Normalization Time of Celiac Serology in Children on a Gluten-free Diet

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ABSTRACT

Objectives: Response to a gluten-free diet (GFD) in children with celiac disease is determined by symptom resolution and normalization of serology. We evaluated the rate of normalization of the transglutaminase (TTG) and antiendomysial (EMA) for children on a GFD after diagnosis.

Methods: Celiac serologies were obtained over 3.5 years after starting a GFD in 228 newly diagnosed children with biopsy-proven celiac disease. Patients were classified into categories based on serology (group A, TTG $\geq 10 \times$ upper limit of normal [ULN] and EMA $\geq$ 1:80; group B, TTG $\geq 10 \times$ ULN and EMA $\leq$ 1:40; and group C, TTG $< 10 \times$ ULN) and by severity of histologic injury at diagnosis.

Results: In children with the highest serology at diagnosis (group A), 79.7% had an abnormal TTG at 12 months after diagnosis (mean TTG 12 months, 68.8 ± 7.3, normal <20 kU/L). At 2 years, an abnormal TTG persisted in 41.7%. In contrast, only 35% of children with the lowest serology at diagnosis (group C) displayed an abnormal TTG at 12 months (mean TTG 14.3 ± 1.9 kU/L). In those with the most severe mucosal injury, Marsh 3C, 74.2% and 33.2% had an abnormal TTG at 1 and 2 years.

Conclusions: Normalization of celiac serology took >1 year in approximately 75% of GFD-compliant children with the highest celiac serology or most severe mucosal injury at diagnosis. Clinicians must consider serology and histology at diagnosis to properly evaluate response to GFD.

Key Words: celiac disease, gluten-free diet, normalization of serology

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What Is Known

- Within 2 years on a strict gluten-free diet, 95% of children display histologic recovery.
- Celiac disease guidelines suggest that serology normalizes by 12 months and recommend no repeat biopsies for children who demonstrate a clinical response to a gluten-free diet.

What Is New

- More than 75% of children with the highest serology at diagnosis display an elevated transglutaminase at 12 months.
- More than 35% of those with a transglutaminase <10 times the upper limit of normal at diagnosis display a minimally elevated transglutaminase at 12 months.
- One third of children with total villus atrophy take more than 2 years to normalize celiac serology.

Celiac disease (CD) is an autoimmune enteropathy that affects approximately 1% of the population (1–3). The IgA antibodies, tissue transglutaminase (TTG), and antiendomysial (EMA) serve as excellent screening tests essential to the diagnostic algorithms for CD diagnosis (4–6). A strict life-long gluten-free diet (GFD) diet is the only accepted treatment for CD.

Present guidelines recommend serial TTG measurements to monitor successful treatment and advise that serology normalization should be achieved after 12 months on a GFD (4,7). Positive serology at 1 year after starting a GFD could suggest gluten contamination (7). Furthermore, these guidelines presume that normalization of antibody tests after starting a GFD reflects mucosal healing. The published pediatric literature confirms that mucosal healing in children often precedes the normalization of TTG and EMA (8–10). These studies, however, have not evaluated serial postdiagnosis antibody levels or correlated rate of decline with prediagnosis antibody levels or severity of intestinal injury. This lack of information on when antibodies should normalize may create confusion for clinicians, who must determine if the response to the GFD is adequate or if further investigations are necessary.

In adults who adhere to a GFD, histological remission occurs in approximately 65% by 2 years (11–13). The recovery in children on a GFD progresses faster than in adults (13), ranging between 88% and 96% histologic recovery within 2 years (8,13) and 100% by 5 years (13). Serologic normalization lags behind histologic recovery in some children (8,9). Present pediatric celiac guidelines advise against performing repeat duodenal biopsies after the diagnosis unless there is an incomplete response to a well-managed GFD or persistent elevation of celiac serology (4,5,9).

We have previously shown that the positive predictive value (PPV) of the TTG and EMA as predictors of CD varies with the degree of TTG and EMA elevation (6). Symptomatic children with a TTG >10 times the upper limit of normal (ULN), and an EMA $\geq$ 1:80, had a 100% PPV for biopsy confirmed CD. In those

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with a TTG <3 times ULN and negative EMA, the PPV of CD was only 13.3% (6). We hypothesized that the degree of elevation of the serology and the severity of intestinal injury at diagnosis influences the rate of antibody decline after the initiation of a GFD. The present study aims to characterize the normalization of the TTG and EMA in children on a strict GFD, based on the degree of elevation of serology or severity of mucosal injury at diagnosis.

METHODS

Case Identification and Data Collection

Consecutive patients (younger than 18 years of age) with celiac serology displayed in the Calgary Laboratory Services database from July 2008 to December 2011 were identified. All patients had a serum IgA (Roche Diagnostics, Laval, Quebec, Canada) and IgA-tissue TTG performed (Euroimmune, Lubeck, Germany). If the TTG was positive (>20 kU/L), an IgA-EMA antibody test was measured by an indirect immunofluorescence method (IMMCO Diagnostics, Buffalo, NY). Positive samples were serially diluted from titers of 1:2.5 to 1:1280.

Intestinal biopsy results were obtained from the Alberta Children's Hospital Pathology Database from July 2008 to April 2012. This hospital is the only pediatric gastroenterology referral center in southern Alberta. Duodenal biopsies were re-reviewed by 1 pathologist (CLT) (6) and a modified Marsh score was assigned (14). The clinic charts and small-bowel pathology reports were reviewed, and data on the following parameters were extracted: all celiac serology (TTG and EMA) performed at the time of diagnosis and over a 3.5-year period of follow-up; clinical information and date of biopsy; small-intestinal biopsy results at diagnosis, including the modified Marsh score; and dietary history including compliance and response to a GFD at each follow-up clinic visit. Diet history included frequency of gluten ingestion. Gluten exposure <3 times per year was considered to be excellent compliance.

Data Analyses

Patients were classified into groups according to the TTG and EMA recorded closest to the time of intestinal biopsy: group A, TTG at least 10 times ULN (≥200 kU/L) and EMA at least 1:80; group B, TTG at least 10 times ULN and EMA at most 1:40; and group C, TTG <10 times ULN. Patients were included if the TTG was measured <6 months before the biopsy to account for time from time of referral to biopsy. We observed that the group of patients with a TTG at least 10 times ULN, and an EMA between 1:80 and 1:1280 displayed similar recovery of antibody levels, as evidenced by overall Kaplan-Meier curves and means (group A). The group with an initial EMA 1:2.5 to 1:40 (group B) also had similar curves and mean values but were distinctly different from group A. Thus, a threshold of an EMA at least 1:80 was selected to divide the patients with an initial TTG at least 10 times ULN as clinically these patients normalized at a different rate from group B. Patients with an initial TTG <10 times ULN (group C) normalized even earlier than group B, and were analyzed separately. An EMA at least 1:80 is also the threshold that we have demonstrated previously to elicit a 100% PPV for the nonbiopsy diagnosis of CD (6). Data were analyzed if the child displayed at least 1 repeat celiac screen after diagnosis and complied with a strict GFD on follow-up visits. Patients were excluded if statements in clinic follow-up letters that raised issues with adherence to the GFD and/or if serology during the follow-up period increased. If serology increased, investigations to evaluate for noncompliance with a GFD were conducted.

The mean and median TTG were calculated at 4 time points: 6 months (range 2–8 months, n = 109), 12 months (range 9–18 months, n = 131), 2 years (range 19–30 months, n = 56), 3 years (range 31–40 months, n = 33). For 93% of the data points (304/329), there was 1 TTG value over the time period. For 7% of data points, values occurred on either side of the time point. For these values, the mean TTG was used for that patient over the specified time period.

Statistics

Results were analyzed using SPSS software version 22 (SPSS Inc, Chicago, IL). To evaluate significant differences between groups, independent t tests were calculated with mean ± SEM reported. Cumulative event rates were assessed by Kaplan-Meier survival curves. The overall log rank (Mantel-Cox) was calculated to compare equality of survival distributions. Where appropriate, median, mean, and 95% confidence intervals (CIs) were calculated. P values with a $P < 0.05$ were considered significant. The University of Calgary Conjoint Health Research Ethics Board approved the present study.

RESULTS

During the study period, 347 children were diagnosed with CD based on positive serology and duodenal biopsy. Of those, 119 patients (34.3%) were excluded for the following reasons: no repeat serology within 2 years after diagnosis (n = 70, 20.1%), noncompliance with a GFD based on history or serology (n = 46, 13.2%), other (n = 3, 0.9%).

The analysis was conducted on the remaining 228 children who were stratified into 3 groups according to the celiac serology at diagnosis—group A: TTG at least 10 times ULN (≥200 kU/L) and EMA at least 1:80, n = 95; group B: TTG at least 10 times ULN and EMA at most 1:40, n = 72; and group C TTG <1.1 to 9.9 times ULN, n = 61 (Table 1). All patients in group A and B had a positive EMA, and in group C, 80.3% (49 patients) had a positive EMA up to a level of 1:80. The mean age at diagnosis was 10.4 ± 4.3 years (range 1.8–18.3 years) and 28 children (12.3%; 95% CI 8.3–16.7) were diagnosed with CD before the age of 5. These young children were more likely to present with the highest degree of elevation of celiac serology (group A 20.0% vs 5.6% and 8.2% in group B and C, $P < 0.05$ A vs B or C). The majority of patients (65.5%) were girls and of all patients, 81.1% were symptomatic (95% CI 75.6–85.7). Of the 43 asymptomatic children, 19 (8.3%) had type 1 diabetes mellitus. There was no significant difference in the time to normalization of celiac serology in asymptomatic versus symptomatic patients or those with versus those without type 1 diabetes mellitus. The intestinal biopsies of patients in group A were significantly more likely to have total villous atrophy (Marsh 3C) than groups B or C (group A 57.7%, group B 21.8%, group C 20.5%, $P < 0.001$ A vs B or C).

Figure 1 provides the median and interquartile ranges of TTG results for each group at 6, 12, 24, and 36 months after intestinal biopsy. In each group, the number of repeat serologies varied by time period. A significantly greater number of patients had a repeat value at 6 months (109/228; 47.8%, 95% CI 41.4–54.3) compared to 24 months (56/228; 24.6%, 95% CI 19.4–30.5) or 36 months postdiagnosis (33/228; 14.5%, 95% CI 10.5–19.6; $P < 0.001$, 6 vs 24 or 36 months and 24 vs 36 months, Fig. 1). In addition, those children with the highest initial serology (group A) had significantly more repeat celiac screens over the 3-year follow-up period than group B or C (12 months postdiagnosis group A 68.4% vs group C 44.3%, $P < 0.01$; 24 months group A 37.9% vs group B 19.4% or group C 9.8%, $P < 0.01$; 36 months group A 24.2% vs group B 11.1%, $P < 0.05$; Fig. 1; Supplemental Digital Content 1, Table 1, *http://links.lww.com/MPG/A703*).

Six Months Postdiagnosis

By 6 months postdiagnosis, the cumulative proportion of patients with an elevated TTG was higher in group A (96.7 ± 1.9%)

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TABLE 1. Baseline characteristics of patients with biopsy-proven CD who had at least 1 repeat celiac screen within 2 years postdiagnosis

	Total all TTG	Group A ≥10 × ULN and EMA ≥ 1:80	Group B ≥10 × ULN and EMA ≤ 1:40	Group C <10 × ULN	P
N	228	95, 41.7%	72, 31.6%	61, 26.7%	
Female (N, %)	150, 65.8%	63, 66.3%	47, 65.3%	40, 65.6%	
Age at diagnosis					
Mean age, y	10.4 ± 4.3	9.5 ± 4.4	10.6 ± 3.9	11.5 ± 4.2	
≤5	28, 12.3%	19, 20.0%*	4, 5.6%*	5, 8.2%*	*P < 0.05
Clinical presentation (N, %†)					
Asymptomatic	43, 18.4%	21, 22.1%	9, 12.5%	13, 21.3%	
Marsh score (N, %‡)					
1 (n, %)	1, 0.4%	0	1, 100%	0	
2 (n, %)	1, 0.4%	0	0	1, 100%	
3A (n, %)	49, 21.5%	15, 30.6%	14, 28.6%	20, 40.8%	
3B (n, %)	99, 43.4%	35, 35.4%	40, 40.4%§	24, 24.2%§	§P < 0.01
3C (n, %)	78, 34.2%	45, 57.7%‖	17, 21.8%‖	16, 20.5%‖	‖P < 0.001

CD = celiac disease; EMA = antiendomysial; TTG = transglutaminase; ULN = upper limit of normal. N represents the total number in each category.
*$P < 0.05$ A vs B or C.
†Percentage was calculated based on the total in each group.
‡Percentage was calculated based on the total in each Marsh category.
§$P < 0.01$ B vs C.
‖$P < 0.001$ A vs B or C.

than group B (85.9 ± 4.1%) or C (68.9 ± 5.9%, overall comparison $P < 0.001$, Fig. 2). The mean TTG at this time period was also higher in group A (93.1 ± 10.4 kU/L, normal < 20 kU/L) than group B (59.4 ± 9.1 kU/L) or C (22.6 ± 3.7 kU/L; A vs B, $P < 0.05$; A vs C or B vs C, $P < 0.001$; Supplemental Digital Content 1, Table 1, *http://links.lww.com/MPG/A703*). Similar to the TTG results, the cumulative proportion of patients with an elevated EMA at 6 months was greater in group A (95.6 ± 2.2%) than B (75.9 ± 5.1%) or C (62.9 ± 6.1%, overall comparison $P < 0.001$, Fig. 2).

Twelve Months Postdiagnosis

At 1 year following diagnosis, the cumulative percentage of children with an elevated TTG in group A was 79.7 ± 4.3% (Fig. 2) with a mean TTG of 68.8 ± 7.3 kU/L, >3 times the ULN (Supplemental Digital Content 1, Table 1, *http://links.lww.com/MPG/A703*). In contrast, in group B 59.1 ± 6.1% of patients had a mildly elevated TTG (mean TTG 28.6 ± 4.7 kU/L). In group C, only 35.4 ± 6.2% had an elevated TTG with a mean TTG in the normal range (14.3 ± 1.9 kU/L). The cumulative proportion of patients with an elevated EMA at 12 months was also higher in group A (69.7 ± 4.9%) than group B (40.6 ± 6.0%) or C (29.1 ± 5.9%, overall comparison $P < 0.001$) (Fig. 2).

It took significantly longer for 50% of children in group A to normalize their TTG (1.94 ± 0.10 years) than group B (1.31 ± 0.10 years) or C (0.95 ± 0.07 years, $P < 0.001$ group A vs B or C; $P < 0.01$ B vs C, Fig. 2). Similarly, the time for 50% of children to normalize the EMA was significantly longer in group A (1.60 ± 0.09 years) than B (1.04 ± 0.08 years) or C (0.81 ± 0.05 years, overall comparison $P < 0.001$, Fig. 2).

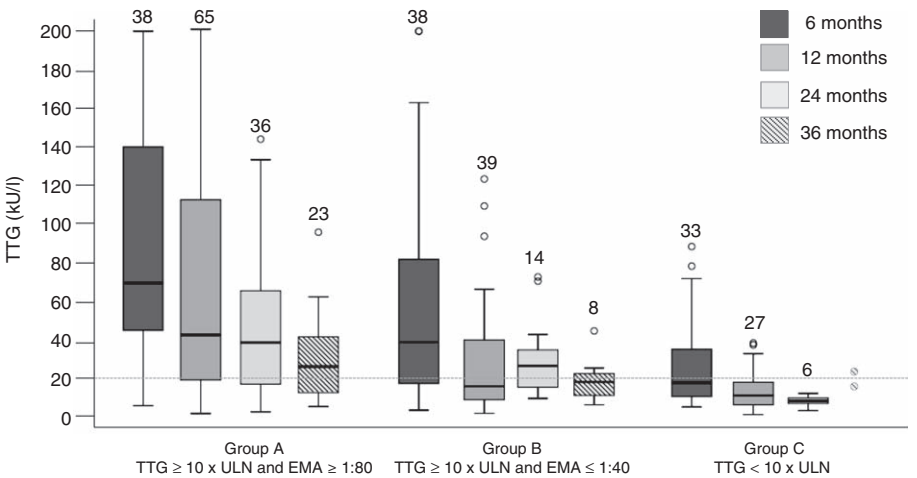

FIGURE 1. TTG levels (kU/L) for groups A, B, and C at 6, 12, 24, 36 months postdiagnosis. Box-and-whisker plots represent the minimum TTG, 25th percentile, median TTG, and 75th percentile and maximum TTG. Outlying values >1.5 times the interquartile range are displayed as open circles. Numbers above box plots represent the number of patients in each group. The dotted line represents the upper limit of normal TTG (<20 kU/L). EMA = antiendomysial; TTG = transglutaminase; ULN = upper limit of normal.

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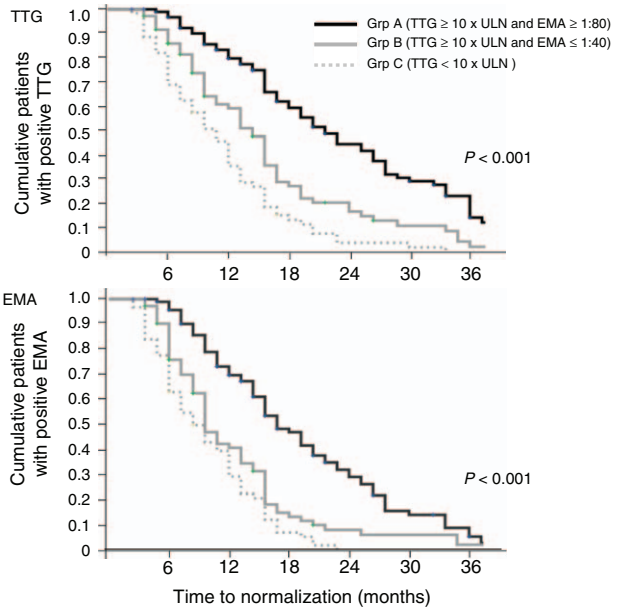

FIGURE 2. Kaplan-Meier survival curves by group of children with CD demonstrating normalization of TTG and EMA over time after starting a GFD. *P* value refers to the comparison of the time to normalization of for groups A, B, and C using the log-rank test. CD = celiac disease; EMA = antiendomysial; GFD = gluten-free diet; Grp = group; TTG = transglutaminase; ULN = upper limit of normal.

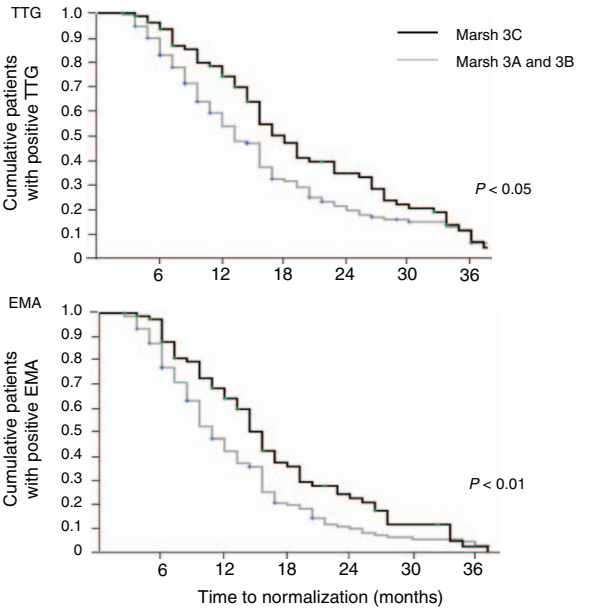

FIGURE 3. Effect of histologic severity at diagnosis on the proportion of children with CD with positive TTG and EMA over time, presented as Kaplan-Meier survival curves. *P* value refers to the comparison of the time to normalization of Marsh 3C versus Marsh 3A and 3B groups using the log-rank test. CD = celiac disease; EMA = antiendomysial; TTG = transglutaminase.

Two Years Postdiagnosis

At 2 years following diagnosis, the cumulative percentage of patients with an elevated TTG in group A was 41.7 ± 5.6% compared with 16.7 ± 4.9% in group B (Fig. 2). The mean TTG in group A was 46.9 ± 6.1 kU/L compared with 29.6 ± 5.4 kU/L in group B ($P < 0.05$; Supplemental Digital Content 1, Table 1, *http://links.lww.com/MPG/A703*). The EMA also remained elevated in 28.9 ± 5.2% of children in group A compared with only 5.9 ± 3.1% in group B (Fig. 2). In contrast, all patients in group C had normalized their TTG and EMA by 2 years (mean TTG 8.1 ± 1.2 kU/L, A or B vs C, $P < 0.01$; Supplemental Digital Content 1, Table 1, *http://links.lww.com/MPG/A703*).

Three Years Postdiagnosis

The cumulative proportion of children with a positive TTG at 3 years postdiagnosis was 14.2 ± 4.4% and 2.2 ± 2.1%, in group A and B (Fig. 2). The mean TTG was still mildly elevated in children in group A (31.3 ± 4.7 kU/L), whereas those in group B and C were in the normal range (19.2 ± 4.2 kU/L and 19.7 ± 4.1 kU/L; Supplemental Digital Content 1, Table 1, *http://links.lww.com/MPG/A703*). Similar to the TTG findings, a small proportion of patients still had an elevated EMA after 3 years (group A 5.2 ± 2.9% vs group B 2.0 ± 1.9%, Fig. 2).

Transglutaminase and Antiendomysial Recovery Compared With Severity of Histology at Diagnosis

In children with total villus atrophy at diagnosis (Marsh 3C), recovery of both TTG and EMA were significantly delayed compared with children with milder intestinal injury (Marsh 3A–3B; overall comparison $P < 0.05$, Fig. 3). Of the children with a Marsh 3C lesion at diagnosis, the mean TTG remained elevated in 74.2 ± 5.1% and 33.2 ± 5.8% at 1 and 2 years postdiagnosis compared with 54.0 ± 4.3% and 19.7 ± 3.6% of children with a Marsh 3A or 3B lesions at diagnosis. Similarly, recovery of EMA was delayed at 1 and 2 years in those with Marsh 3C histology at diagnosis compared with those with milder intestinal injury ($P < 0.01$, Fig. 3).

DISCUSSION

Our study is the largest thus far to examine the normalization of the celiac serology in children with CD after starting a GFD (9,10,15). Excellent guidelines have been developed to assist physicians to diagnose children with CD. These guidelines also recommend that caregivers obtain serial TTG measurements to follow response to the GFD (4,5,7). Some recommend that further investigations be carried out if serology remains abnormal after 1 year on a GFD (7). Minimal evidence-based information, however, exists on longitudinal follow-up about the rate of normalization of celiac serology in children with CD.

The present study addressed the important question of how quickly the TTG and EMA fall after starting a GFD. Intuitively one may expect those with higher titers at diagnosis to take longer to normalize, with some support for this in the literature (15). In the present study, children with the most abnormal serology or total villus atrophy at diagnosis took up to 3 years to normalize TTG and EMA values while strictly adhering to a GFD. Furthermore, this information is especially relevant for clinicians caring for children diagnosed by the new ESPGHAN ''non-biopsy'' algorithm for CD (4), as children who qualify for a ''non-biopsy'' diagnosis would fall into the study groups A (TTG ≥ 10 × ULN and EMA ≥ 1:80) or B (TTG ≥ 10 × ULN and EMA ≤ 1:40).

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The prompt normalization of celiac serology on the GFD is listed as one of the major criteria used to assess the response of children who fulfill the ''non-biopsy'' algorithm for the diagnosis of CD (4). At 6 and 12 months postdiagnosis, <5% and 15% of patients with the highest TTG and EMA (≥1:80) at diagnosis displayed normal serologies. After 2 years on a GFD, 40% of these children displayed a mildly elevated TTG, and 14% were still abnormal after 3 years. In contrast, 40% of children with a TTG at least 10 times ULN and lower EMA values (≤1:40) and two thirds of those with TTG <10 times ULN at diagnosis were seronegative within 12 months after starting a GFD. Almost all children with a TTG <10 times ULN and over 70% of those with a TTG at least 10 times ULN and EMA at most 1:40 at diagnosis were seronegative by 18 months. These children warrant expert evaluation for inadvertent gluten exposure if their serology remains elevated at 18 to 24 months after diagnosis. Children with the highest serological values at diagnosis who demonstrate a consistent decline in serology while reportedly adhering to a GFD, likely do not require evaluation for gluten exposure until 3 years after diagnosis. Our data are in keeping with previous pediatric evidence that demonstrates 55% and 80% of children are seronegative at 1 and 2 years following diagnosis (10). This smaller study did not evaluate the rate of recovery by degree of serologic abnormality at diagnosis. In all 3 groups, despite variations in the overall rate of complete normalization of serology, the mean TTG declined by at least 60% at 6 months after starting a GFD. Of particular importance, in those with the highest serologic elevations at diagnosis, the mean TTG fell from at least 10 times ULN to a mean of 3 times ULN at 1 year. When the decline in TTG and EMA were compared, there were no statistical differences in the time to normalization within each group Caregivers must consider TTG and EMA antibody levels at the time of diagnosis when interpreting serology results after 6 months to 3 years on a GFD to eliminate unnecessary repeat endoscopy in children who report no symptoms and strict adherence to a GFD.

Pediatric guidelines do not recommend a repeat biopsy in children when symptoms resolve and serology normalizes on a GFD (4). They do not, however, address the management of a child who is asymptomatic, reports adherence to a GFD and displays minimal elevation of serology, TTG <3 times ULN, and a negative EMA. In approximately 20% of patients in our study, the last measured TTG was <3 times ULN and in all of these, the EMA was negative. The time period for these minimally elevated values ranged from 3.5 to 36 months postdiagnosis. Previously, we demonstrated that only 13% of patients with a positive TTG <3 times ULN and a negative EMA displayed biopsy evidence of CD (6). Furthermore, a pediatric study that evaluated the ability of serology to predict mucosal healing demonstrated that a negative EMA is the best predictor of healing (8). Thus, children with a TTG <3 times ULN and a negative EMA likely have healed their mucosa.

We also described the trend in normalization based on histologic severity at diagnosis using the modified Marsh classification (14). Children with total villous atrophy at diagnosis (Marsh 3C) took significantly longer to normalize serology than those with partial (Marsh 3A) or subtotal (3B) villous atrophy. Only 26% with Marsh 3C histology at diagnosis had normalized serology after 12 months on a GFD compared with 45% with Marsh 3A or 3B injury. At 2 years postdiagnosis, more than one third of patients with Marsh 3C injury displayed mildly (<3 × ULN) abnormal TTG levels with no symptoms. By 3 years, 7% of TTGs in this group remained abnormal. Children with total villus atrophy at diagnosis take longer to normalize serology on a GFD than those with milder injury.

Emerging evidence demonstrates that serial follow-up of patients with CD improves overall dietary compliance. In particular, the compliance in teenagers is especially problematic (16,17) with compliance rates as low as 34% (18). Our retrospective study demonstrates that the frequency of follow-up serology dramatically drops off after 2 years postdiagnosis. Those patients with milder elevations at diagnosis were even less likely to have repeat serology after it normalized. In addition, 20% of patients received no follow-up serology after diagnosis. Furthermore, an additional 13% did not adhere to a GFD. The pediatric celiac guidelines emphasize the importance of regular follow-up of children with CD (4,5,7). At minimum, patients with CD should be seen periodically by a health care professional to assess growth, symptoms, dietary compliance, and perform annual celiac serology and hemoglobin with periodic thyroid screening. Families should be offered access to a registered dietitian knowledgeable in the GFD. More research needs to be performed to determine how frequently and effectively these recommendations are performed for North American children. Better strategies need to be developed and evaluated to help children and young adults who struggle with the GFD.

Potential limitations in this retrospective review include that repeat serologies were not collected at uniform serial time points after diagnosis. Thus some patients may have normalized their serology sooner than the time of blood collection. Furthermore, at the time of the study, our center did not use a standardized tool to assess adherence to a GFD. Adherence to a GFD was determined on questioning during the follow-up visit including frequency of gluten contamination. Some but not all patients met with a registered dietitian knowledgeable in the GFD to assess dietary gluten content. Thus some patients without full compliance to a GFD may have been included in the analysis. We did, however, exclude the 13% of patients who either reported nonadherence to a GFD or displayed an increase in serology during follow-up. In both of the above cases, our results could overestimate the length of time for celiac-related serology to normalize. Our study does not provide information on the correlation between antibody values and mucosal recovery. Thus, the significance of elevation in celiac-related serology is mainly extrapolated from adult data. A pediatric follow-up study, however, demonstrated excellent correlation with negative celiac serology results, a negative report using a simple dietary questionnaire and mucosal healing in children on a GFD (9). Furthermore, only 22% with positive serology displayed evidence of intestinal injury and some of these reported gluten ingestion on a standardized questionnaire. Better noninvasive tools to assess mucosal healing need to be developed for children.

In summary, serologic recovery in newly diagnosed children with CD varies by the degree of elevation in serology and the severity of mucosal injury at diagnosis. Physician knowledge about the expected rate of decline of celiac serology is important to appropriately counsel patients, to avoid additional family stress, excessive blood work, and invasive investigations. At the same time, it is imperative to distinguish those patients with probable inadvertent gluten exposure based on an increase or a slow rate of decline in serology to implement prompt dietary review and intervention.

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