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Short Report

Congenital gastrointestinal defects in Down syndrome: a report from the Atlanta and National Down Syndrome Projects

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We report Down syndrome (DS)-associated congenital gastrointestinal (GI) defects identified during a 15 year, population-based study of the etiology and phenotypic consequences of trisomy 21. Between 1989 and 2004, six sites collected DNA, clinical and epidemiological information on live-born infants with standard trisomy 21 and their parents. We used chi-squared test and logistic regression to explore relationships between congenital GI defects and infant sex, race, maternal age, origin of the extra chromosome 21, and presence of a congenital heart defect. Congenital GI defects were present in 6.7% of 1892 eligible infants in this large, ethnically diverse, population-based study of DS. Defects included esophageal atresia/tracheoesophageal fistula (0.4%), pyloric stenosis (0.3%), duodenal stenosis/atresia (3.9%), Hirschsprung disease (0.8%), and anal stenosis/atresia (1.0%). We found no statistically significant associations between these defects and the factors examined. Although not significant, esophageal atresia was observed more often in infants of younger mothers and Hispanics, Hirschsprung disease was more frequent in males and in infants of younger mothers and blacks, and anal stenosis/atresia was found more often among females and Asians.

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We designed the Atlanta Down Syndrome Project (ADSP) and its successor, the National Down Syndrome Project (NDSP), to investigate the etiology and phenotypic consequences of trisomy 21. The ADSP/NDSP is the largest population-based study to combine infant medical records, maternal questionnaire responses and DNA methodology to study the Down syndrome (DS) phenotype. We recently presented our findings concerning congenital heart defects (1). The present report examines congenital gastrointestinal (GI) abnormalities in this same population-based sample.

GI defects are second to heart defects among the common serious structural birth defects associated with DS (2–6). The strengths of the combined ADSP/NDSP, namely its large size, national scope, population basis and ethnic (racial/ethnic) diversity permit us to report details of the occurrence of DS-associated GI defects that should contribute to our search for their etiologies.

Materials and methods

Based at Emory University in Atlanta, GA, the population-based ADSP identified eligible cases as live-born infants with standard trisomy 21 (i.e. three free-standing chromosomes 21) or

mosaic trisomy 21 born to women living in metropolitan Atlanta between 1989 and 1999. The NDSP, active between 2000 and 2004, expanded the scope of the ADSP to include five additional sites: Arkansas, Iowa, New Jersey (all statewide), California and New York (selected geographic areas of both). The NDSP further limited recruitment to English or Spanish-speaking mothers and excluded infants who died or were adopted prior to enrollment. Methodological details of both studies are available (7, 8). Each site was linked to a birth defects surveillance system described in detail elsewhere (9), and all sites obtained institutional review board approvals and informed consent from families. For the present study of GI defects, we include only those live-born ADSP/NDSP-eligible infants with non-mosaic, standard trisomy 21 as documented by routine clinical cytogenetic testing and no other clinically relevant chromosome abnormality.

Each site abstracted the medical records of eligible infants and recorded the information on forms that asked specifically about the presence or absence of each GI defect [esophageal atresia, tracheoesophageal fistula, pyloric stenosis, duodenal stenosis/atresia, annular pancreas, Hirschsprung, anal stenosis/atresia and other (specify)]. The methods of diagnosis were recorded. All abstracts were reviewed by a single, clinically trained individual. Coding of ethnicity varied somewhat by site, but for this report, we consolidated the coding into white non-Hispanic, black non-Hispanic, Hispanic, Asian and other.

We examined the frequency of each major GI defect by ethnicity, sex, presence of a congenital heart defect and maternal age (<35 and ≥ 35) using simple chi-squared analyses or Fisher's exact tests depending on sample size. Where appropriate, we calculated odds ratio by logistic regression. Using DNA extracted from buccal cells or blood samples obtained from participating parents and child, we studied chromosome 21 DNA markers (8) to determine the parent and meiotic stage of origin of the extra chromosome and then examined the relationship between the origin of the extra chromosome and the existence of the individual GI defects.

Results

Among 1892 eligible infants (ADSP 423; NDSP 1469), major GI abnormalities were documented in the medical records of 126 (6.7%). Table 1 summarizes the frequencies of these defects in all eligible infants and presents the data by maternal age and ethnicity, infant sex and presence of congenital heart defects. The GI abnormalities of interest are listed separately: esophageal atresia ± tracheoesophageal (0.4%), pyloric stenosis (0.3%), duodenal stenosis/atresia ± annular pancreas (3.9%), Hirschsprung disease (0.8%) and anal stenosis/atresia (1.0%). The frequency of other GI defects combined was 0.2%. We did not find any co-occurrences of these GI abnormalities.

We asked whether ineligible infants differed from those of eligible families with respect to congenital GI defects. We excluded 177 ineligible families for the following reasons: 52 because the mother did not speak English or Spanish, 78 in which the infant died after birth and before enrollment, 29 who were adopted and 18 for other reasons. Although we did not collect medical information systematically on all ineligible infants, of 57 for whom medical records were available, 3 (5.3%) had a GI defect [duodenal atresia/stenosis (2) and ileal atresia (1)].

We enrolled 1387 infants (ADSP 299; NDSP 1088) for a combined participation rate of 73% (1387/1892). Among enrolled families, we identified five (0.4%) GI defects reported by the mothers in the maternal questionnaires but not found in medical records (Table 1). By adding 0.4% (2) of the 505 non-enrolled cases (no questionnaire available), we estimated the maximum occurrence of GI defects in the entire eligible sample to be approximately 128 (6.8%).

In our search for factors that might modify the risk for GI defects, we found no statistically significant association between GI defects and infant sex, race, maternal age or presence of a congenital heart defect (Table 1). Among participating families, we examined the relationship between the GI defects and the origin of the non-disjunction error. Among 1068 cases for which we were able to determine parent and meiotic stage of the non-disjunctional error that led to an extra chromosome 21, 6% (61 cases) were paternal in origin and 94% (1007 cases) were maternal. Of maternal meiotic errors, 76% occurred during meiosis I. We found no differences in the frequencies of any GI defects by parent or stage (data not shown).

Discussion

The frequency of congenital GI defects in the ADSP/NDSP, 6.7%, is consistent with other population-based studies, which have reported 4–10% (2–6, 10, 11). When considering all GI defects together, we did not find any association with maternal age, race, infant sex or origin of the chromosome error. However, even with small numbers, it is probably preferable to examine the

Table 1. Congenital gastrointestinal defects in Down syndrome: results from two population-based studies

	n	Esophageal atresia ± tracheoesophageal fistula, *n* (%)[b]	Pyloric stenosis, *n* (%)[b]	Duodenal stenosis/ atresia, *n* (%)[b]	Hirschsprung disease, *n* (%)[b]	Anal stenosis/ atresia, *n* (%)[b]	Other[a], *n* (%)[b]	Total GI, *n* (%)[b]
All eligible	1892	8 (0.4)	6[c] (0.3)	74[c] (3.9)	16[c] (0.8)	18 (1.0)	4 (0.2)	126 (6.7)
ADSP	423							
NDSP	1469							
Mother's age[d]								
<35	1015	7 (0.7)	3 (0.3)	40 (3.9)	10 (1.0)	9 (0.9)	3 (0.3)	72 (7.1)
≥35	860	1 (0.2)	3 (0.4)	33 (3.8)	6 (0.7)	8 (0.9)	1 (0.1)	52 (6.0)
Mother's ethnicity								
White	833	2 (0.2)	3 (0.4)	37 (4.4)	6 (0.7)	5 (0.6)	1 (0.1)	54 (6.5)
Black	345	0 (—)	0 (—)	10 (2.9)	7 (2.0)	0 (—)	1 (0.3)	18 (5.2)
Hispanic	595	6 (1.0)	3 (0.5)	25 (4.2)	2 (0.3)	9 (1.5)	2 (0.3)	47 (7.9)
Asian	87	0 (—)	0 (—)	2 (2.3)	1 (1.2)	3 (3.4)	0 (—)	6 (6.9)
Other/unknown	32	0 (—)	0 (—)	0 (—)	0 (—)	1 (3.1)	0 (—)	1 (3.1)
Infant sex[e]								
Male	1014	4 (0.4)	4 (0.4)	36 (3.6)	12 (1.2)	8 (0.8)	3 (0.3)	67 (6.6)
Female	874	4 (0.5)	2 (0.2)	37 (4.2)	4 (0.5)	10 (1.1)	1 (0.1)	58 (6.6)
Infant heart defects								
AVSD								
Yes	255	1 (0.4)	0 (—)	10 (3.9)	3 (1.2)	4 (1.6)	0 (—)	17 (7.1)
No	1637	7 (0.4)	6 (0.4)	64 (3.9)	13 (0.8)	14 (0.9)	6 (0.4)	110 (6.7)
ASDII								
Yes	337	1 (0.3)	1 (0.3)	16 (4.8)	5 (1.5)	4 (1.2)	1 (0.3)	28 (8.3)
No	1555	7 (0.4)	5 (0.3)	58 (3.7)	11 (0.7)	14 (0.9)	5 (0.3)	100 (6.4)
VSD								
Yes	345	3 (0.9)	2 (0.6)	17 (4.9)	3 (0.9)	2 (0.6)	0 (—)	27 (7.8)
No	1547	5 (0.3)	4 (0.3)	57 (3.7)	13 (0.8)	16 (1.0)	4 (0.3)	99 (6.4)

ASDII, secundum atrial septal defect; AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
[a]Other includes one ileal atresia, one malrotation from medical records and two intestinal blockage, not otherwise specified, from maternal questionnaire.
[b]Percentage in category (e.g. racial category) with specified gastrointestinal defect.
[c]Information from maternal questionnaire only in 2/6 pyloric stenosis, 1/74 duodenal stenosis/atresia and 2/16 Hirschsprung.
[d]17 cases missing mother's age.
[e]Four cases missing infant sex.

various abnormalities separately because their embryological origins differ. For example, esophageal atresia results from defects in mesenchyme proliferation and partitioning of the esophagus and trachea at 4–5 weeks of development (12): most cases of duodenal atresia follow from failure to recanalize the intestinal lumen at 8 weeks (13); and Hirschsprung disease represents failure of neural crest cells to migrate and colonize the submucosal and myenteric plexuses of the enteric nervous system between the 5th and 12th week (14). In the following sections, we review our findings on each GI defect in the context of the literature. As we observed only a few cases of pyloric stenosis and as Torfs and Christianson (6) reported no link between DS and PS, we do not discuss this trait further.

Esophageal atresia ± tracheoesophageal fistula

Esophageal atresia has been shown to be more prevalent in DS than in the general population (4, 6). A frequency of 0.42% in the current study falls within the range reported by others for infants with DS (0.3–0.8%) (2–4, 6). While the numbers are small, we found esophageal atresia more often in the offspring of younger mothers and Hispanics. Similar to the findings of Kallen et al. (4), we noted no gender differences.

Duodenal stenosis/atresia

Duodenal atresia is clearly the most common structural GI defect seen in DS with rates ranging from approximately 1% to 5% and no reported association with maternal age or infant sex (2, 4, 6, 11). Among all infants with duodenal stenosis/atresia, at least 25% have DS (6, 15, 16). Similar to previous reports, we found duodenal atresia in 3.9% of ADSP/NDSP infants with no significant relationship to maternal age or ethnicity, infant sex or presence of a heart defect. Twelve per cent (9/74) of ADSP/NDSP infants with duodenal atresia had an annular pancreas. Fabia and

Drolette (2) reported an annular pancreas in 23.8% of DS infants with duodenal atresia. Annular pancreas is currently thought to be the result not the cause of duodenal atresia, although the topic has been debated (17–20).

Hirschsprung disease

The recent literature indicates that Hirschsprung disease is found in about 1–3% of infants with DS (3, 6, 11). Approximately 3–11% of Hirschsprung disease occurs in association with DS (6, 21–24). The frequency of this disorder in our sample, 0.85%, is similar to previous reports. Our results suggest that Hirschsprung disease may occur more frequently in males, in infants of younger mothers and in black infants, although the differences were not significant. Most previous studies have shown Hirschsprung to be more common in male infants with and without DS (4, 21, 23–26). The preferential occurrence of Hirschsprung disease in infants of younger mothers has been reported previously in both infants with and without DS (2, 4, 23, 26). In a population-based survey of all infants with Hirschsprung disease, Torfs (26) found significant ethnic differences with rates from highest to lowest occurring in Asians, blacks, whites and Hispanics. Similarly, our rates from highest to lowest were blacks, Asians, whites and Hispanics. Goldberg (23) also found more non-whites among affected infants (± DS) in Baltimore, MD, where the non-white population is predominantly black. Interestingly, in our recent study of congenital heart defects in ADSP/NDSP infants with trisomy 21, we found a similar ethnic pattern in association with atrioventricular septal defects (8). Black infants had the highest incidence of this type of heart defect followed by whites then Hispanics and Asians. It is notable that we did not observe associations between ethnicity and either all GI defects combined or all heart defects combined, but only for specific anomalies.

Torfs and Christianson (27) reported that infants with DS and either duodenal atresia or Hirschsprung disease had a significantly higher rate of heart defects than DS infants in general (85.7% and 70% *vs* 56%). In the ADSP/NDSP, heart defects were present in 41% of all infants, 53% of those with duodenal atresia and 38% of those with Hirschsprung disease (differences not significant).

Anal stenosis/atresia

Among the 18 (1.0%) ADSP/NDSP infants with an anal abnormality, we noted a higher incidence in females and in Asians, although not statistically significant, and no difference by maternal age. Other reports have found anal atresia rates ranging from <1% to approximately 4% with no significant differences reported by race or infant gender (2, 3, 6, 11, 28, 29).

Limitations and future studies

In summary, this report describes the frequencies of congenital GI defects in a population-based sample of 1892 live-born infants with DS and presents several observations related to maternal age, race, infant sex and the presence of heart defects. A limitation of this study is that we did not include pregnancy losses, terminations or stillbirths. It is possible that some fetuses were diagnosed with trisomy 21 after first being identified through ultrasonography as having a GI abnormality. With early detection, pregnancy termination would have been an option. Several large studies have found differences in the extent to which the various GI abnormalities can be successfully diagnosed with prenatal ultrasonography. For example, duodenal atresia is more readily detected than esophageal atresia or large bowel and anal abnormalities (30–33). Despite the option of termination of these prenatally diagnosed pregnancies, the rates of GI defects in the NDSP infants are similar to rates obtained in studies that span the past 30 years (2–4, 6, 21–24, 28, 29, 34). The strengths of the ADSP/NDSP include its large size, national scope, population basis, ethnic diversity, as well as a study design that combined medical information on infants, questionnaire responses from their mothers, and biological samples. With the frequencies of GI defects now well established, future studies can focus on identifying contributing risk factors that lead to these defects among infants with DS. For example, yet to be explained is the observation that several GI abnormalities with seemingly distinct embryological origins are all more common in individuals with an extra chromosome 21. Both environmental and genetic factors may play a role in both the occurrence and the reduced penetrance of these disorders among those with trisomy 21. The increased frequencies of several types of birth defects including those of the heart and GI track are hallmarks of DS. There are efforts underway to bring emerging molecular technologies to bear on the question of how the presence of an extra copy of chromosome 21 results in characteristic birth defects in only a subset of individuals with DS. Recent reviews outline the current state of knowledge in this area and propose novel

approaches in generating genotype–phenotype correlations (35, 36).

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