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Frequency of Celiac Disease in Individuals with Down Syndrome in the United States

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Summary

Ninety-three individuals with Down syndrome (DS) were screened to investigate the prevalence of celiac disease (CD) in the United States. Five of the 93 individuals were antiendomysial antibody (EMA) positive. Of the 5 who tested positive for EMA, 4 were biopsied, 1 refused biopsy. Three of the 4 individuals biopsied manifested changes of CD on small bowel biopsy. This gives a frequency of 3.2% of confirmed CD in our DS individuals and suggests the need for periodic screening for celiac disease in this population.

Introduction

The high prevalence of immune-related disorders, such as autoimmune thyroid disease, diabetes mellitus, alopecia, and vitiligo, in individuals with Down syndrome (DS) is well recognized. In 1976, Bently¹ described, for the first time, a relationship between DS and celiac disease (CD) in a case study. Since then, a number of epidemiologic studies originating in countries such as Canada,² Netherlands,³ Sweden,⁴ Italy,⁵ and Australia⁶ have recognized a prevalence of CD varying from 1% to 7% in individuals with DS. This is in contrast to the incidence of CD of 1:3000–10,000^{4,7} in the general population in the United States. Classic signs and symptoms of CD include large bulky stools, diarrhea, steatorrhea, excess flatus, bloating, weight loss, short stature, failure to thrive, fatigue, and personality changes.⁴ In clinical practice though, symptoms in CD range from absent to characteristic, thus making the diagnosis obscure unless specifically investigated. In asymptomatic siblings of index cases of CD, a high incidence of positive antiendomysial antibodies has been found, suggesting that certain children may have latent CD that is manifested with immunologic markers but not yet with clinical symptoms. The increased frequency of CD in children with DS from European studies and the preliminary data from the United States reporting a prevalence rate of 4% to 5% of CD in DS,^{8,9} in addition to the subtle symptoms of the disease, which can overlap with the natural history of DS, raised our concern about the absence of guidelines for evaluating CD in DS. We developed, therefore, a clinical algorithm to screen for and further investigate the prevalence of CD in our DS clinic population in the United States.

Methods

Reported herein is the experience with 93 consecutive patients with a confirmed diagnosis of DS evaluated in our clinic for CD as part of a routine assessment for conditions known to be more prevalent in this population. All patients were older than 12 months and had gluten in their diets. Patients were clinically assessed for signs and symptoms of CD and had serologic tests. These tests included IgG anti gliadin antibodies (IgG-AGA), IgA anti gliadin antibodies (IgA-AGA), and antiendomysial antibodies (EMA). Children who were symptomatic, those with IgG-AGA greater than twice the reported upper limit of normal value, and those with positive EMA or positive IgA-AGA at any titer with or without symptoms were referred for a clinical evaluation and small bowel biopsy by a pediatric gastroenterologist. At least 3–6 small bowel biopsies were taken endoscopically from multiple areas in the third and fourth portions of the duodenum with standard biopsy forceps. In cases where the IgG-AGA was elevated with a normal IgA-AGA and a negative EMA, an immune profile was performed to exclude selective IgA deficiency. Upon referral, parents/caregivers were asked to complete a stool and symptom diary for a 1-week period before biopsy.

Results

Ninety-three patients (57 males and 36 females; ages 1 to 22 years, mean age 5.6 years) were screened for CD according to the algorithm. Seventy-one were Caucasian of mixed descent, 16 African-American, 5 Hispanic, 1 Asian, and 1 Native American. Of the 25 children who met criteria for referral to the gastroenterologist, 16 underwent small bowel biopsy and 9 were lost to follow-up or refused to undergo biopsy. Five patients had a positive EMA. Villous atrophy, reversed crypt-to-villous ratio, and intraepithelial lymphocytes consistent with CD were found in 3 Caucasian patients, ages 3, 6, and 10 years (2 males and 1 female). These 3 children had a positive EMA at titers from 1:10, 1:40, to 1:640. One of the 5 children (age 3 years) with a positive EMA titer of 1:40 had normal findings from small bowel biopsy including no evidence of intraepithelial lymphocytes. Four of these 5 patients had a biopsy. The one patient (age 3½ years) with a positive EMA titer of 1:5 refused biopsy. Of the remaining 12 children who were biopsied, 5 were IgG-AGA and IgA-AGA positive and EMA negative, and 7 were just IgG-AGA positive (Table 1). These results give a frequency of confirmed CD in our DS population of at least 3.2%. This indicates a high degree of sensitivity (100%) and specificity (~93%) for EMA concurring with the findings in previous studies.⁵ If the other 2 EMA-positive patients are included in the calculation, the prevalence of CD in this population increases to approximately 5.4%. All 3 children described abnormalities in stooling pattern: 1 with loose stools and gas, and 2 with a history of constipation. Families did not appear to be concerned with these changes, and growth velocity was not affected when plotted on the growth chart normed for children with DS. None of these 3 patients had thyroid disease or diabetes mellitus. Currently, all 3 are on a gluten-elimination diet, which resulted in improvement in the diarrhea in 1 patient and disappearance of constipation in the other 2 patients.

Discussion

The prevalence of confirmed CD in our patients with DS is at least 96 times greater than the prevalence of CD in the general US pediatric population, taking an incidence of 1:3,000. If the 2 patients with positive EMA markers are included and the incidence of CD taken as 1:10,000, then this proportional increase is even more dramatic. Reports of latent CD in other populations including relatives of index cases and patients with type I diabetes have suggested that patients with positive EMA antibodies and normal findings from small intestinal biopsies are still at risk of later development of overt symptoms of celiac disease.^{10,11} Early in the course, CD may be patchy and biopsies may miss affected areas. Host genetic and immune factors may determine the extent of villous atrophy and lymphocyte infiltration of epithelial mucosa, and

more subtle signs of immunologic activation may go unnoticed without specialized testing of mucosal biopsy specimens.¹²

This prospective study confirms the findings from other reported studies in the United States of an increased prevalence of CD in individuals with DS.^{8,9} It also supports the findings by others of a very low yield of identifying individuals with CD on biopsy if they are only IgG-AGA positive, thus virtually eliminating the need of an invasive procedure in this clinical setting. Since CD is often a silent disease, and children with DS tend to have constipation, diarrhea, and/or short stature attributed to their primary diagnosis (the only symptoms identified in our 3 patients diagnosed with biopsy-confirmed CD), screening of this at-risk population is needed.¹³ The Health Care Guidelines for Individuals with Down Syndrome 1999 revision¹⁴ recommends CD screening between ages 2 to 3 years. We agree with these guidelines; however, we further recommend serial evaluations with reliance on EMA after age 2 years. For under the age of 2, antiendomysial antibody screening is less reliable, and less specific antigliadin antibodies must be used for screening.¹⁵ For patients who are EMA positive and biopsy negative, a yearly clinical follow-up with attention to growth and gastrointestinal symptomatology is reasonable. These patients should also have yearly celiac disease screening. For other DS individuals, CD screening should be performed at least every 3 years or earlier if clinically indicated since CD could develop with age. Furthermore, since CD frequently has an atypical presentation in the older child and adult with DS,² we would advise that screening be continued into adulthood. Previous studies have also documented a very high prevalence of positive AGA (IgG and IgA) in patients with DS. Storm¹⁶ found that 31/78 (40%) cases of DS had abnormal values of AGA but only 6 (8%) had abnormal values of both IgG and IgA-AGA and only 2 of these 6 showed histologic changes of CD in the small bowel. We found that 39/93 (42%) of our patients had a positive AGA but only 7/93 (7.5%) were positive for both IgG and IgA-AGA and only 1 of these was EMA positive and had a small bowel biopsy consistent with CD (Table 1). The high prevalence of pathologic AGA levels is clearly not a specific immunologic marker of CD in DS patients and might indicate the occurrence of an altered mucosal immune system or simply nonspecific mucosal anomalies resulting in gluten permeability (i.e., gastroenteritis and food allergy).

The number of patients in our study was small, but our results are consistent with the approach of using EMA in combination with IgA-AGA to screen for CD in individuals with DS. Reported low sensitivity of EMA analysis in children <2 years of age suggests that a combined IgA-AGA and EMA analysis must be performed in that age group.⁴ IgG-AGA had both a low sensitivity and specificity and is not clinically useful. Recent reports indicate that an enzyme-linked immunosorbent assay (ELISA) determining quantitative titers of IgA antitissue transglutaminase antibody is highly sensitive and specific for detection of celiac disease, but high variability of values between laboratories has been a problem.¹⁷ Our clinical study, which shows a frequency of CD in our DS patients of at least 3.2%, provides further evidence of an increased prevalence of CD in DS in the United States. Further studies are needed to address the many remaining questions about the relationship of CD and DS including geographic and ethnic influence, age relationship to onset, symptomatic versus asymptomatic presentation, natural history of asymptomatic disease, and frequency of screening.

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REFERENCES

1. Bently D. A case of Down's syndrome complicated by retinoblastoma and celiac disease. *Pediatrics* 1976;56:131-133.

2. Russo P, Chartrand L, Seidman E. Comparative analysis of serologic screening tests for the initial diagnosis of celiac disease. *Pediatrics* 1999;104:75–78. [PubMed: 10390263]
3. George D, Mearin M, Bouquet J, et al. Screening for coeliac disease in Dutch children with associated diseases. *Acta Paediatr* 1996;412(suppl):52–53.
4. Trier J. Diagnosis of celiac sprue. *Gastroenterology* 1998;115:211–215. [PubMed: 9649477]
5. Bonamico M, Rasore-Quartino A, Mariani P, et al. Down syndrome and coeliac disease: usefulness of antigliadin and antiendomysium antibodies. *Acta Paediatr* 1996;85:1503–1505.
6. Gale L, Wimalaratna H, Brotodiharjo A, Duggan J. Down's syndrome is strongly associated with coeliac disease. *Gut* 1997;46:492–496. [PubMed: 9176077]
7. Nelson, W.; Behrman, R.; Kliegman, R.; Arvin, A., editors. *Nelson Textbook of Pediatrics*. Vol. 15th ed. WB Saunders Company; Philadelphia: 1996. p. 1095-1096.
8. Pueschel S, Romano C, Failla P, et al. A prevalence study of celiac disease in persons with Down syndrome residing in the United States of America. *Acta Paediatr* 1999;88:953–956.
9. Book L, Neuhausen S, Hart A, et al. Increased prevalence of celiac disease in Down's syndrome (abstract). *J Pediatr Gastroenterol Nutr* 1999;29:503.
10. Boudraa G, Hachelaf W, Benbouabdellah M, et al. Prevalence of coeliac disease in diabetic children and their first-degree relatives in West Algeria: screening with serologic markers. *Acta Paediatr* 1996;412(suppl):58–60.
11. Arranz E, Ferguson A. Intestinal antibody pattern of celiac disease: occurrence in patients with normal jejunal biopsy histology. *Gastroenterology* 1993;104:1263–1272. [PubMed: 8482440]
12. Picarelli A, Maiuri L, Mazzilli MC, et al. Gluten sensitive disease with mild enteropathy. *Gastroenterology* 1996;111:608–616. [PubMed: 8780564]
13. Zubillaga P, Vitoria J, Arrieta A, et al. Down's syndrome and celiac disease. *J Pediatr GastroenterolNutr* 1993;6:168–171.
14. Cohen W. Healthcare guidelines for individuals with Down syndrome: 1999 revision. *Down Syndrome Quarterly* 1999;3:1–15.
15. Vitoria JC, Castano L, Rica I, et al. Association of insulin-dependent diabetes mellitus and celiac disease: a study based on serologic markers. *J Pediatr Gastroenterol Nutr* 1998;27:47–52. [PubMed: 9669725]
16. Storm W. Prevalence and diagnostic significance of gliadin antibodies in children with Down syndrome. *Eur J Pediatr* 1990;149:833–834. [PubMed: 2146127]
17. Sugai E, Selvaggio G, Vazquez H, et al. Tissue transglutaminase antibodies in celiac disease: assessment of a commercial kit. *Am J Gastroenterol* 2000;95:2318–2322. [PubMed: 11007235]

Table 1
RESULTS OR CELIAC SCREENING OF 93 PATIENTS WITH DOWN SYNDROME—PREVALENCE OF 3.2%