

Avoiding Small Intestinal Biopsies for Diagnosis of Celiac Disease in Children: A Reliable Strategy for All Patients?

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ABSTRACT

Background: Current reports applying ESPGHAN exception criteria (EEC) to diagnose celiac disease (CD) without duodenal biopsies indicate that a high percentage of patients with CD may be identified when applied correctly in specialized settings. Application of the EEC, however, in “daily life conditions” at the different levels of medical services is not clear.

Methods: EEC was applied to 130 pediatric patients evaluated for CD at 5 public hospitals in Santiago, Chile, during 2010 to 2015. Clinical presentation, serum anti-tissue transglutaminase 2 and anti-endomysium antibodies (EMA), genotyping, and small intestinal histology were obtained from clinical charts.

Results: A total of 78 of 130 patients reviewed had some of the data required for analysis, but EMA was determined in 54% and genotyping in 2.3% of patients, limiting the study. After offering free genotyping, only 12 of 78 (15%) had all data required for EEC application. In this small group, 10 of 12 (83.3%) patients could avoid duodenal biopsies and 2 (16.7%) with potential CD were misdiagnosed. Main reasons for not doing EMA and genotyping were that they are expensive, unavailable in the local health care center, and considered “not necessary” for diagnosis.

Conclusion: Limited resources in clinical settings reduce availability of EMA and genotyping, making application of EEC criteria difficult and only possible only in 15% of our patients. Within this subgroup, biopsies could be avoided in 83.3%, and 16.7% of patients with potential CD were misdiagnosed. Insufficient studies and incorrect interpretation of EEC contributed to incomplete assessment in 52 of 130 (40%) patients. The Chilean public health system is likely representative of several others present in developing and developed countries.

Key Words: celiac disease, diagnosis, duodenal biopsy, ESPGHAN

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What Is Known

- Diagnosing celiac disease requires a specialist and costly studies.
- Anti-tissue transglutaminase 2 antibodies and anti-endomysium antibodies have high sensitivity/specificity, are easily accessed, and are less expensive than endoscopic duodenal biopsies.
- ESPGHAN 2012 exception criteria propose to avoid biopsies in patients with well-defined characteristics, an attractive strategy for public health systems.

What Is New

- Assessed in the public health system of a middle-income country, the diagnostic process did not include all data required for application of ESPGHAN 2012 exception criteria.
- In our small group of patients with celiac disease meeting ESPGHAN 2012 exception criteria, 83% could have avoided biopsies, and 17% with suspected celiac disease were misclassified.
- Misinterpretation of the criteria contributed to incomplete assessment in 40% of patients.

In 2012, ESPGHAN defined exception criteria (EEC) for the diagnosis of celiac disease (CD) (1): children and adolescents with signs or symptoms suggestive of CD and high IgA-tissue transglutaminase 2 (TTG) titers with levels >10 times upper limit of normal have a high likelihood for villous atrophy (Marsh 3). The EEC suggest that “the pediatric gastroenterologist discuss with the parents and patient (as appropriate for age) the option of performing further laboratory testing (EMA, HLA) to make diagnose CD without biopsies.”(1)

The possibility that patients may not require small intestinal biopsies for diagnosis has raised much interest. Published results, however, are still inconclusive, mainly because most available studies address only 1 of two separate questions that must be answered: whether EEC correctly identify celiac patients, and in daily life, do nonspecialized medical services have the capability to provide all necessary data to apply EEC correctly? Benelli et al (2) and Wolf et al (3) showed that 11% of patients could avoid small intestinal biopsy. These results contrast with the report of Donat et al (52%) who found a higher percentage (4), but this report does not clarify the proportion of patients that did not enter analysis because they did not fulfill EEC requirements. Indeed, in most publications, the proportion of patients diagnosed by EEC

application is calculated against the number of patients that already have complete data, therefore responding to the first question (5–11). Mills et al expressed concern that the EEC strategy is highly dependent on targeting a high-risk population with a high pretest probability of CD (12). In addition, results are influenced by the serology assays used, which are not always standardized and applied using appropriate cutoffs (13). Additionally, in all reports to date, a proportion of patients are diagnosed with potential CD without histological information while still being classified in the studies as having confirmed CD (14,15,16). As the course and prognosis of potential CD are not clear, future studies should clarify the consequences of this potential error. Individuals without CD and with transitory high TTG titers have also been reported (17).

We hypothesized that in standard clinical settings, which include all levels of medical services, some with limited resources, EEC may lead to relevant diagnostic errors if inappropriately applied. To test this hypothesis, we assessed patients referred for evaluation of CD in 5 public pediatric hospitals in Santiago, Chile. Chile has a per capita income of US\$ 23,460 (2015) and a well-structured wide-coverage public health system. In this context, specialists are available only in tertiary centers (hospitals), and the waiting list for endoscopy may be a few months, especially in places distant to main cities. At the same time, economic constraints are relevant to meet health costs for a large segment of population. We report the proportion of patients that could avoid small intestinal biopsies, potential CD patients that would be misclassified, and the main factors found that impede the application of the EEC.

METHODS

Study Group

We report on 130 patients younger than 18 years consulted for diagnostic evaluation of CD in the 5 participating public hospitals in Santiago, during 2010 to 2015. Study flowchart is presented in Supplemental Figure 1 (Supplemental Digital Content, <http://links.lww.com/MPG/B195>). Data including clinical characteristics, blood studies, small intestinal biopsies, and genotyping were obtained from clinical charts. INTA's Institutional Review Board approved the study protocol. Legal guardians and patients signed an informed consent or assent before inclusion in this protocol.

Diagnostic Procedures

Data on serum total IgA, IgA-TTG, anti-endomysium antibodies (EMA), genotyping, and endoscopic duodenal biopsies were recorded. The routine local diagnostic procedure for biopsies was applied, obtaining 1 biopsy from bulb and at least 4 from duodenum. TTG was measured at each hospital, using commercial ELISA kits (AESKU®, INOVA, IMMCO, or EUROINMUN) and following manufacturer's instructions and limits of normalcy. As only 3 of 130 patients were initially genotyped, patients were contacted, and a free genetic study was offered in our laboratories; only 75 accepted and the remaining patients refused the test as "not necessary." Genotyping was performed using a commercial kit DQ-CD Typing plus (BioDiagene, Palermo, Italy) (18). Statistical analyses included descriptive statistics for metric and non-parametric variables.

RESULTS

Clinical Characteristics

TTG was positive and serum IgA was within normal levels in all 130 patients. In 118 of 130 (90.8%), duodenal biopsies were classified Marsh ≥ 2 , CD was diagnosed, gluten-free diet was

TABLE 1. Main clinical characteristics at diagnosis in 78 patients diagnosed celiac disease by IgA-antitransglutaminase antibodies, duodenal biopsy, and genotyping

	N (%)
Sex, girls	47 (60.0)
Age, y	
<4	33 (42.3)
4–8	20 (25.6)
8–12	15 (19.2)
12–18	10 (12.8)
Gastrointestinal symptoms	
Abdominal pain	44 (70.0)
Diarrhea	41 (65.0)
Weight loss	32 (50.8)
Abdominal distention	31 (49.2)
Vomiting	19 (30.2)
Under nutrition	17 (27.0)
Constipation	14 (22.2)
Extragastrintestinal symptoms	
Short stature	21 (26.9)
Anemia	13 (20.6)
Nutritional status	
Malnutrition	9 (11.5)
Under nutrition	11 (14.1)
Eutrophic	27 (34.6)
Overweight	9 (11.5)
Obesity	2 (2.6)
No data	20 (25.6)
Genetic/autoimmune diseases	
Down syndrome	7 (9.0%)
Diabetes type 1	5 (6.4%)
Autoimmune thyroiditis	4 (5.1%)
First-degree relative with celiac disease	17 (22%)

initiated, and patients responded satisfactorily. Duodenal biopsies classified Marsh 0 to 1 in 12 of 130 patients (9.2%); these patients were diagnosed "potential CD." Only 78 (60%) patients had data available for serum IgA, TTG, and genotyping and entered EEC analysis (Table 1). EMA was only measured in 42 of 78 patients (54%). Mean age at diagnosis (years \pm SD) was 6.37 ± 1.13 years, 43% were diagnosed before 4 years of age, and time from onset of symptoms to diagnosis was 23.9 ± 15 (range 1–144) months.

Intestinal symptoms were present in 63 of 78 patients (81%). One patient was admitted for celiac crisis. Approximately one-third had normal growth (Table 1). Extraintestinal manifestations were observed only in children older than 3 years. Among 7 patients with Down syndrome, 2 also experienced type 1 diabetes and hypothyroidism.

Applying EEC

In 73/78 (94%) patients, TTG results were available for both a numerical value and laboratory cutoff, while five (6%) reported a numerical value but no cutoff. In 21/73, TTG values were >10 times the normal value (Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/MPG/B195>). EMA, determined in 14 of 21, was positive in 12; all these were genotyped. Thus, only 12 patients fulfilled the ESPGHAN criteria (Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/MPG/B195>). Analysis of data for EEC application showed that although TTG was expressed as needed in 21 patients and EMA was positive in 35 (Table 2), both tests were positive only in 12 patients

TABLE 2. Histology, genotyping, IgA-TTG and, EMA values in 78 patients diagnosed celiac disease

Duodenal biopsy Marsh classification	Genetics DQ2/DQ8	IgA-TTG			EMA Positive
		>10 times cut off	<10 times cut off	Numeral value No cut off	
0	6	2	4	0	1
1	6	1	5	0	2
2	3	1	2	0	1
3	62	17	41	5	31
Total	77*	21	52	5	35

EMA = anti-endomysium antibodies; IgA-TTG = immunoglobulin A-tissue transglutaminase 2.

*One genotype not identified.

(15%) (Supplemental Figure 1, Supplemental Digital Content, <http://links.lww.com/MPG/B195>); 2 of these 12 patients (17%) were cases of potential CD; one was asymptomatic, carried HLA-DQ2, and his duodenal biopsy was classified Marsh 0; the other reported occasional diarrhea and abdominal pain, carried HLA-DQ2 and HLA-Q8, and his duodenal biopsy was classified Marsh 1.

In 41 of 52 (79%) patients with TTG <10 times the cut-off, severe mucosal injury was present (Table 2). Severity of histological damage showed no differences by age. Distribution of higher/lower TTG titers did not differ in patients with different degrees of duodenal damage. All patients carried HLA-DQ2 and/or DQ8, except for one whose genotype was not identified (Table 2), a 4-year and 10-month-old girl with diarrhea and abdominal pain, IgA-TTG 115 U/mL, positive EMA, and duodenal biopsy categorized as Marsh 3b. Her response to gluten-free diet has been clearly positive and satisfactory. Gastrointestinal symptoms were the presenting manifestations in 34, 5 presented with under nutrition, and 4 had no symptoms except short stature (n = 2) or diabetes type 1 (n = 2).

DISCUSSION

Only 78 of 130 (60%) patients had data necessary for analysis; 12 of these 78 (15%) fulfilled the all requisites to apply EEC. In this small group, 83.3% could have avoided upper endoscopy with duodenal biopsy. This indicates that the answer to the first question is yes; EEC may be a potent tool in pediatric patients when necessary data are available, which is likely limited to highly specialized centers where patients have all necessary tests done and specialists are available (2,3,12,13). Yet, EEC seems unsuitable to be used indiscriminately at all levels of medical service. That 85% did not meet the requisites to apply the exception criteria should not be ignored. Smarrazo et al recently reported results of a study of 14 Mediterranean countries that assessed the routine diagnostic process for CD including total IgA and IgA-TTG determination in blood and endoscopic duodenal biopsies. Neither EMA nor genotyping were performed routinely because the cost of EMA had to be covered by the patient, and genotyping was available only in a few clinics in the capital city at a high cost and not covered by health insurance (18). These findings are relevant because the different levels of the Chilean public health care system are likely representative of those present in several other less developed as well as developed countries.

In our study, EEC was usually misinterpreted both by patients and health professionals as acceptable to diagnose CD without intestinal biopsies. This misunderstanding contributes to an adverse diagnostic situation, in this case, that 40% of patients did not complete their diagnostic studies with the argument that more studies are expensive and “not necessary.” As in Smarrazo et al’s study (18), our results reveal limitations of the public health systems

and economic constraints of patients and public health services that encourage acceptance of diagnostic procedures excluding and ignoring other well-known criterion standards. Accepting the EEC criteria so that patients correctly assessed could avoid duodenal biopsy deserves attention because at present some authors state that serological diagnosis has proven to be accurate and beyond discussion (19,20). These authors, however, ignore current data strongly suggesting that results depend on the tests that are offered in the local area and whether a specialist is available to take responsibility for their interpretation. An additional concern is that patients with potential CD are misclassified when histological information is absent (9,15–17,20). Applying the diagnostic procedure that includes biopsies, 9.2% of the patients with potential CD were recognized correctly, in contrast to the 16.7% assigned wrongly in absence of histology.

Our study results, that 79% of patients with IgA-TTG <10 times the upper normal value showed severe lesions (Marsh 3) in small intestinal biopsies, corroborates other studies (5,18) and supports the contention that TTG is unreliable in predicting histologic changes, both at time of diagnosis and during follow-up (21–23). In adult patients, Holmes et al found that when TTG is 45 U/mL (>8× upper limit of normal plus 2SDs), its positive predictive value for diagnosing CD is 100% (7). Indeed, establishing the upper limit of normal threshold deserves further study; differences between assays make it difficult to harmonize results between centers as different performance characteristics are observed with each assay (13).

In summary, results confirm that EEC may be a practical clinical tool when correctly applied to pediatric patients because it diminishes the need for small intestinal biopsies, decreases time to diagnosis, is less invasive for the child and family, and is likely to be financially beneficial to health services. EEC, however, should not be used by medical services without the capacity to perform all necessary tests and/or when the population receiving medical care and the health systems involved have relevant economic constraints. How to manage patients with potential CD (15,16,18) that will be incorrectly categorized as confirmed celiac disease awaits further investigation.

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