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Original Article

Disorders of Gut-Brain Interaction in a National Cohort of Children With Down Syndrome

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Background/Aims
Disorders of brain-gut interaction (DGBIs) are present in adults and children around the world. Down syndrome (DS) is the most common chromosomal condition in humans. While DS has associations with many organic medical conditions, the frequency of DGBIs in children and adolescents with DS has not previously been studied. We assess the rate of DGBIs in children and adolescents 4-18 years of age with DS in the United States using the Rome IV criteria by caregiver report.

Methods
This is a cross-sectional national survey study in which caregivers (n = 114) of children with DS completed an online survey about their child's gastrointestinal symptoms and quality of life (QoL).

Results
Using the Rome IV parent-report diagnostic questionnaire, 51.8% of children met symptom-based criteria for at least 1 DGBI. Functional constipation (36.0%) and irritable bowel syndrome (14.9%) were the most common disorders identified. QoL was lower in children with at least 1 disorder as compared to children who did not meet criteria for any disorders (mean QoL = 62.3 vs mean QoL = 72.9, $P < 0.001$). Almost all children with DS and concomitant autism (87.5%) had at least 1 DGBI.

Conclusions
DGBIs are common in children with DS and are associated with diminished QoL.
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Key Words
Abdominal pain; Constipation; Down syndrome; Dyspepsia; Nausea

Introduction

Down syndrome (DS) (including Trisomy 21, translocation associated Trisomy 21, and mosaic Trisomy 21) is an autosomal aneuploidy that is associated with characteristic physical findings and intellectual disability.[1] It has been estimated that 1 in 700 children born in the United States has DS.[2] DS is likewise associated with several medical issues, gastrointestinal (GI) and otherwise, that impact quality of life (QoL).[1,3-8] Children with DS are more likely

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to have congenital or acquired GI diseases. Congenital GI diseases, like duodenal atresia or Hirschsprung disease, are present in 1-4% of children with DS.[9,10] Acquired GI disorders, such as achalasia or celiac disease, are found in 3.4% and 5.8% of children with DS, respectively.[11,12]

Disorders of gut-brain interaction (DGBIs), formerly called functional gastrointestinal disorders, are a group of non-organic, chronic disorders frequently diagnosed in children around the world.[13-15] In the United States, up to a quarter of children meet criteria for at least 1 DGBI based on Rome IV criteria.[16] No study to date, however, has examined DGBIs in children with DS. Establishment of such rates would provide information for primary care providers, pediatric gastroenterologists, and parents alike.

The goal of this study is to establish the prevalence of DGBIs in children with DS in the United States. It likewise sought to relate the presence of DGBIs to QoL measures. It also aims to uncover associations between various medical and surgical comorbidities frequently seen in individuals with DS and the presence of a DGBI.

Materials and Methods

Parents and caregivers of children and adolescents with DS ages 4-18 years (herein referred to as respondents) were invited to participate in the study via recruitment from registry databases belonging to DS-Connect (https://dsconnect.nih.gov/) and/or the Down Syndrome Association of Central Ohio (https://dsaco.net/). DS-Connect is a national registry wherein individuals with Down syndrome and their families can choose to express interest in participating in clinical studies and surveys. The Down Syndrome Association of Central Ohio is a non-profit organization supporting individuals with DS and their families. Information on the study was included in an issue of their quarterly electronic newsletter.

Respondents accessed the study via a secure website wherein questions were administered in English pertaining to the respondent's child with DS (herein referred to as the subjects). Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Nationwide Children's Hospital. REDCap is a secure, web-based software platform.[17,18] No personal information was collected. Certain questionnaire items were conditionally displayed based on response to prior questions. Respondents were able to change and review their answers and were likewise able to leave the survey and return later with a unique passcode. If the respondent happened to care for more than 1 child with DS, they were asked to respond to all queries with the child whose first name appears first in the alphabet in mind. No incentive was offered and participation was voluntary. Data were collected from October to December 2020. The study was approved by the Institutional Review Board of Nationwide Children's Hospital (Study 0001085).

Respondents completed the Rome IV Diagnostic Questionnaire on Pediatric Functional Gastrointestinal Disorders Parent-Report form for children 4 years and older.[19,20] QoL was also assessed using the Pediatric Quality of Life Inventory version 4.0 (PedsQL 4.0). Pediatric QoL parent report forms were used based on the age of the subject with DS (age 4, toddler; ages 5-7, young children; age's 8-12 children; and age's 13-18 teen). The PedsQL 4.0 allows for assessment of physical, emotional, social and school/daycare functioning via 21-23 questions with multiple choice responses (never, almost never, sometimes, often, and almost always). Responses were converted as outlined in the instrument's scoring instructions from a scale of 0-4 to 0-100, with higher scores indicating higher QoL.[21]

Demographic items included age, sex, caregiver and child race/ethnicity, habitation status, insurance status, child grade level, household income, caregiver education, and state of residence. The presence of concomitant medical diagnoses and prior surgeries were also ascertained by respondent selection of several pre-populated diagnoses and procedures with the option to free text conditions as well.

Averages and standard deviations or percentages of the sample were calculated as appropriate. *t* tests were used to analyze continuous variables and chi-square tests for categorical variables. Significance was set at $P = 0.05$. There were no missing data in the Rome criteria section as the software was programmed to require a response to all queries before proceeding. Missing data in the QoL section were managed as outlined in the instrument's scoring instructions.[21] Specifically, when more than half of the items on a scale were completed, the mean of the items completed was imputed for the missing response(s) of that scale to obtain a score.[21] The Shapiro-Wilkes test demonstrated that the QoL data were normally distributed.

Results

The survey was distributed to an estimated 2064 database e-mail addresses whose owners' demographics and eligibility were not known. A total of 158 respondents initiated the survey and 114 completed the demographics and Rome questionnaire in their entirety (72.2% completion rate). One-half of the subjects with DS were female with a mean age of 10.2 years (standard

deviation 3.7 years). Respondents resided in 36 states and Washington, DC. Twelve surveys (10.5%) were completed by Ohio residents. Ninety-six percent (109) of the subjects attended school with a range of grades from pre-Kindergarten to 12th grade (median fourth grade). Table 1 provides demographics on the subjects.

The study identified 59 children (51.8%) who met symptom-based criteria for at least 1 DGBI. Nine subjects (7.9%) met criteria for 2 diagnoses and 12 subjects (10.5%) met criteria for 3 or more diagnoses. Race and ethnicity comparisons within the cohort were not possible due to the relatively homogeneous sample (subjects were 88.6% white and 92.0% non-Hispanic). There were no statistically significant differences between those subjects with and without a DGBI in terms of gender, age, living arrangements, and insurance status nor were there any differences when the highest level of caregiver educational attainment was accounted for. Subjects

Table 1. Subject Demographics

Subject demographics	Total population (n = 114)	No Rome IV criteria met (n = 55)	At least one Rome IV criteria met (n = 59)
Gender (female)	57 (50.0%)	30 (54.5%)	27 (45.8%)
Age (yr)	10.2 (3.7)	10.3 (3.4)	10.2 (3.9)
Race			
White	101 (88.6%)	49 (89.1%)	52 (88.1%)
Black	2 (1.8%)	1 (1.8%)	1 (1.7%)
Asian Indian	2 (1.8%)	2 (3.6%)	0 (0.0%)
Chinese	1 (< 1.0%)	1 (1.8%)	0 (0.0%)
Other Asian	1 (< 1.0%)	0 (0.0%)	1 (1.7%)
Multiple	5 (4.4%)	2 (3.6%)	3 (5.1%)
Declined to answer	2 (1.8%)	0 (0.0%)	2 (3.4%)
Ethnicity			
Hispanic/Latino	9 (7.9%)	4 (7.3%)	5 (8.5%)
Living arrangement			
Lives with both parents	99 (86.8%)	47 (85.5%)	52 (88.1%)
Lives with mother only	11 (9.6%)	6 (10.9%)	5 (8.5%)
Shared parenting	3 (2.6%)	1 (1.8%)	2 (3.4%)
Lives with grandparent(s)	1 (< 1.0%)	1 (1.8%)	0 (0.0%)
Estimated annual household income (USD)			
< 25 000	4 (3.5%)	0 (0.0%)	4 (6.8%)
25 000-50 000	5 (4.4%)	3 (5.5%)	2 (3.4%)
50 000-100 000	20 (17.5%)	10 (18.2%)	10 (16.9%)
100 000-150 000	29 (25.4%)	8 (14.5%)	21 (35.6%)
> 150 000	47 (41.2%)	28 (50.9%)[a]	19 (34.5%)
Declined to answer	9 (7.9%)	6 (10.9%)	3 (5.1%)
Highest caregiver education level			
Completed high school	1 (< 1.0%)	0 (0.0%)	1 (1.7%)
Some college	4 (3.5%)	1 (1.8%)	3 (5.1%)
Completed college	28 (24.6%)	16 (29.1%)	12 (20.3%)
Some post-graduate	8 (7.0%)	4 (7.3%)	4 (6.8%)
Completed post-graduate	73 (64.0%)	34 (61.8%)	39 (66.1%)
Medical Insurance			
Private insurance	76 (66.7%)	36 (65.5%)	40 (67.8%)
Public insurance	16 (14%)	6 (10.9%)	10 (16.9%)
Both public and private insurance	21 (18.4%)	13 (23.6%)	8 (13.6%)
Declined to answer	1 (< 1%)	0 (0%)	1 (1.7%)

[a] $\chi^2 = 5.7$, n = 103, $P = 0.017$.
USD, United States dollar.
Data are presented as n (%) or mean (SD).

whose annual household income was below $150 000 were more likely to have at least 1 DGBI than those whose annual income was $150 000 or greater ($\chi^2 = 5.7$, n = 103, $P = 0.017$).

Table 2 provides information relating to prior medical/surgical issues for the subjects. No subjects had a history of lymphoma, achalasia (or history of surgical myotomy), or annular pancreas.

Table 2. Subject Demographics, Prior Medical and Surgical History, and Quality of Life[a]

Subject demographics	Total population (n = 114)	No Rome IV criteria met (n = 55)	At least one Rome IV criteria met (n = 59)
Prior medical diagnoses			
Congenital heart disease	42 (36.8%)	22 (40.0%)	20 (33.9%)
Hypothyroidism	40 (35.1%)	15 (27.3%)	25 (42.4%)
Autism	16 (14.0%)	2 (3.6%)	14 (23.7%)[b]
Celiac disease	6 (5.3%)	1 (1.8%)	5 (8.5%)
Duodenal atresia	6 (5.3%)	3 (5.5%)	3 (5.1%)
Hirschsprung disease	3 (2.6%)	2 (3.6%)	1 (1.7%)
Inflammatory bowel disease	2 (1.8%)	1 (1.8%)	1 (1.7%)
Leukemia	2 (1.8%)	1 (1.8%)	1 (1.7%)
Omphalocele	1 (< 1.0%)	1 (1.8%)	0 (0.0%)
Prior surgical procedures			
Open heart surgery	28 (24.6%)	14 (25.5%)	14 (23.7%)
Cardiac catheterization	11 (9.6%)	6 (10.9%)	5 (8.5%)
Hernia repair	5 (4.4%)	3 (5.5%)	2 (3.4%)
Fundoplication	4 (3.5%)	3 (5.5%)	1 (1.7%)
Hirschsprung disease surgery	3 (2.6%)	2 (3.6%)	1 (1.7%)
Colectomy/ileostomy	3 (2.6%)	0 (0.0%)	3 (5.1%)
Cecostomy	1 (< 1.0%)	0 (0.0%)	1 (1.7%)
Quality of life			
Total score (0-100)	67.5 (15.7)	72.8 (14.2)	62.3 (15.4)[c]

[a]Quality of life data only available for 113 subjects.
[b]$P = 0.022$.
[c]$P < 0.001$.
Data are presented as n (%) or mean (SD).

Table 3. Disorders of Gut-Brain Interaction in Children 4-18 Years of Age with Down Syndrome and Quality of Life

Diagnosis	Criteria met (n =114)	Female gender	QoL[a]
Functional constipation	41 (36.0%)	19 (46.3%)	63.4 (15.4)
Irritable bowel syndrome	17 (14.9%)	8 (47.1%)	50.9 (14.0)[b]
Functional dyspepsia: post-prandial distress syndrome	14 (12.3%)	8 (57.1%)	55.7 (12.0)
Aerophagia	6 (5.3%)	3 (50.0%)	53.8 (8.8)
Abdominal migraine	5 (4.4%)	1 (20.0%)	59.4 (7.7)
Non-retentive fecal incontinence	5 (4.4%)	1 (20.0%)	64.8 (7.7)
Functional vomiting	3 (2.6%)	2 (66.7%)	52.5 (15.3)
Functional dyspepsia: Epigastric pain syndrome	2 (1.8%)	1 (50.0%)	64.1 (15.2)
Functional abdominal pain-NOS	1 (< 1.0%)	1 (100.0%)	NA
Functional nausea	1 (< 1.0%)	1 (100.0%)	NA
Cyclic vomiting syndrome	1 (< 1.0%)	0 (0.0%)	NA
Adolescent rumination syndrome	1 (< 1.0%)	0 (0.0%)	NA

[a]Quality of life (QoL) data only available for 113 subjects.
[b]Irritable bowel syndrome QoL was lower than any other single diagnosis ($P < 0.001$).
NOS, not otherwise specified; NA, not applicable.
Data are presented as n (%) or mean (SD).

From the total population, 16 children (14.0%; 5 female) had a respondent reported comorbid diagnosis of autism. Subjects with reported autism were more likely to have a DGBI diagnosis than those without autism ($P = 0.022$) with 14 of the 16 subjects (87.5%) with autism meeting criteria for at least 1 DGBI diagnosis. Autism was the only medical or surgical condition with such a statistically significant association. Sixty-three percent of those with autism met criteria for functional constipation while 44.0% met criteria for irritable bowel syndrome (IBS).

Subjects with at least 1 DGBI had a lower PedsQL 4.0 score as compared to those without (62.3 vs 72.8, $P < 0.001$). Furthermore, the 21 subjects who had more than 1 DGBI diagnosis had lower PedsQL 4.0 scores than those with only 1 DGBI diagnosis (mean 53.3 vs 67.2; $P = 0.002$).

Table 3 provides the prevalence of each of the Rome IV diagnoses and the associated QoL for each group. There were no differences in the diagnoses in terms of gender. QoL data were available for 113 of the 114 subjects. Data were imputed for only 9 of the 2599 QoL related responses (0.3%). Functional constipation (36.0%) and IBS (14.9%) were the most commonly identified disorders. Less than 1.0% of children had either functional abdominal pain-not otherwise specified, functional nausea, rumination, or cyclic vomiting syndrome. No child met criteria for the overlap between both sub-types of functional dyspepsia. Those with IBS had a significantly lower QoL when compared to all subjects with at least 1 DGBI diagnosis (mean QoL if at least one DGBI 62.3 vs 50.9 for those with IBS, $P < 0.001$). Independent of the specific QoL questions, respondents were also asked to rate their child's overall QoL on a generic 5-item scale (excellent, very good, good, fair, and poor); 89.0% considered their child to have an excellent or very good QoL.

Discussion

This is the first study to assess the rate of DGBIs in children with DS according to the Rome IV criteria. It revealed a high frequency of parentally reported DGBIs among children with DS. The frequency of these disorders was higher than the prevalence found in a large group of healthy children in the United States.[16] Notably, 51.8% of children with DS had at least 1 DGBI compared with 25.0% of children in a healthy US cohort.[16] This rate was higher than any previous studies examining the presence of DGBIs in a variety of demographic groups.[15,16,22-27]

The rates of DGBIs were also greater in our study for the majority of individual disorders with a notably larger proportion meeting criteria for functional constipation (36.0% vs 14.0%) and IBS (14.9% vs 5.0%) as compared to a prior healthy United States cohort.[16] However, like the previous study, low rates of functional nausea and vomiting, rumination and cyclic vomiting syndrome were found. The fact that some disorders had a 3-fold higher frequency in children with DS in our study as compared to prior studies—while in most other disorders a fairly similar rate was found using the same questionnaire—suggests that such comparative differences found in the current study are not methodological. Moreover, no organic causes, including celiac disease, explained the increased frequency of these disorders. A handful of prior studies have touched on constipation in children with DS. A retrospective Brazilian study reported constipation in 49.0% of subjects with DS.[28] A retrospective quality improvement study from a dedicated DS clinic found that 15.0% of subjects already carried a diagnosis of constipation with an additional 19.0% receiving such a diagnosis after attending the clinic.[29] It did not appear, however, that the Rome criteria were used in either study.

The rate of comorbid autism in children with DS found in this study was similar to previous studies.[30] Fourteen percent of children in the current sample had caregiver reported comorbid autism. A prior study of 500 children with DS from England and Wales found that 16.0% of children also met diagnostic criteria for an autism spectrum disorder.[31] That study found that children with DS and autism experienced more emotional symptoms, behavioral problems, and hyperactivity than children with DS alone. In our study, children with concomitant autism were more likely to meet criteria for at least 1 DGBI than not to meet criteria for any disorder. A higher prevalence of DGBIs, particularly functional constipation, has also been found in studies comparing children with autism (both with and without DS) with neurotypical children.[32,33] Eight-five percent of children with autism were found to meet criteria for constipation with those who were the most socially impaired and lacking in expressive language being particularly at risk.[32] Previously, parents reported GI symptoms in 42.0% of children with autism compared with 12.0% in their unaffected siblings.[34] Another study found that children with autism were almost 8 times more likely to have a DGBI than non-related healthy peers.[35] The recognition of this association underscores the importance of early detection of autism in children with DS. Prompt intervention for GI symptoms in children with DS with and without comorbid autism provides an opportunity to perhaps decrease their impact on children and families.

The PedsQL accounts for the physical, social, emotional and school functioning of children. Children with DS are known to have

lower health related QoL than children with typical development independent of the GI issues.[3] The lower QoL for the subjects who met criteria for at least 1 condition highlights the relevance and importance of these diagnoses on an individual's life and presumably, that of their caregivers as well. Notably, QoL for those with IBS is significantly lower when compared to those with another DGBI diagnosis. The low QoL scores of children with DGBIs, with and without DS, highlights the impact of these disorders on the individual's life and that of their caregivers as well. Interestingly, despite the lower QoL scores reported, most caregivers reported excellent or very good QoL for their child when given the option of assigning excellent, very good, good, fair or poor to their child's overall QoL. Future studies should further investigate QoL and parental perception to help the medical community understand the impact of DGBIs in families of children with Down syndrome and its comorbidities.

Children with and without DGBIs had similar age and gender. The absence of gender differences in our study stands in contrast to certain international studies but yet coincides with other similar studies that, like ours, have not shown gender predominance in DGBIs.[15,36,37] Of note, hypothyroidism was not a risk factor for having a DGBI. Likewise, those with hypothyroid were not at increased risk of having functional constipation. The finding that those whose annual family income was less than $150 000 were more likely to have at least 1 DGBI mirrors other studies wherein lower income has been associated with more GI symptoms.[38,39]

Strengths of this investigation include the wide age range and geographical dispersion of the subjects. The use of standardized, validated questionnaires facilitated comparison with historical study data. However, the response rate of this study could not be calculated due to the nature of how the invitation was sent; it is not known how many of the 2064 potential respondents who were in the distribution databases were even eligible for the study in the first place. Likewise, the study relied on caregiver reporting of symptoms which may not necessarily reflect the subject's report of symptoms. Certainly, difficulty in communication between an individual with DS and caregiver could lead to over- (or under-) estimation of symptoms. Many of the symptoms needed to make a DGBI diagnosis require keen observation of the subject on the caregiver's behalf. This was particularly important in relation to toileting and events that may occur in school and/or in private, in the absence of the caregivers. Some, or all, of these items may account for the 27.8% respondent dropout rate for those who began the survey but did not finish it. Furthermore, stooling based diagnoses may have been confounded by the developmental abilities of the individual with Down syndrome.[40]

Another limitation of our study is our limited ability to assure external validity. However, despite our relatively small sample size, there are numerous elements that suggest our sample adequately reflects the demographics of those with DS in the United States. The frequency of autism, congenital heart disease, celiac disease, Hirschsprung disease, hypothyroidism, and duodenal atresia in our sample were similar to those found in prior national studies suggesting we obtained a satisfactory cross-section of subjects.[9-11,30,41,42] Furthermore, while race and ethnicity data were not available from the DS-Connect® database, they were similar between the Down Syndrome Association of Central Ohio (81.0% white; 4.0% Latino) and our respondents (88.6% white; 8.0% Latino). As such, we feel our results can reasonably be applied to the greater population of those with DS at large. Adding further credence to this, the mean QoL for the entire population (67.5) was similar to what has been found in prior studies in DS.[3,4,43] However, we do acknowledge that respondents were only English speaking, possessed an e-mail address, and were members of the distribution list of one (or both) of the organizations with whom we partnered. As such, we may have excluded some marginalized groups unintentionally.

Given the medical complexities of individuals with DS, one cannot exclude the possibility of other occult organic diagnoses masquerading as a functional disorder, particularly in light of the observation that those with disabilities are more likely to have unmet health needs.[44] However, prior studies have shown that few organic issues are likely to meet criteria for a functional disorder making the possibility of a missed organic diagnosis less likely.[45,46] Furthermore, while a large number of respondents completed graduate degrees and were in the highest level of income earners, even in larger unselected cohorts of DS families, it has previously been seen that children with DS are more likely to live in families that have social advantages due to the opportunity for the caregivers to acquire more education and financial resources prior to the child's birth.[47-49]

While this study demonstrated increased frequency of many DGBIs in those with DS, the etiology of this observation is not clear.[14,50] The pathophysiological mechanism for DGBIs is not known. There is evidence of ENS variations in both humans and murine models of DS and the ENS is known to play a role in DGBIs.[51,52] Alterations in the ENS and the CNS system in children with DS as the etiology of the differences found herein merits further investigation. Furthermore, muscular hypotonia seen in children with DS, which is thought to contribute to motor issues, may be in part responsible for the increased rate of functional con-

stipation seen in our study.[53] We intend to investigate this possibility in future clinical studies.

In conclusion, DGBIs are common in children with DS. The study also suggests a lower QoL in those with such disorders and highlights the need for future studies related to DGBIs in individuals with DS. The results of this investigation also speak more broadly to the importance of the study of DGBIs in vulnerable groups. Parental and provider education and awareness regarding DGBIs in children with DS may help improve the recognition of these disorders and in turn, perhaps, improve the QoL of children with DS.

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