial or possible/questionable. Descriptions referring to major anomalies (having surgical or cosmetic consequences like cleft palate) were retained for analysis, while anomalies designated possible/questionable, interpreted as minor (e.g., epicanthal folds) with minimal medical impact, deemed secondary to the primary AWD (e.g., intestinal malrotation or microcolon), considered transient or physiologic (e.g., patent foramen ovale or mild heart valve insufficiencies), or judged not to be true congenital anomalies (e.g., hepatosplenomegaly or pyloric stenosis) were excluded. We retained AWD with potentially different mechanisms (limb-body wall defect, pentalogy, or cloacal/bladder extrophy) to avoid biasing the data with a priori judgments. AWD cases that contained these defects comprised a small percentage of the whole, and separate analysis demonstrated that their exclusion did not significantly alter percentages of AWD cases with associated anomalies or their anomaly spectra.

2. Results

2.1. Numbers of abdominal wall defects and their associated anomalies

After possible AWD cases were excluded, 1831 cases of gastrochisis (944 or 52% with associated anomalies), 814 cases of omphalocele (729 or 90% multiple), and 180 cases of UAAW (158 or 88% multiple) constituted a total of 2825 validated AWD cases. These figures represent a prevalence of 4.8 per 10,000 for gastrochisis and 2.1 per 10,000 for omphalocele with 7.4 per 10,000 for AWD overall among the 3,806,299 TBDR live births registered from 1999 to 2008. The prevalence figures are identical to the average prevalence for gastrochisis and omphalocele derived from annual figures listed on the TBDR website [40]. The prevalence of omphalocele was fairly constant, ranging from 1.89 to 2.33 per 10,000 over that period while the TBDR website [40]. The prevalence of omphalocele was fairly constant, ranging from 1.89 to 2.33 per 10,000 over that period while the TBDR website

Fig. 1. A. Percentages of AWD cases with associated anomalies after excluding defects qualified as minor, mild, possible, or physiologic; B, spectra of associated anomalies by system; Sk, skeletal, Mus-Sk, combines all skeletal (cranial, axial, limb, and contractures) plus very few muscular defects; Sk-Contract, contractures like camptodactyly or club foot; CNS, central nervous system; RES, reticuloendothelial system, mainly lymphatic abnormalities like ascites, cystic hygroma. Only mus-Sk and cardiac associated anomalies were significantly different (p < 0.05) by the student t test (†).
Table 1

<table>
<thead>
<tr>
<th>System/Region</th>
<th>Gastroschisis</th>
<th>Omphalocele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>1302</td>
<td>2827</td>
</tr>
<tr>
<td>Urinary</td>
<td>117 (9.0)</td>
<td>75 (2.7)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>165 (12.7)</td>
<td>27 (0.96)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>123 (9.7)</td>
<td>38 (1.3%)</td>
</tr>
<tr>
<td>Renal</td>
<td>16 (1.2%)</td>
<td>10 (0.35)</td>
</tr>
<tr>
<td>Biliary/gall bladder</td>
<td>7 (0.54)</td>
<td>16 (0.57)</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>7 (0.54)</td>
<td>16 (0.57)</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>4 (0.32)</td>
<td>12 (0.42)</td>
</tr>
<tr>
<td>Anal atresia*</td>
<td>10 (0.77%)</td>
<td>53 (1.9)</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>3 (0.23)</td>
<td>12 (0.42)</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>16 (1.2%)</td>
<td>10 (0.35)</td>
</tr>
<tr>
<td>Club foot</td>
<td>37 (2.8)</td>
<td>89 (3.2)</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>141 (11.1)</td>
<td>66 (2.3%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>191 (15%)</td>
<td>648 (23%)</td>
</tr>
<tr>
<td>Urorectal spectrum</td>
<td>72 (5.7)</td>
<td>188 (6.6%)</td>
</tr>
</tbody>
</table>

Percentages show more than a 2-fold difference for gastroschisis association over omphalocele. Intestinal atresias (14-fold more common), colonic atresias (7-fold), cryptorchidism (3.4-fold), biliary defects (2.8-fold), and hydrocephalus (2-fold) are more common with gastroschisis while tetralogy of Fallot (11-fold), coloboma (>10-fold), cloacal extrophy (8-fold), macroglossia (6.6-fold), esophageal/stomach anomalies (6-fold), anal atresia (3.4-fold), pulmonary hypoplasia (3.1-fold), and VSD (2.4-fold) are more common with omphalocele.

The higher frequency of macroglossia likely reflects the 41 cases (6.3% of multiple-anomaly omphalocele cases) designated as Beckwith–Wiedemann syndrome while those of esophageal defects, coloboma, anal atresia, diaphragmatic hernia, and thumb defects can be attributed to cases of chromosome disorders as these anomalies are typical of aneuploidy—11 cases (1.5% of multiple-anomaly gastroschisis cases) were designated as Trisomy 13 or 18 associated anal atresia were not interpreted as complex). Gastroschisis indicates a different mechanism than that from neural tube defects, since the latter are more commonly associated with omphalocele (2.9% vs. 1.5%). Urogenital defects including ambiguous/malformed genitalia and renal anomalies are also more common with omphalocele.

2.2. Cases of complex gastroschisis show different anomaly spectra

There were 124 gastroschisis cases with associated intestinal atresias that were regarded as complex gastroschisis (those with associated anal atresia were not interpreted as complex). Associated with these complex gastroschisis cases were 289 major, primary anomalies of which 145 were outside of the digestive system, compared to 470 simple gastroschisis cases with 1013 associated anomalies of which 956 were outside of the digestive system (note that the total number of associated anomalies equals the 1302 shown in Fig. 1B). Fig. 2 shows their differing system/region distribution with higher percentages of
cardiac, excretory, and reticuloendothelial system anomalies associated with complex gastroschisis and a lower percentage of limb defects.

3. Discussion

We demonstrate that gastroschisis occurs with other congenital anomalies in almost a third of cases, less than the 80% of multiple defect cases with omphalocele but with distributions of associated anomalies that were significantly different only for the musculoskeletal and cardiac systems (Fig. 1, Table 1). Analysis of the Texas Birth Defects Registry (TDBR) provides large numbers of birth defects from one region, here including 1831 cases of gastroschisis and 814 of omphalocele among 12,599 birth defect entries registered from 1999 to 2008 (3,806,299 births). These case numbers translate to average prevalence of 4.8 per 10,000 births for gastroschisis and 2.1 per 10,000 for omphalocele that agree with current estimates [1,2,25,27,28] and cover a time period when gastroschisis prevalence increased from 3.92 to 6.17 per 10,000 in Texas [40].

Although an inherent weakness of registries is variable ascertainment of congenital anomalies and their syndromes, the TDBR uses standard ICD9 codes, uniformly trained medical personnel, and additional review by epidemiologic and clinical genetic staff [40]. We compared gastroschisis and omphalocele through individual inspection and systematic classification [39], first excluding 8.5% of AWD cases as ambiguous (those qualified as possible, questionable, or as other unspecified anomalies of the abdominal wall—UAWA). The 9680 entries describing associated abnormalities were sorted to define 1302 major congenital anomalies associated with 594 multiple-defect cases of gastroschisis (32% of cases averaging 2.2 associated anomalies per case) and 2827 with 654 multiple-defect omphalocele (80% of cases averaging 4.3 associated defects per case). Both abdominal wall defects (AWD) exhibit associations with anomalies not secondary to bowel entrapment or altered abdominal pressure, like those of the heart or neural tube, and these associations support embryonic origins well before the 10–12 weeks of mid-gut hernia reduction [35–38]. These gastroschisis and omphalocele associations have implications for pre- and postnatal management, especially since their conjoint anomalies are not always explained as known conditions and certainly not, in the case of gastroschisis, by simple vascular disruption [36–38].

In order to reflect on associated anomalies presenting for initial medical management, Fig. 1B and Table 1 include known disorders like trisomy 13/18 (1.9% of multiple-anomaly gastroschisis cases, 18% of multiple-anomaly omphalocele cases) and Beckwith syndrome (6.3% of omphalocele cases) or those that likely reflect different embryonic mechanisms like amniotic bands or ectopia cordis. The latter cases comprised small fractions of the total AWD, including amyoplasia/arhothogyrosis (7 of 594 or 1.2% of multiple-defect gastroschisis cases, 0 among 654 multiple-defect omphalocele cases) or amniotic bands (1.0%, 0.25%) that were more common in gastroschisis and limb-body wall defects (0.52%, 1.1%), cloacal/bladder ektrophy (0.4%, 2.9%), ectopia cordis/pentalogy (0.87%, 2.5%), and Omphalocele-Exstrophy-Imperforate anus-Spina bifida (OESI) complex (0%, 2.6%) that were more common with omphalocele. Even when in the latter cases, known conditions, and fetal-stillborn cases are excluded, 510 (30%) of 1705 gastroschisis cases had associated anomalies compared to 330 (69%) of 475 omphalocele cases. Despite the large number of known conditions seen with omphalocele, the spectra anomalies after these exclusions were similar to those shown in Fig. 1 and Table 1.

Mastroiacovo et al. [4] studied 3322 cases of gastrochisis derived from several birth defect registries, including 726 TDBR cases ascertained from 1996 to 2002 (577 of which are included in this article). They found 404 (12.2%) multiple-defect cases with an additional 41 (1.2%) of chromosomal and 24 (0.7%) of other syndrome cases. These authors excluded transient cardiac and associated intestinal defects as well as contractures (club foot, hip contractures), hydrophrosis, or enlarged pelvis. Their exclusions would total 239 or 20% of our associated anomalies and switch 36 gastrochisis from multiple to single with a 28% frequency of multiple-defect cases. Their lower frequency of multiple-defect cases may reflect heterogeneity in ascertainment among multiple birth defect registries, since percentages of multiple-defect gastrochisis cases ranged from 1.9% to 26.6% for the 19 registries contributing at least 20 gastrochisis cases [4].

The spectra of major anomalies associated with gastrochisis and omphalocele defined in Table 1 and Fig. 1B include cardiac (15% and 23%), digestive (15% and 6.8%), fetal-stillborn group (53% vs. 32%), important cardiac and associated intestinal defects as well as contractures (club foot, hip contractures), hydrophrosis, or enlarged pelvis. These anomalies gave frequencies of 21% and 24% for musculoskeletal defects, 24% and 21% for urogenital defects (Table 1). The multicenter study of Mastroiacovo et al. [4] found CNS (4.5%), cardiac (2.5%), limb (2.2%), and urinary tract anomalies (1.9%) to be most frequent, perhaps biased by centers like that in Mexico with higher frequencies of neural tube defects. Stoll et al. [5] found a 17% frequency of associated anomalies in 60 cases of gastrochisis from France, compared to a 74% rate for 86 patients with omphalocele of whom 29% had chromosome aberrations—they cite ranges of 5% to 27% multiple-defect cases for gastrochisis and 27% to 63% for omphalocele [4–16]. Their non-chromosomal omphalocele cases had a 23.5% frequency of musculoskeletal, 20.4% of urogenital, 15.1% of cardiac, and 9.1% of CNS defects [5].

With regard to fetal-stillborn cases, Ahktar and Skarsgard [13] compared 506 surviving gastrochisis cases to 22 suffering abnormal perinatal events and found a 73% frequency of multiple-anomaly cases of which 38% were cardiac, 32% genitourinary, 16% musculoskeletal, and 8% CNS. We also found a higher fraction of multiple anomaly gastrochisis cases in the fetal-stillborn group (53% vs. 32%), important figures to bear in mind when planning care for the fetus or infant with gastrochisis. Increasing malformation complexity with earlier embryogenesis of gastrochisis is supported by the different spectra of associated anomalies found for complex versus simple gastrochisis cases (Fig. 2), suggesting that the associated gastrointestinal (but not anal) atresia is part of the primary dysmorphogenetic mechanism rather than produced as a secondary anomaly.


