The Utility of Anti-tissue Transglutaminase Antibody-IgA (tTG-IgA) Testing for Celiac Disease in Adults with Down Syndrome

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Abstract

Objectives: We assessed the diagnostic accuracy of the anti-tissue transglutaminase IgA antibody (tTG-IgA) test compared to esophagogastroduodenoscopy (EGD) in adults with Down syndrome (DS).

Methods: Retrospective chart review of 152 adult patients with DS who were diagnosed with celiac disease (CD).

Results: Of these patients, 141 (92.8%) had a positive tTG-IgA and 11 (7.2%) had a negative result. Eighty-one (53.3%) did not have an EGD performed due to patient or legal representatives declining. Of the 71 who had a biopsy, the result of the tTG-IgA in 29 (40.8%) was a true positive, 35 (49.3%) a false positive, 2 (2.8%) a true negative, and 5 (7.0%) a false negative. The sensitivity was 85%, specificity 5%, positive predictive value 45%, and accuracy 43.7%.

Conclusions: The low specificity, accuracy, and positive predictive values of tTG-IgA in people with DS have significant clinical and financial implications in diagnosing, treating, and screening for CD in people with DS.

Introduction

Celiac disease (CD) is an autoimmune reaction to the protein gluten that can damage the villi of the small intestine and interfere with the absorption of nutrients. When left untreated, CD can lead to malnutrition, anemia, osteoporosis, liver diseases, and cancer (particularly non-Hodgkin's lymphoma).[1,2] Symptoms include abdominal bloating and pain, chronic diarrhea, vomiting, constipation, weight loss, anemia, fatigue, bone or joint pain, arthritis, bone loss or osteoporosis, seizures, depression, anxiety, canker sores in the mouth, and dermatitis herpetiformis.[1]

During the typical diagnostic process of CD, an antibody blood test, such as the anti-tissue transglutaminase IgA antibody (tTG-IgA) test, is performed. Positive antibody blood tests are confirmed through the "gold standard," duodenal biopsy, performed during an esophagogastroduodenoscopy (EGD).[3] TTG-IgA testing has been studied extensively and the sensitivity and specificity for untreated CD has been reported to be 95%.[4,5]

Upon making the diagnosis, treatment consists of eating a diet free of gluten. Apart from requiring significant patient education, motivation, and follow-up, following a gluten-free diet for a lifetime can be challenging due to the high prevalence of gluten-containing foods.[6] Furthermore, a gluten-free diet costs more than an average gluten-containing diet.[7] Therefore, an inaccurate diagnosis can cause unnecessary challenges in both dietary compliance and financial cost.

The need for an accurate diagnosis is particularly important in people with Down syndrome (DS) as a subpopulation with a higher incidence of CD.[8-11] DS is the most common known chromosomal cause of an intellectual disability. It is associ-

ated with a higher incidence of some health problems such as hypothyroidism, type 1 diabetes mellitus, and congenital heart disease and a lower incidence of others such as atherosclerotic disease, hypertension, and solid tumors.[12,13] Despite the higher incidence of CD in people with DS, studies of the diagnostic accuracy of antibody tests have primarily emphasized individuals in the population without DS[6], and less is known about their accuracy in individuals with DS.

Although there is lack of information regarding the accuracy of tTG-IgA in people with DS, some patients with DS and their families may elect to proceed to a gluten-free diet based on the blood test results and avoid undergoing an EGD with biopsy. Because anesthesia complications are more common in people with DS[14], patients with DS or their families may elect to avoid the biopsy because it requires anesthesia; thus relying on an unsubstantiated and potentially inaccurate diagnosis of CD. An improved understanding of the accuracy of tTG-IgA is needed to assist people with DS and their families to make the decision regarding proceeding with or foregoing the EGD with biopsy and proceeding with the diet. This study examined the diagnostic accuracy of the tTG-IgA test compared to EGD with biopsy in adults with DS. The social effects and financial costs of adopting a gluten-free diet based on the tTG-IgA blood test alone are also discussed.

Methods

Study Design: This is a retrospective chart review study of 152 adult patients with DS who received care for CD at the Advocate Medical Group Adult Down Syndrome Center located in Park Ridge, Illinois, from January 1, 2000, to October 31, 2012. This study was approved as expedited by the Advocate Health Care's Institutional Review Board on December 10, 2012. A waiver of consent was granted for accessing patients' records to collect information about their age, gender, tTG-IgA, and EGD with duodenal biopsy results.

Analysis: Due to lack of evidence about the diagnostic characteristics of the tTG-IgA as compared to the EGD with duodenal biopsy in the population with DS and the exploratory purpose of the study, we relied on a convenience sample of all patients with DS who were diagnosed with CD at our institution during a 12-year timeframe. Descriptive statistics (means, standard deviations, range) are reported for age and frequencies (%) for gender and test results. Sensitivity, specificity, positive and negative predictive value, prevalence, and accuracy of the tTG-IgA test were calculated. The data for this study were analyzed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL).

Results

There were 152 patients who met the study's inclusion criteria. The patients were adults with a mean age of 42.3 (± 12.1, range 20-64); 77 (50.7%) were female and 75 (49.3%) were male. Of these patients, 141 (92.8%) had a positive tTG-IgA result, while 11 (7.2%) had a negative result. However, only 71 (46.7%) patients had an EGD performed. The EGD results were positive for 34 (22.4%) and negative for 37 (24.3%), while 81 (53.3%) did not have an EGD performed due to patient or legal representatives declining (Table 1).

Table 1: Patients characteristics and test results (n = 152)

Variable	Value
Age, mean (SD), range	42.3 (12.1) [20-64]
Gender, n (%)	
Male	75 (49.3)
Female	77 (50.7)
tTG-IgA Result, n (%)	
Positive	141 (92.8)
Negative	11 (7.2)
EGD Result, n (%)	
Positive	34 (22.4)
Negative	37 (24.3)
Declined	81 (53.3)

tTG-IgA = anti-tissue transglutaminase immunoglobulin A; EGD = esophagogastroduodenoscopy

Of the patients who underwent an EGD with biopsy, 29 (40.8%) had a true positive result, 35 (49.3%) had a false positive result, 2 (2.8%) had a true negative result, and 5 (7.0%) had a false negative result. The sensitivity of the tTG-IgA was 85%, specificity was 5%, positive predictive value was 45%, negative predictive value was 29%, accuracy was 43.7%, and prevalence was 47.9% (Table 2).

Table 2: Diagnostic values of the tTG-IgA (n = 71)

Variable	Value
True Positive, n (%)	29 (40.8)
False Positive, n (%)	35 (49.3)
True Negative, n (%)	2 (2.8)
False Negative, n (%)	5 (7.0)
Sensitivity, %	85
Specificity, %	5
Positive Predictive Value, %	45
Negative Predictive Value, %	29
Accuracy, %	43.7
Prevalence, %	47.9

tTG-IgA = anti-tissue transglutaminase immunoglobulin A

Discussion

The assessment of CD includes evaluating symptoms, physical exam, blood testing, and EGD with biopsy. During the EGD, at least 2-3 biopsies of the duodenum are taken as the standard diagnostic approach used at our institution for the diagnosis of CD in adults with and without DS. The most common histological findings expected include villous atrophy, crypt hyperplasia, thickening of the basement membrane under the surface epithelium, increased intraepithelial lymphocytes, and influx of immune cells in the lamina propria with enterocyte changes.[15]

Although the incidence of CD is higher in people with DS, the presentation of symptoms of CD is similar for people with and without DS.[16] One exceptional note is the higher likelihood of adults with intellectual disabilities, including DS, of presenting with behavioral changes in response to physical health conditions.[17] Therefore, in the diagnostic assessment for CD in adults with DS, both their psychological and physical symptoms should be carefully considered by both primary care and specialty physicians so that health problems like celiac disease are not missed and/or under-assessed.

The next step in the diagnostic approach is blood testing, and tTG-IgA is the preferred test.[6] The recommendation for tTG-IgA as the preferred test is partly based on the reported high sensitivity and specificity in the general population.[4,5] However, the present study found much lower values for these statistical measures of tTG-IgA in people with DS, thus making the test less accurate in the diagnostic process. However, without the findings of the present study of a low specificity and thus, an assumption of the same high specificity noted for those without DS, many patients with DS and their families opted to proceed with the gluten-free diet without a biopsy. With a positive predictive value of only 45%, more than 50% of the individuals who elected to proceed with the diet without biopsy may be on the diet despite not having CD.

To proceed with the diet without a diagnosis of CD has the potential to cause unnecessary cost. The cost of gluten-free food is $1.10 more per 100 grams.[7] Since an average individual eats 420 grams per day[18], the increased cost is $4.62 daily and $1,686.30 per year. The cost may be further increased because in order for a person with DS to follow the diet, our clinical experience has found that the whole household may need to follow a gluten-free diet. In a family of three (including the person with DS), the potential annual cost increase may thus be over $5,000.00. If the diet is followed for 30 years by this family, the potential cost increase of the food alone is over $150,000.00. While the cost difference of gluten-free food may decline over time, presently, the cost differential can be substantial over a lifetime. In addition to the financial cost, there is potential social cost. Increased independence is a social goal for people with DS[19] and this may be hampered by the inability of some individuals with DS to manage a gluten-free diet independently. As a result, inaccurate diagnosis may increase the number of individuals whose efforts at independence are unnecessarily imposed.

The issue of screening also arises. At present, there is not a recommendation to screen all people with DS with blood testing. However, while the American Academy of Pediatrics health guidelines for children with DS recommends assessing for symptoms at annual visits in early childhood[20], others have recommended universal serology screening.[16] One argument for screening is to prevent lymphoma of the gastrointestinal tract. Swigonski et al[21] found that the cost of universal serology screening of children with DS was more than $500,000.00 per life-year gained from lymphoma and almost $5 million to prevent a single case of lymphoma. This cost was based on their use of a positive predictive value of 93%. However, with our finding of a positive predictive value of less than half of that, the potential cost of prevention of lymphoma in screening could double.

The overall cost of annual universal screening for people with DS would also be substantial. There are an estimated 250,000 people with DS in the United States.[22] At our hospital, the cost of the tTG-IgA blood test is $141.00. If all 250,000 were screened in a year, the cost of the blood test alone would be $35,250,000.00. However, this cost could decrease as some individuals who were diagnosed with CD would no longer need annual screening.

Another substantial excess cost of using a test with a low sensitivity would be in the follow-up EGDs. Using the incidence of CD in DS of 15% and the number of people with DS as 250,000, theoretically, 37,500 people with DS will be diagnosed with CD. However, even if we assume those with a false positive tTG-IgA underwent only one biopsy in a lifetime, with a positive predictive value of 45%, an additional 45,833 individuals with a false positive tTG-IgA would require a biopsy that would ultimately be negative. With a national average cost of an EGD estimated to be $2,700.00[23], the total cost of 83,333 EGDs is estimated to be $224,999,100.00. The cost of the additional 45,833 EGDs for those with a false positive tTG-IgA would be $123,749,100.00. It is important to note that the actual cost for people with DS is likely to be higher due to the frequent need for greater anesthesia, difficulty complying with testing, the potential for increased anesthesia complications, and the potential cost of treating those complications.[14]

The American College of Gastroenterology (ACG) guidelines for evaluating and treating CD include tTG-IgA as the recommended serology test for CD.[6] High sensitivity and specificity of tTG-IgA in people without DS is important in recommending this test. However, even with a highly accurate tTG-IgA, the recommendation for the assessment of CD still includes evaluation of symptoms, serology testing, and EGD with biopsy for diagnosing CD. The need for assessing all three components of the evaluation (symptoms, tTG-IgA, and EGD with biopsy) is increased when one component is less accurate such as tTG-IgA in people with DS. Another reason to assess all three components is the complicating issue of gluten sensitivity. There is a group of individuals whose tTG-IgA and biopsy are not consistent with CD but have gluten sensitivity, and who may benefit from a gluten-free diet.[6] When assessing symptoms in these individuals, the ACG recommends a full evaluation in-

cluding serology evaluation and EGD with biopsy to rule out CD before proceeding with a gluten-free diet. Less is known about gluten sensitivity in people with DS.

While celiac disease has been strongly linked to human leukocyte antigens (HLA) located on chromosome 6, with 85% to 100% of people with CD carrying either a HLA-DQ2 or HLA-DQ8 heterodimer, these tests are not part of the standard diagnostic approach to CD.[24,25] Although HLA-DQ2 or HLA-DQ8 have been found to have better specificity than tTG-IgA, to date, no studies have assessed their diagnostic characteristics in people with DS. Also, genetic tests like HLA-DQ2 or HLA-DQ8 confirm the genetic predisposition rather than the presence of the celiac disease, and they are usually expensive and not covered by insurance, thus incurring additional financial costs. Until the diagnostic characteristics of HLA-DQ2 or HLA-DQ8 in people with DS are confirmed, EGD with biopsy remains the gold standard for making an accurate diagnosis.

This study found a lower sensitivity, specificity, and positive predictive value for tTG-IgA in patients with DS when compared to those without DS.[5] The importance of assessing symptoms and performing an EGD with biopsy to make an accurate diagnosis is heightened when the tTG-Ig is less accurate. Furthermore, the low values for these measures of test accuracy will limit tTG-IgA as a potential screening tool for asymptomatic people with DS. The overall financial, social, and medical costs are substantial and need to be considered when screening for asymptomatic CD in people with DS.

This study has limitations that should be carefully considered when interpreting the study results. First, we relied on a convenience sample of patients with DS who were diagnosed with CD at our institution during a given timeframe, thus limiting the generalizability of the study findings to other patients with DS. Second, we relied on retrospective data that were collected through patients' charts, thus limiting the amount of information collected for individual patients. Taking into account these two important limitations, we recommend that future studies employ prospective study designs with larger sample sizes to confirm the diagnostic characteristics of the tTG-IgA in adult patients with DS. Further research should also include evaluation of a protocol that carefully assesses pre-treatment symptoms, tTG-IgA or other serology, EGD with biopsy, and post-treatment symptoms in people with DS. It is important, however, to carefully take into consideration the feasibility, practicality, and ethics of the prospective study designs when conducting research with adults with DS.[26] Finally, additional studies should include assessment of the potential need and benefit of universal screening as well as cost issues, and possibly, alternative serologic tools needed in assessing CD in adults with DS.

Acknowledgement

We would like to thank Inna Trey, MD, for her help with data collection.

Previous Presentations: *Portions of this project have been presented as a poster at the American Academy of Family Physicians Scientific Assembly in San Diego, CA, in September 2013; at the Family Medicine Midwest - Illinois Association of Family Physicians in Milwaukee, WI, in October 2013, and at the 2013 Advocate Research & Innovation Forum at Advocate Lutheran General Hospital in Park Ridge, IL.*

Potential Financial Conflicts of Interest: By AJCM® policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The authors have stated that no such relationships exist.

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