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Incidence of Celiac Disease in Down Syndrome: A Longitudinal, Population-Based Birth Cohort Study

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Abstract

American Academy of Pediatrics (AAP) guidelines for children with Down syndrome (DS) include assessment for celiac disease (CD), although data to support this recommendation have been inconsistent. We determined the incidence of CD among children with DS in a population-based birth cohort of children born from 1976 to 2000 in Olmsted County, Minnesota. Individuals with karyotype-confirmed DS and CD (using diagnosis codes, positive serology, and duodenal biopsies) were identified. The incidence of CD in DS was compared with the published incidence of CD for Olmsted County residents (17.4 [95% confidence interval = 15.2–19.6] per 100 000 person-years). Among 45 individuals with DS from the birth cohort, 3 (6.7%) were identified with positive celiac serology and confirmatory biopsies at ages 9, 12, and 23 years, for an incidence of 325 per 100 000 person-years. Thus, individuals with DS have more than 18 times the incidence rate of CD compared with the general population, supporting the AAP guidelines.

Keywords

trisomy 21; Down syndrome; celiac disease

Introduction

Down syndrome (DS) is a genetic condition caused by either the complete or partial addition of the 21st chromosome secondary to early abnormal cell division. DS is the most common chromosomal abnormality diagnosed in the United States, with prevalence estimates of 11 to 14 per 10 000 live born infants.^{1–6} Individuals with DS are at risk for a number of serious medical comorbidities; however, the life expectancy for individuals with DS has steadily

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Author Contributions

KKO, SMM, SKK and RCV contributed to the conceptualization and design of the study, drafted the initial manuscript, and reviewed the final manuscript, ALW and RES contributed to the data collection, performed the statistical analyses, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of this work.

Declaration of Conflicting Interests

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increased to 50 to 60 years.^{7,8} This increased life expectancy is largely related to improvements in medical and surgical techniques, as well as improved medical screening for comorbidities.

Celiac disease (CD) is an immune-mediated systemic disorder that results in inflammation and damage to the small intestine when foods or other products containing gluten are ingested in genetically predisposed individuals.⁹ CD is thought to be more common among white populations and those of European descent, as well as certain high-risk groups, such as children with DS.¹⁰ The rate of CD among children with DS is estimated at 5% according to the 2011 American Academy of Pediatrics (AAP) Health Supervision Guidelines for Children with Down Syndrome.¹¹ This is higher than the expected CD rate for the general population of 1% to 3%.^{12–16} However, previous studies have reported rates of CD in DS that vary widely from 0% to 13%.^{17–31} Many of these previous studies have been limited by the use of cross-sectional cohorts of referred samples of children with DS from specialty clinics or various regional or national registries. Methods used for the diagnosis of CD in these studies have also varied widely from the use of billing codes, parental report, serology, or biopsy. Additionally, the symptoms of CD, such as diarrhea, constipation, abdominal discomfort, and irritability, are often observed in children with DS without CD, and complaints about these symptoms may be masked by intellectual disability and limited expressive language skills needed for reporting symptoms. This has led to clinical confusion regarding whether screening and testing for CD in children with DS is truly indicated.

To address some of the limitations from previous studies, the objective of this study was to determine the incidence of biopsy-confirmed CD among children with karyotype-confirmed DS using a large longitudinal, population-based birth cohort to provide accurate information regarding the incidence of CD to guide the clinical care provided to individuals with DS.

Methods

Study Setting

The setting for this study was Olmsted County, Minnesota, which is geographically located in southeastern Minnesota. Virtually all medical care for residents in the county is provided by Mayo Clinic, Olmsted Medical Center, and their 3 affiliated hospitals. Based on the US census data in 2000, the Olmsted County population is comparable to the United States with regard to median age (35.0 years vs 35.3 years), household income (\$51 316 vs \$41 994), and male gender (49.1% vs 49.1%), but it is more racially homogeneous than the United States (%white, 90.3% vs 75.1%).³²

This population-based study utilized the resources of the Rochester Epidemiology Project (REP). The REP has a medical records linkage system that links the medical records of persons residing in Olmsted County and maintains an electronic index of medical diagnoses and surgical procedures from health care providers in the REP catchment area.³³ This study was approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center.

Subjects

Birth Cohort.—Subjects for this study were members of a birth cohort of all children born between January 1, 1976, and December 31, 2000, to mothers who were residents of Olmsted County at the time of the child's birth (N = 43 215).³⁴ The analysis was restricted to the 39 893 subjects who had not denied access to their medical records for research purposes at the time of this study.

Identification of Down Syndrome.—Members of the birth cohort with DS were initially identified using International Classification of Diseases, Ninth Revision (ICD-9), diagnosis code 758.0 and Hospital Adaptation of the International Classification of Diseases (HICDA) diagnosis codes 07593110–07593115. The medical records of these patients were then reviewed to identify karyo-type-confirmed cases, including nondisjunction, translocation, and mosaic forms of trisomy 21.

Identification of Celiac Disease.—Among the birth cohort members with DS, those diagnosed with CD were identified by diagnosis codes (HICDA 02690210 or 02690211; ICD-9 579.0; ICD-10 K90.0) up through June 30, 2017. Their diagnoses were corroborated by positive serology and confirmed by duodenal biopsies.

Statistical Methods

Among the subset of patients with DS, the incidence of serology/biopsy-confirmed CD was derived using the number of CD cases as the numerator and the total person-years of follow-up among all patients with DS as the denominator. Each patient's person-years was calculated as the time from birth to serology/biopsy-confirmed CD or from birth to last clinical visit prior to June 30, 2017, for those without CD. The incidence was then expressed as a rate per 100 000 person-years. A 95% confidence interval (CI) for the incidence rate was constructed, assuming the number of CD cases follows a Poisson distribution and the number of person-years is fixed. The incidence of CD in DS was then compared with the overall published age- and sex-adjusted incidence of CD for Olmsted County residents during 2000 to 2010.³⁵ Statistical analyses were performed using the SAS version 9.3 software package.

Results

Among children born to residents of Olmsted County from 1976 to 2000, research authorization for medical record review was available for 39 893 patients, who were then considered in this analysis. Of these, 49 patients with karyotype-confirmed DS were identified. Follow-up was available for 45 of these 49 patients; 3 were stillborn and 1 was lost to follow-up. Among the remaining 45 patients with DS, all of whom had non-dysjunctions (trisomy 21), 27 (60.0%) were female and 42 (93.3%) were white. Median age at the last clinical visit was 22.9 years (interquartile range = 16.6–29.9 years); 5 were deceased; and 34 had a clinic visit at a REP-affiliated provider in the past year.

Of these 45 patients with DS, 25 (56%) had negative celiac serology, and 17 (38%) were never tested for CD, possibly related to changes in recommendations for screening or

advancements in serology testing over the study period. Five of the 45 patients with DS had received a diagnosis code in the medical record of CD. None of these patients had a family history of CD recorded in the medical record. Three (6.7%) of these 45 patients (or 12% of those tested) were identified with positive celiac serology (anti-endomysial antibody positive and antitissue transglutaminase antibody (tTG-IgA) levels in the 90 to 250 range, with levels >20 indicating a positive result). The other 2 patients had negative anti-endomysial antibodies and tTG-IgA levels <20, and were not identified as being on a gluten-free diet. Diagnosis of CD for the 3 serology positive patients was made at ages 9, 12, and 23 years, between 2002 and 2007. A confirmatory biopsy was performed for all 3 of these patients. The Marsh grading stage for 1 patient was 1 to 2, and the other 2 patients had a Marsh grading stage of 3. The total person-years of follow-up for the 45 patients was 923.4 years, yielding an overall incidence of serology/biopsy-confirmed CD of 325 (95% CI = 67–949) per 100 000 person-years. The published overall age- and sex-adjusted incidence rate of CD for Olmsted County residents of all ages during 2000 to 2010 is 17.4 (95% CI = 15.2–19.6) per 100 000 person-years.³⁵

Discussion

We found that serology/biopsy-confirmed CD occurs in 6.7% of children with DS, for an overall incidence of 325 per 100 000 person-years (95% CI = 67–949). To our knowledge, this study is the first to use data from a longitudinal, population-based birth cohort with DS confirmed by karyotype and CD confirmed by biopsy. These results provide robust evidence to support AAP guidelines for children with DS to receive routine assessments through a targeted medical history at each preventative care visit, and serology testing for those with suggestive symptoms.

The incidence rate of CD among this population-based birth cohort of children with DS, 325 per 100 000 person-years, is more than 18 times the previously published general Olmsted County CD incidence rate of 17.4 per 100 000 person-years in 2000 to 2010³⁵; however, CD incidence appears to be increasing in the general population in Olmsted County, Minnesota, with more recent published incidence rates of 21.5/100 000 person-years in 2011 to 2014.³⁶ It is not clear if these general population published incidence rates for Olmsted County, Minnesota, include confirmatory biopsy information for all patients, but histopathology reports are included in the analysis. Despite this increase in CD incidence in the general population, the CD incidence rate in individuals with DS among children born between 1976 and 2000 is still higher by a factor of more than 15. Previously published occurrence rates of CD among individuals with DS have been quite variable. A previous study from Serbia reported a 0% rate of CD in their DS population,¹⁷ but a Brazilian study reported a rate of 13%.³⁰ The majority of published studies investigating the co-occurrence of DS and CD are from white populations; however, varying genetic predispositions, diets, and other environmental factors around the world may partially explain some differences in prevalence rates. Interestingly, published rates can differ even within the same country at different times. Published rates in the United States range from 2.6% to 10.3%,^{18,20,21,29} and in the Netherlands from 5% to 8%.^{22,26,27} Increasing rates of CD within the general population of Olmsted County, Minnesota, may suggest an environmental factor, given that this population is predominately white.³⁶ Increasing rates in the general population may also reflect greater

awareness of CD among providers and patients, as well as the clinical availability of sensitive diagnostic tests.

The mechanism producing an increased incidence of CD in DS is not fully understood. Research suggests a link with the interferon- α receptor coded on the 21st chromosome. Interferon- α is an inflammatory cytokine that has a role in eliciting intestinal immune responses. With a potential increase in receptors, this may trigger the autoimmune response needed to develop CD.³⁷

Diagnosis for CD typically starts with obtaining serum serology for tTG-IgA. This laboratory test is considered highly sensitive and specific for CD when total IgA levels are normal. If total IgA levels are low, as would be seen in IgA deficiency, false-negative tTG-IgA can arise. If a patient has a positive serology screen for CD, it is considered “gold standard” to confirm this diagnosis with a small bowel biopsy. Recent guidelines from one professional gastroenterology society suggests that a small bowel biopsy could be eliminated if tTG-IgA titers are greater than 10 times normal and anti-endomysial antibodies and HLA-DQ2 and HLA-DQ8 haplotypes are present.³⁸ Prospective HLA-DQ2 and HLA-DQ8 screening of young children with DS has also been suggested as a reasonable approach to identify children at risk for developing CD.²² Our DS patient cohort found to have CD was diagnosed before these recommendations were published; and therefore, prior “gold standard” recommendations regarding small bowel biopsies were used to confirm the diagnosis.

Celiac disease screening in DS continues to be an area of controversy. Some suggest obtaining serology only when clinical symptoms arise,¹¹ while others suggest universal screening^{30,39} or targeted annual CD screening only for those who are at risk after positive HLA screening.²⁷ It has also been suggested that screening asymptomatic children is not cost-effective to prevent intestinal lymphoma.⁴⁰ Additionally, placing asymptomatic patients on a gluten-free diet may decrease an individual’s quality of life. Difficulties can also arise when screening for CD only in those who are clinically symptomatic, as symptoms of CD can be vague. Common clinical symptoms thought to be attributable to CD include the classic symptoms of diarrhea, poor weight gain, and recurrent abdominal pain. Other symptoms might include constipation, anemia, short stature, and refractory developmental or behavioral problems.^{11,25} These symptoms often overlap with common behaviors and symptoms noted in individuals with DS. To confuse matters more, a Dutch study found that almost half of their patient population did not present with any symptoms relatable to CD.²⁷ However, an Italian study reported that 80% of their patients presented with symptoms attributable to CD.³¹ Conversely, it has also been reported that even in individuals who presented with concerning CD symptoms, very few were ultimately diagnosed with CD.¹⁸

Celiac disease screening in DS also should not be considered a “one time” endeavor, as it can develop over time. In our population, the average age of receiving a CD diagnosis was 16 years, considerably higher than previously suggested ages for routine screening.³⁹ Previous studies with lower rates of CD are noted to generally have a younger population,¹⁷ and conversely, those with higher rates were found in populations with older subjects.^{28,41} A recent study showed that older patients were more likely to have positive serology screens

but not necessarily positive biopsies, although only about 70% of this population with positive screens received biopsies.¹⁸ It appears that a high clinical suspicion for CD in individuals with DS should continue across the life span.

The main strength of this study is its longitudinal, population-based birth cohort design, and the availability of a medical record infrastructure that collects essentially all medical data for Olmsted County residents. This allowed us to karyotype-confirm all individuals with DS and review serology and histopathology data for those diagnosed with CD, rather than relying on parental report of CD diagnosis, which could lead to erroneous data.²¹ Most previous studies reporting the association between DS and CD have been based on data abstracted from regional subspecialty clinics, which may lead to a referral bias. Other previous studies have relied on national or regional registries or have recruited families from local parent support groups or newsletters,^{17–31} which may lead to information or selection biases.

This study also has limitations that should be taken into consideration. Olmsted County, Minnesota, is a predominately white population, and therefore, these results may not be generalizable to more diverse communities or minority groups. There is also the potential of missed cases that were not identified clinically, as 38% of our population was never tested for CD. Therefore, the 6.7% figure represents a minimum estimate of the incidence of CD in our population. Alternatively, Olmsted County is served by the Mayo Clinic, which is the main provider of health care for its county residents, and physicians at the Mayo Clinic may have a higher clinical suspicion for CD when caring for patients. Additionally, our 95% CI was wide (67–949) secondary to the low number of patients with DS.

In conclusion, we found CD to be far more common in patients with DS than in the general population. Rates of CD in DS vary widely across populations and are likely influenced by genetic and environmental factors; variations in published rates of CD in DS are also possibly influenced by selection bias or differences in diagnostic testing. Our data from a longitudinal population-based birth cohort support the AAP guidelines for children with DS to receive universal clinical screening for CD, but universal serology screening for CD remains more controversial. Routine serology screening for children with DS who are considered high risk by HLA testing could be a reasonable alternative.

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