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Screening for Celiac Disease In A Pediatric Primary Care Setting

Maureen M Leonard, MD¹, Rhonda Fogle, MD², Alexander Asch, MD², and Aubrey Katz, MD¹

¹Department of Pediatrics/Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Massachusetts General Hospital for Children, Boston, U.S.A.

²Department of Pediatrics Massachusetts General Hospital for Children, Boston, U.S.A.

Abstract

Celiac Disease (CD) is an autoimmune enteropathy in genetically predisposed individuals triggered by the ingestion of gluten. The prevalence in adults in the U.S. is increasing. Despite recognition of asymptomatic patients that benefit from screening and improved diagnostics, the majority of patients remain undiagnosed. The purpose of this study is to determine the prevalence of CD in at-risk and not at-risk pediatric patients in a primary care practice routinely screening for CD. The records of 2325 pediatric patients who underwent serological testing with IgA tissue transglutaminase (tTG) during a 5 year period were reviewed. Patients were categorized as at-risk or not-at-risk for CD. The prevalence of CD in at-risk patients was 1:26, the prevalence of CD in not-at-risk patients was 1:111. Our results suggest that the prevalence of CD in children approximates that of U.S. adults and that the true prevalence in children without known risk factors may be increasing.

Keywords

Adolescent; Autoantibodies/blood; Celiac Disease/Diagnosis; Celiac disease/epidemiology; Child; Diagnosis; Prevalence; Risk Factors; Screening; Transglutaminases/Immunology

Background

Celiac disease (CD) is a chronic, inflammatory enteropathy caused by the ingestion of gluten in a genetically predisposed individual.¹ The overall prevalence of CD in the United States has been reported as one in 133; those with a family history of CD are at a much greater risk.² The prevalence of CD in adults has increased from a global prevalence of 0.03% in the 1970's to current reports of 0.5% to 1.26% in Europe and the US.^{2,3,4,5} A large screening of a healthy population in the U.S. reports a frequency of 1:105 in adults without risk factors and 1:320 in children.²

Corresponding Author: Dr. M.M Leonard Department of Pediatrics/ Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Massachusetts General Hospital for Children. 175 Cambridge Street, CPZ-575 Boston, MA 02114 Phone: 617.724.2561 Fax: 617.724.2710. mleonard7@partners.org.

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According to the North American Society For Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines, children presenting with persistent diarrhea, poor growth, gastrointestinal symptoms, short stature, delayed puberty, dental enamel defects and iron deficient anemia resistant to oral therapy should undergo screening for CD. Individuals with a first degree family member with CD and those with associated diseases such as type 1 diabetes mellitus (T1DM), Down syndrome, thyroiditis, Turner's syndrome, or immunoglobulin A deficiency are suggested to undergo testing even if asymptomatic.⁶ Although guidelines from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) have expanded the atypical symptoms for which testing is recommended, an estimated 33-67% of patients are asymptomatic at the time of diagnosis.^{4, 7} Despite improved serological tests to diagnose CD and increased awareness of asymptomatic patients in high risk groups, the majority of individuals with CD are undiagnosed.

The evolution of the presentation of CD, increasing prevalence, and improvement in serological screening methods has led many to consider the utility and cost-effectiveness of screening programs in the United States(U.S).⁸ The purpose of this study was to determine the prevalence of CD in at-risk and not at-risk pediatric patients over a five year period in a primary care practice that has chosen to routinely screen their patients.

Methods

Setting

Serological testing for CD took place at a private practice consisting of two board-certified pediatricians with two office locations in the Greater Boston metropolitan area, Middlesex County, Massachusetts. Patients included in the study were referred over a five year period. Study procedures were approved by the Institutional Review Board at Massachusetts General Hospital.

Practice Population

Patients and families seen in this practice are primarily residents of Essex and Middlesex County, Massachusetts. The practice cares for approximately 3103 patients under twenty-years of age. According to U.S. Census data from 2008-2013, the local population is predominately white (>80%). Nearly 90% of persons aged twenty-five years or older have completed high school or obtained a higher degree. The median household income in these counties is between \$66,918 and \$79,691.⁹ The practice population reflects this description.

Subjects

Eligible subjects included patients between the ages of six months and twenty years who had serology testing for CD between January 2009 and May 2014. Patients were excluded from the study if they already carried a diagnosis of CD prior to 2009 except in the total practice prevalence calculation.

Patients were identified by review of the practice data which included all IgA tissue transglutaminase (tTG) serological tests run over the course of the study period. This list

was cross referenced with data obtained by referral physician name and ICD-9 code for CD at Massachusetts General Hospital for Children (MGHfC).

Charts of patients identified were reviewed. All patients who underwent testing for CD were classified as at-risk or not at-risk according to available data. At-risk individuals were defined as children with a first-degree family member with CD, those who presented with CD-associated symptoms such as abdominal pain, diarrhea, constipation, or poor growth. Subjects with CD-associated disorders such as anemia, osteoporosis, alopecia, and autoimmune thyroid disease were included in the at-risk group. Finally patients younger than 9 years were also included in the at-risk group as routine testing of patients occurred in patients older than 9 years of age. Patients classified as not-at risk were asymptomatic at diagnosis, did not have any CD associated symptoms or conditions reported according to attainable records, and were older than 9 years of age.

Screening Protocol

The time period for patient inclusion into the study was chosen based on the time during which the practice began routine screening for CD. This practice aims to screen adolescents, at the same time they are sending a lipid panel in accordance with the recommendation of the Expert Panel guidelines for cardiovascular health and risk reduction in childhood, commissioned by the National Heart, Lung, and Blood Institute.¹⁰ In approximately 2008 when this decision was made to begin screening, physicians screened patients that were at least 9 years of age and older at routine visits. Once a child was found to have abnormal celiac serology, their siblings were screened at the next visit if they were older than two years of age and parents were encouraged to undergo screening as well.

Serology

Serum specimens for IgA tTG, and in certain cases anti-endomysial antibody (EMA) were sent to Quest Diagnostics for immunoassay. All tests sent for IgA tTG were reviewed; EMA testing was reviewed in selected cases. During the study period, the reference lab designated threshold for a normal IgA tTG value changed. Between 2009 and 2012 the value was 9 units per milliliter with equivocal values between 5-8 units per milliliter. After 2012, a positive value was designated as greater than 4 units per milliliter. EMA antibody testing was deemed negative if the titer was less than 1:5 per the reference lab.

Histology

Biopsies were obtained via upper endoscopy and specimens from the distal duodenum and bulb were studied. Histology reports of patients were reviewed by one of the authors of the study. Biopsy's were scored using Marsh Criteria modified by Oberhuber (0=normal, I=increased intra-epithelial lymphocytes, II= increased intra-epithelial lymphocytes and crypt hyperplasia, III= increased intra-epithelial lymphocytes, crypt hyperplasia, and partial, sub-total, and total villous atrophy; types IIIa, IIIb, and IIIc respectively.^{11,12} If biopsy revealed multiple Marsh scores, the most severe was used.

Diagnosis of CD

Patients were referred to Pediatric Gastroenterology and Nutrition Unit at MGH/C for duodenal biopsy if they had an elevated or equivocal IgA tTG as defined by the reference lab and in one case an isolated elevated IgA EMA. Patients were diagnosed with CD if they had compatible serology and intestinal damage consistent with a score of Marsh III.

Statistical Analysis

Descriptive statistics were used to evaluate IgA tTG performance and the means and standard deviation of age. The students T test was used to evaluate the age of presentation. The BMI did not approximate normal distribution and thus the median is reported. The Wilcoxon Rank Sum test was used to determine significance between groups comparing BMI at diagnosis.

Results

A total of 2325 patients (51% male) were tested for CD over the 5 year study period which represented approximately 75% of the practice patients twenty years of age or younger. Since screening aims to occur after age nine, we expected that a certain number of individuals in the practice would not have been screened. The mean age of individuals tested for CD was 13.3 years with the range from 6 months to 20 years. Sensitivity and specificity of IgA tTG (Table 1) is in agreement with previous studies. Upon review, a total of 37 patients were diagnosed with CD during this time period. Ten patients who were diagnosed with CD prior to the study period were monitored via serology with IgA tTG during this time period. Only one of the 37 newly diagnosed patients did not undergo duodenal biopsy. This patient had a positive IgA tTG, positive IgA EMA and had a sibling diagnosed with CD with confirmatory biopsy on account of this practices' screening process. For the purpose of this study, this patient was categorized having CD. At the end of the study period, the practice prevalence in patients under twenty years of age was 1.5%.

Patients diagnosed with CD were characterized as at-risk or not at-risk in order to better assess the prevalence of CD in these groups; their characteristics are shown in Table 2. The prevalence of patients at-risk for CD was 3.2%. In this population, 70% of patients classified as at-risk presented with intestinal complaints such as abdominal pain, diarrhea, or constipation (Table 3). The prevalence of CD in children without known risk factors or symptoms was 1%. Patients with newly diagnosed CD were evaluated for a family history of autoimmune disease, including CD or other autoimmune disease, in first or second degree family members. This presence of a first or second degree family member with CD is known to increase a child's risk of developing CD.^{2,13} In this study two of fourteen patients identified via case finding methods had a first degree family member with CD and both were asymptomatic. There were no known 2nd degree family members with CD in patients in the at-risk group. In patients not at-risk with newly diagnosed CD, there were no individuals with a first degree member with CD, as that would have placed them into the at-risk group, however one siblings pair were diagnosed at the same time via screening and four of the twenty (20%) newly identified patients with CD had a second degree family member with known CD.

Conclusion

The prevalence of CD in adults in the U.S. is approximately 1% and has increased 5 fold in the past thirty years.¹⁴ In this pediatric practice, the prevalence of CD was 1.5%. The prevalence of CD in at-risk children was 3.2% and the prevalence in children not at-risk was 1%. We classified patients as at-risk according to the current NASPGHAN and ESPGHAN guidelines regarding who should be screened for CD based on presenting symptoms and family history as well as age since routine screening in the practice would not have occurred before age 9. Our findings are comparable to previous studies which place the prevalence of CD in children in the U.S. between 1.7% and 3.2%.^{15,2}

The presence of a first-degree family member with CD increases a child's risk of developing CD to nearly 14 times that of the general pediatric population.² In children with a second degree relative with CD their risk increases by 10 times that of the general pediatric population.² As a secondary analysis we matched our risk groups to that from Fasano *et al* in 2003 which took into account patients with a second degree family member with CD.² In our practice population, the prevalence of CD in at-risk children was 1:26 compared to the previously reported 1:25 in 2003 and 1:57 reported in 2000.^{2,15} The prevalence of CD in our cohort of pediatric patients without a known risk factor for CD was 1:111 compared to 1:320 in 2003.² Although exploratory in nature, this increase in likelihood of having CD despite a lack of signs, symptoms, or a family history of CD may be clinically meaningful and is suggestive of a potential increase in the prevalence of CD in the pediatric population. This increase is in accordance with previous research that showed the prevalence of CD has doubled every fifteen years for the past thirty years in adults.¹⁴

In our cohort, 60% of all newly diagnosed patients were asymptomatic which is consistent with recent data.⁴ At-risk children diagnosed with CD were significantly younger than patients identified by general screening, which is expected given that they had risk factors which prompted early testing. BMI was significantly lower in the at-risk patients which would also be expected since the majority of these children (86%) had intestinal complaints. Current NASPGHAN guidelines suggest screening for CD in patients with first-degree relatives with CD. In this practice we may have identified an additional four individuals by expanding the family history intake to include a history of CD in second-degree family members. Therefore, expanding the screening guidelines to include this group may be useful. Additionally, by following NASPGHAN guidelines and testing first degree relatives once a diagnosis of CD is made, an additional four patients were found to have CD, two of which were parents of index cases.

Our results are limited by the study population which is restricted to a private practice location with residents from primarily two Massachusetts counties. However, the study with which we compared our findings obtained 87% of their not-at risk pediatric study population from schoolchildren in a total of four West Virginia counties while at-risk children were recruited at routine office visits and CD support group meetings. It is unclear how different these populations may be but certainly both are from a fairly localized region. Age and gender representation were similar between cohorts. Our population, given the large

Caucasian representation may have been biased towards a higher prevalence of CD. However, sampling in both cohorts is comparable.

The practice prevalence of 1.5% is the lower limit in this population given that 25% of the practice has not been tested for CD. This is expected since a percentage of patients should not have yet met the age criteria for routine testing. In addition, since CD can present at any age it is possible that patients tested in 2009 may have seroconverted by the end of the study. Due to the retrospective nature of this study, it is possible that the calculated prevalence of patients at-risk for celiac disease is exaggerated as the number of patients with a family history of CD or associated autoimmune disorders may have been underreported. This limitation highlights the increased prevalence of CD in our otherwise not-at risk group, as an underrepresentation of the family history data would further increase the likelihood of CD in the not at-risk group, which has already increased nearly 3 fold compared to 2003.

Routine screening for CD remains a controversial topic. Asymptomatic individuals with a positive EMA receive benefit from a gluten free diet (GFD) in terms of intestinal, serological, and symptomatic measures.¹⁶ However, compliance with a GFD in asymptomatic adolescents found via screening is poor.¹⁷ Although IgA tTG has been shown to be effective in screening for CD, CD can develop at any age. Thus, the timing and frequency of optimal serological screening is unknown. As the cost of HLA testing decreases, stratifying individuals by risk given their HLA haplotype may help to better identify this optimal screening time. Earlier identification of individuals at-risk through HLA testing, potentially at birth may allow for better identification, closer monitoring, and potentially improved compliance with the GFD once diagnosed in children at the highest risk.^{18,19} A recent study found that 38% of patients with a first degree family member with CD and homozygosity for HLA DQ2 may develop CD by age 10.¹⁹ IgA tTG is a relatively inexpensive test, its use may be maximized if high risk ages are known and screened. Combining celiac screening with other tests, in this case the lipid panel generally performed between age 10 and 12, may be a feasible way to screen high risk patients and minimize risks. Ongoing studies evaluating the natural history of CD, especially those based on haplotype, will contribute greatly to our understanding of this issue.^{18,19} Prospective studies evaluating the cost-effectiveness and adherence to a GFD in a screened positive pediatric population are needed.

This study suggests that the prevalence of CD in children approximates that of U.S. adults and that the true prevalence in children without known risk factors may be increasing.² By strictly adhering to NASPGHAN and ESPGHAN guidelines on identifying at risk patients and additionally screening healthy patients older than 9 years old, this practice increased the prevalence of CD in their practice by 5 fold. Following current screening guidelines and expanding them to include screening of second-degree family members with CD, resulted in diagnosing approximately only half of the individuals in this practice ultimately diagnosed with CD. While genetic screening for patients with a family history of CD may help to stratify patients known to have an increased risk, screening patients without a known history remains a challenge especially for asymptomatic patients. Physicians should keep CD at the top of their differential diagnosis for the wide variety of gastrointestinal symptoms, extra intestinal manifestations and well described CD-associated conditions. Obtaining a detailed

family history paying particular attention to history of autoimmune disease and CD in first and second degree relatives may improve diagnostic rates.

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Table 1

IgA tTG Performance

Sensitivity	97.4%
Specificity	<u>99.9%</u>

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Table 2

Characteristics of Celiac Disease Cases Found According to Risk Status

	Case Finding (17)	Screening (20)
Gender	7 F (39%)	11 F (61%)
* Age (mean $\pm$ SD)	8.4 (6)	15 (3.2)
** BMI (median)	16.5	21.2
Prevalence	3.2%	1%

* Statistically significant p=0.0002

** Statistically significant p=0.019

Table 3

Symptoms reported by Children At-Risk for Celiac disease

Abdominal Pain, diarrhea, constipation	12 (70%)
Reflux alone	1 (6%)
Asymptomatic	2 (12%)
Fatigue	1 (6%)
Alopecia	1 (6%)
	Total 17