

Presentation of Pediatric Celiac Disease in the United States: Prominent Effect of Breastfeeding

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Summary: Childhood celiac disease (CD) is considered rare in the United States. Consequently there are few data concerning its clinical presentation. A validated questionnaire was distributed to families of children with CD. One hundred forty-one children with biopsy-proven CD were included in the study. We found significant differences in the clinical spectrum of children based on their infant feeding history. Exclusively breastfed children were significantly less likely to report failure to thrive (69% vs 88%, $p < 0.05$) and short stature (37% vs 62%, $p < 0.05$), and had a higher rate of "atypical" symptoms ($p < 0.01$). Breastfeeding alters the presentation and contributes to atypical presentations of CD and diagnostic delay. Pediatricians need to be aware of the diverse manifestations of celiac disease to reduce diagnostic delay. *Clin Pediatr.* 2005;44:249-258

Introduction

Celiac disease (CD), or gluten-sensitive enteropathy, is an immune-mediated intolerance to gluten, the main storage protein found in wheat, and to similar proteins

found in rye and barley. It is a life-long disorder that requires individuals to completely avoid ingestion of gluten.¹⁻³ Celiac disease has traditionally been thought to be a rare disorder in American children, affecting 1 in every 2,000 to 5,000.⁴⁻⁶ The classic pic-

ture of a child with celiac disease is one of less than 2 years of age with typical malabsorption symptoms, including large, foul-smelling, diarrheal stools; abdominal bloating; and poor growth. The past few decades have revealed an increase in celiac disease in Europe that has not been seen in the United States.^{1,6} In recent years many European studies have shown a striking increase in the prevalence of childhood celiac disease based on serologic screening of both healthy blood donors and symptomatic patients. Typically, prevalence rates of 1:184 to 1:500 have been de-

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scribed.⁷⁻¹⁰ Most recently, studies of Finnish school children and English 7-year-olds have revealed a prevalence of 1%.^{11,12} Similarly, serologic screening in the United States has revealed a surprisingly high prevalence.¹³⁻¹⁷ The rate of clinical diagnosis, however, lags far behind, suggesting that many American children with celiac disease are going undiagnosed. There are, however, no data on the current clinical spectrum of pediatric celiac disease in the United States. We have used a survey directed to the families of pediatric patients with celiac disease in an attempt to discern the clinical spectrum of celiac disease in North American children, the effect of breastfeeding, and the impact of the disease on the lives of patients and their families.

Materials and Methods

A questionnaire was distributed to children with celiac disease 20 years of age or less and their parents. An outline of the questionnaire is shown in Table 1. The study was approved by the Institutional Review Board of the Columbia-Presbyterian Medical Center. The questionnaire was initially validated by administration to a small group of parents and patients and then distributed by (1) e-mail to members of an internet celiac disease discussion group; (2) inclusion in a celiac disease newsletter with nationwide distribution (*Gluten Free Living*, Hastings-on-Hudson, NY); and (3) direct mail to members of celiac disease support groups in New York, New Jersey, Michigan, and California. Responses were entered into a computer database (Excel Version 7, Microsoft Corporation, Redmond, WA) and analyzed by 2 different investigators. Statistical analyses comparing pa-

Table 1

OUTLINE OF QUESTIONNAIRE

Demographic and personal data
Gender, date of birth
Geographic origin, ethnic background
Feeding history—breast vs formula, age at introduction of wheat
Family history of celiac disease
Prediagnosis data
Symptoms
Presence of associated diseases
Age at presentation of symptoms, duration of symptoms before diagnosis
Number and type of physicians consulted before diagnosis
Diagnosis data
Age at diagnosis
Method of diagnosis—biopsy vs serologies
Who made the diagnosis?
Family's perspective on diagnosis and treatment
Was the diagnosis prompt?
Were your physicians knowledgeable about diagnosis, treatment, and management?
Follow-up management
Did the patient have follow-up biopsies or serologies done on a gluten-free diet?
Were family members screened for celiac disease?
Gluten-free diet (GFD)
Adherence to the diet
Intentional dietary lapses
Sources of information regarding celiac disease and the GFD
Family's and patient's rating of quality of life before and after diagnosis

tients diagnosed at age <2 years, 2–5 years, and >5 years, and those comparing patients with varying infant-feeding practices were carried out using STATA (Intercooled Version 7, Stata Corporation, College Station, TX). For comparisons, linear regression analysis and probit analysis were used to

isolate the impact of individual variables for continuous and discrete measurements, respectively. “Exclusively breastfed” children (EBF) were those who received only breast milk for at least the first 6 months of life. This group was compared with all the other children (called “not breastfed”).

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Results

Characteristics of Respondents

Responses were received from 156 individuals from 30 different states within the United States. Biopsy confirmation of the diagnosis was performed in 90% of cases (n=141). As intestinal biopsy is the gold standard of diagnosis; we considered only those who were biopsy-proven for further analyses. The characteristics of this cohort are shown in Table 2.

The mean age of symptom onset was 2 years 7 months (range, birth to 17 years 1 month). The diagnosis was made on average at 3 years 6 months (range, 9 months–17 years 9 months) with 38% diagnosed before 2 years of age, 43% between 2 and 5 years, and 19% after age 5. As there was no significant difference in age of onset of symptoms or age at diagnosis by gender, the results for males and females are combined.

Infant Feeding

The vast majority of respondents were both breastfed and formula-fed as infants. Eighty-two percent were breastfed to varying degrees during infancy (at least until 1 year of age), 28% (n= 40) exclusively so. The mean duration of breastfeeding was 7 months (range, 1 month–4 years 2 months). Additionally, 72% of respondents were formula-fed, 18% exclusively so. Among children who were formula-fed, 44% received cow milk-based formula, 46% soy, and 14% other types of infant formulas.

Exclusive breastfeeding (EBF) in the first 6 months was associated with a later age of onset of symptoms and age of diagnosis (Figures 1, 2), with symptoms developing, on average 15 months later, at 3 years 7 months of age (p<0.05). EBF children were diag-

Table 2

CHARACTERISTICS OF BIOPSY-PROVEN CELIACS (n=141)

Patient Characteristic	
Male-to-female ratio	1:2
Mean age at diagnosis	3 years 6 months
Mean age of onset of symptoms	2 years 7 months
Mean duration of symptoms before diagnosis	11 months
Mean age of respondents at time of survey	8 years 4 months
Mean duration since diagnosis at time of survey	4 years 8 months
Percentage breastfed (exclusively)	82% (28%)
Mean age wheat introduced	7 months
Family history of celiac disease	21%
Mean time for antibodies to return to normal	9 months
Mean number of physician visits before diagnosis	7.8
Mean number of physicians seen	3.9
Pediatrician considered NOT to be knowledgeable about celiac disease	59%
Diagnosis considered to have been made promptly	55%

nosed at a mean of 4 years 10 months older than the others (2 years 11 months, p<0.05). Linear regression analysis confirms that even after controlling for current age and sex of the child, EBF children were diagnosed almost 2 years later than the remainder of the children (p<0.05). The mean duration of symptoms before diagnosis was 11 months (range, 1 month–10 years 6 months); for EBF children it was 8 months longer: 1 year 3 months, more than twice as long as the others (p<0.05).

Cereals were introduced into the diet at 5 months on average (range, 2 months–1 year 3 months) and wheat at 7 months (range, 1 month–1 year 9 months). A comparison of children exposed to cereal, with or

without wheat, before and after 6 months of age, reveals no significant difference in the mean age at diagnosis. Linear regression analysis further confirms that even after controlling for current age, gender, and breastfeeding, neither the introduction of cereal nor of wheat before 6 months of age had any significant impact on age at diagnosis.

Symptomatology

The presenting symptoms are shown in Table 3. Fatigue, diarrhea, and failure to thrive were the most commonly reported problems, nearly half the sample presenting with all 3 symptoms. The age-related distribution of symptoms is also shown in Table 3. The age groups (<2 years, 2–5 years, and >5 years) correspond to

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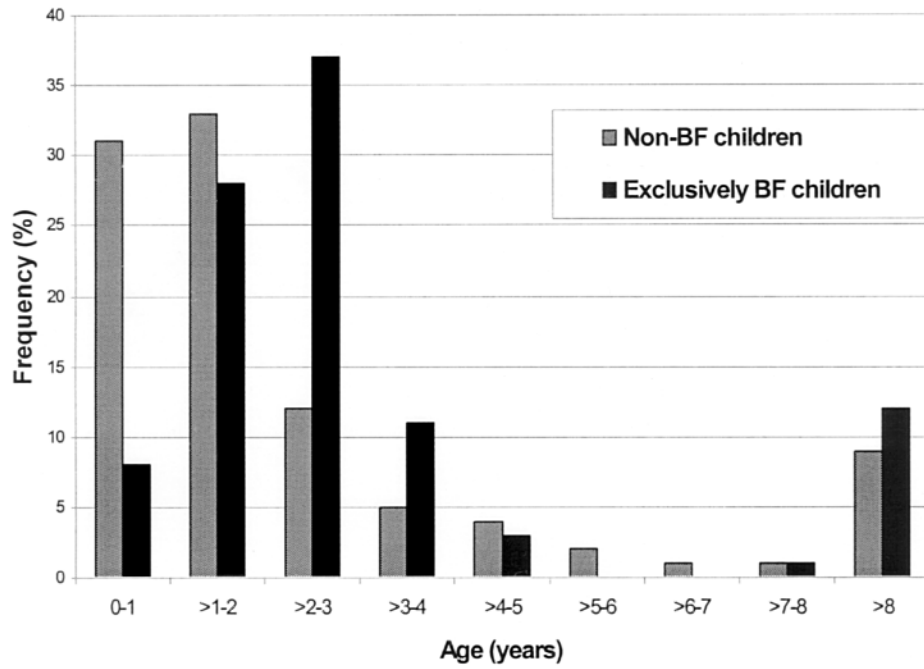


Figure 1. Age of onset of symptoms by feeding practice.

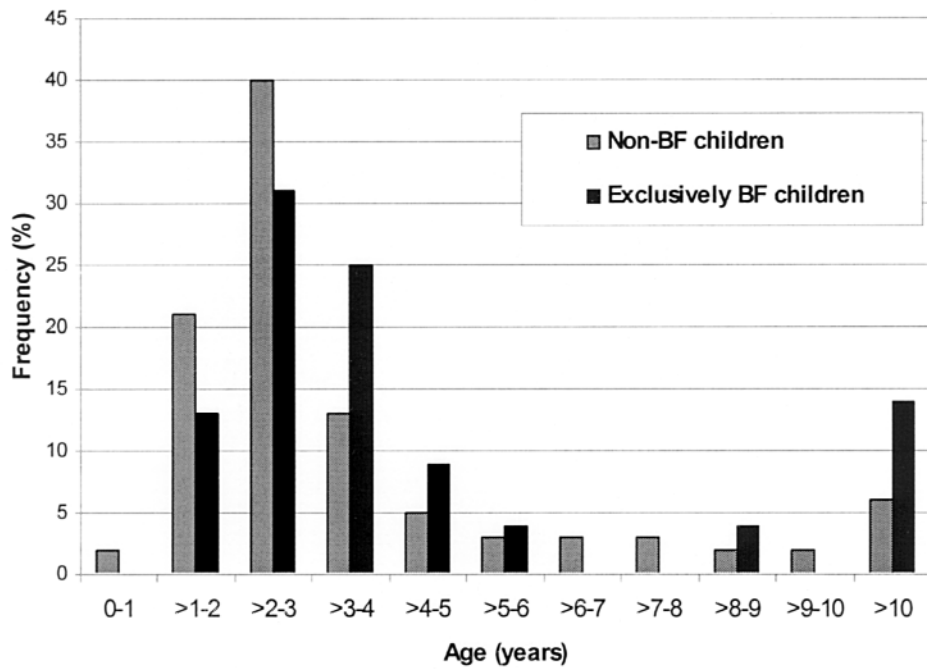


Figure 2. Age at diagnosis by feeding practice.

*Pediatric Celiac Disease in the United States***Table 3****SYMPTOMS AND ASSOCIATIONS AT DIAGNOSIS FOR ALL BIOPSY-PROVEN RESPONDENTS AND BY AGE GROUPINGS—FREQUENCY (%)**

Symptom/Characteristic	All	<2 Years	2–5 Years	>5 Years
Fatigue	84	68	80	91
Diarrhea	81	84	74	57
Failure to thrive	73	75	66	26
Anemia/Fe deficiency	48	23	55	58
Short stature	41	12	47	56
Behavioral problems	30	18	19	35
Constipation	26	28	25	20
Vomiting	25	21	22	29
Abdominal pain/distension	24	21	23	27
Skin problems	18	13	16	23
Learning disabilities	12	4	6	19
Diabetes	5	2	2	10
Weight loss	4	2	3	8
Seizures	2	0	0	2
Downs syndrome	1	0	1	0
Thyroid disease	<1	0	1	0
Other*	4	1	2	7

*Other, less commonly reported, symptoms included weakness, wasting, hair and dental changes, edema, personality changes, and 1 report of pancreatitis.

infants, preschoolers, and school-aged children, respectively, and characterize periods during which major transitions occur in diet, activity, and socialization. Ninety percent of children with the constellation of “classic” symptoms—diarrhea and failure to thrive—are diagnosed with celiac disease within the first 5 years of life. Nearly half of those presenting with “classic” symptoms are diagnosed before age 2 years. Furthermore, children who present with “classic” symptoms are diagnosed at a younger age (2

years 6 months) than those who do not (4 years 9 months, $p < 0.01$). Probit analysis confirms that even after controlling for current age, gender, and breastfeeding, children who present with “classic” symptoms are 24% more likely to be diagnosed before age 2 years ($p < 0.01$). Notably, 40% of children with neurocognitive or behavioral problems were diagnosed at more than 5 years of age compared to only 16% of those not reporting any such symptoms. *T*-tests verify this to be a significant difference ($p < 0.05$). Probit

analysis confirms that even after controlling for current age, gender, and breastfeeding, children who present with these symptoms are 34% more likely to be diagnosed after age 5 years than those who do not report neurologic or behavioral pathology or learning difficulties ($p < 0.05$).

The relationship between various feeding practices and symptomatology was also examined. When compared to children who were formula-fed exclusively, EBF children were significantly less likely to report failure to thrive

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(69% vs 88%), short stature (37% vs 62%) and vomiting (24% vs 52%) (*t*-tests, $p < 0.05$, $p < 0.05$, $p < 0.01$, respectively). Furthermore, probit analysis indicates that even after adjustment for current age and gender, breastfeeding reduces by 20% the likelihood that a child presents with either failure to thrive or short stature ($p < 0.05$). Respondents introduced to wheat before 6 months of age were significantly more likely to exhibit failure to thrive before diagnosis ($p < 0.1$) than those with a later introduction.

Table 4 shows the main symptom that led to the diagnosis and the age-related distribution. Diarrhea (38%) and failure to thrive (26%) were the most commonly reported main symptoms for the whole sample. This distribution generally holds for infants and

preschoolers, but the symptomatology changes for school-aged children. Among those diagnosed at school-age, only 18% reported diarrhea and 0% reported failure to thrive, while 18% reported abdominal pain or distension, 13% vomiting, and 22% "other" complaints. Twelve percent of these school-age children were asymptomatic and diagnosed after screening owing to having a relative with celiac disease.

The reported main symptom varied by feeding practice as well. EBF children reported failure to thrive as the main symptom almost 50% less frequently ($p < 0.01$). They had a significantly higher rate of atypical symptoms, specifically constipation ($p < 0.05$). Breastfed children were significantly more likely to be diagnosed by screening methods

($p < 0.05$). Children who were formula-fed or who were introduced to wheat before the age of 6 months presented much more commonly with classic symptoms of diarrhea and failure to thrive as the main symptom ($p < 0.05$ and $p < 0.01$, respectively).

Diagnosis

Of the 141 respondents who had biopsy-proven celiac disease, 110 (78%) also indicated they had antibody testing done for celiac disease. Ninety-four percent of them had positive antibody tests for celiac disease.

Respondents were asked to provide information regarding the number of physician visits they made. The mean number of total visits to any physician for the related symptoms before the diagnosis was made was 7.8 (range

Table 4

**MAIN SYMPTOM LEADING TO DIAGNOSIS FOR ALL BIOPSY-PROVEN
RESPONDENTS AND BY AGE GROUPINGS—FREQUENCY (%)**

Symptom/Characteristic	All	<2 Years	2–5 Years	>5 Years
Diarrhea	38	47	35	18
Failure to thrive	26	33	29	0
Abdominal pain/distension	9	7	8	18
Vomiting	7	7	10	13
Anemia/Fe deficiency	2	0	5	4
Fatigue	2	2	0	4
Short stature	2	0	0	9
Other*	8	2	8	22
Screening/asymptomatic†	6	2	5	12

*Other reported main symptoms included constipation, behavioral problems (mainly irritability), learning difficulties, personality changes, hair and dental changes, and skin problems.

†These patients were diagnosed after screening serologic tests because of having a family member with celiac disease.

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1–60). The mean number of physicians seen before the diagnosis was 3.9 (range, 1–30); the mean number of gastroenterologists was 1.1 (0–10); and the mean number of other specialists was 0.7 (range, 0–10). Other specialists included endocrinologists, allergists, neurologists, psychiatrists, chiropractors, and kinesiologists. The diagnosis was made by a gastroenterologist 87% of the time, a pediatrician 6%, and parent or “other” 7%. Fifty-nine percent of respondents stated that the general pediatrician did not consider the diagnosis of celiac disease.

For children who were breastfed the mean number of total physician visits before the diagnosis was made was 10.3—significantly greater than for those not breastfed (6.5, $p < 0.1$). Additional data that show making the diagnosis of celiac disease in breastfed children was delayed include a greater number of physicians seen (mean, 5.7 vs 3.0, $p < 0.05$) and greater number of other specialists (nongastroenterologists) seen (mean, 2.2 vs 0.4, $p < 0.01$). The number of pediatricians and gastroenterologists was not different.

Parental Perceptions

Only forty-one percent of parents responded that their children's pediatricians were knowledgeable regarding the diagnosis of celiac disease; 40% stated they were knowledgeable about treatment and 33% about follow-up care. In contrast, 96% of parents stated their children's gastroenterologists were knowledgeable about the diagnosis, 85% about treatment, and 81% about follow-up care. Only 55% of parents felt their child's diagnosis was prompt.

Follow-up Care

Repeat biopsies on the gluten-free diet (GFD) were performed

in 25% of respondents with 45% reporting it was recommended. Repeat antibody testing was performed on 75% of the antibody-positive respondents once on a GFD. The antibody tests returned to normal in 94% after an average of 9 months (range, 1 month–4 years 3 months) on the diet. Additionally, 64% of respondents had first-degree relatives screened for celiac disease after their diagnosis, or such screening was recommended to them—45% by a physician, 45% by a support group.

Gluten-Free Diet

Respondents obtained most of their information regarding the GFD from the pediatrician 1% of the time, gastroenterologist 9%, dietitian/nutritionist 11%, the Internet 11%, or support groups 68%. All respondents (100%) indicated that they were advised that compliance with the GFD must be lifelong. Ninety-eight percent reported they were advised that gluten must be totally excluded from their diet. In regard to their children's compliance, 91% stated they usually follow the diet, though intentional lapses were reported by 51% of respondents. The setting in which they occur are the home (6%), school (12%), parties or social events (17%), and other (16%). The mean time respondents were on the diet was 4 years 7 months (2 months–17 years 6 months). Twenty-one percent reported a change in adherence over time. Compliance deteriorated for 13% of all respondents. The mean age when the change in compliance occurred was 5 years 6 months (3 months–18 years). This coincides with the time most North American children are beginning school. Compliance with the diet was reported as difficult for the parent by 42% and difficult for

the child by 47% of respondents. Eighty-six percent felt that food labeling is inadequate.

Psychological/Behavioral/School Problems

Significant psychological or behavioral problems before the diagnosis was made were reported by 30%. Of these, 70% reported their children as irritable and 23% stated they were lethargic or depressed. A 50% reduction in these problems being reported was seen after the diagnosis of celiac disease was made and treatment instituted. Of these 15% that report continued psychological or behavioral problems, almost one third report that their child becomes irritable or has mood changes after ingestion of gluten, usually within minutes to hours. Others report continued depression (22%), developmental delay, or learning disability (13%).

School difficulties were associated with academic problems by 11% of respondents, lack of teacher support by 13%, and lack of school nurse support by 8%. Adherence to the diet in school was reported as a problem by 17%.

Quality of Life

Before the diagnosis of celiac disease was made, 50% of parents responded that their quality of life and that of their child was “bad.” Twenty-two percent reported it was fair, 10% good, and 18% excellent. After the diagnosis was made, respondents reported that quality of life improved in 82%, remained the same in 11%, and worsened in 7%. However, 99% reported that their child has done well overall since starting the GFD. The children's perception of their own quality of life before the diagnosis was bad in 47%,

fair in 24%, good in 12%, and excellent in 17%. The children reported that after the diagnosis their quality of life was the same (9%), improved (81%), or worse (9%).

Discussion

Celiac disease is diagnosed infrequently and considered rare in the United States.^{5,6,16} As a result there is a paucity of literature devoted to childhood celiac disease and relatively little research emanating from North America.^{7,16} We obtained information, therefore, on 141 biopsy-proven North American pediatric patients with celiac disease. We used a survey, distributed by a variety of methods, to obtain information on children diagnosed with celiac disease from different regions of North America. The majority of respondents were from the 2 coasts, with 30 different states represented. The clinical features of these children differed from those of children with celiac disease from Europe. While there was a similar female predominance,^{18,19} the age at onset of symptoms and age at diagnosis in Europe are less than we found in American children. Approximately 75% of European children are diagnosed before the age of 2 years,²⁰ whereas only 38% were diagnosed in our study.

We are aware of the limitations of our study. These include the bias of parental recall as well as our inability to know the percent response rate from our widely distributed questionnaire. While there are inherent problems in this technique, information about celiac disease²¹ and breastfeeding²² has been previously obtained by this method. The reliability of our data is sup-

ported by the report that serologic tests returned to normal a mean of 9 months after commencement of a GFD, as expected from the literature.²³

Overall, the symptom profile of celiac disease in our series of children in the United States is similar to that reported in Europe with comparable prevalence rates of the classical symptoms such as diarrhea, failure to thrive, short stature, and abdominal distension or bloating.²⁴⁻²⁶ However, when one considers symptoms in relation to infant-feeding practice and age at diagnosis, stark contrasts can be seen.

Breastfeeding is extremely common in the United States, with rates approaching 70%, and with almost 30% breastfeeding for the first 6 months of life.^{27,28} In contrast, Europeans generally breastfeed their children less often and for a shorter duration.^{22,29} In our study 82% of the respondents were breastfed, 28% exclusively. Breastfeeding influences the presentation of celiac disease. For those breastfed, the age at onset of symptoms and age at diagnosis were significantly greater than for European children²⁰ and than for those children in our study who were not exclusively breastfed. Breastfed children have less classic presentations, including less diarrhea, growth disturbance, vomiting, and abdominal pain or distension. However, they had a longer duration of symptoms before diagnosis, they had more visits to physicians, and they saw a greater number of physicians and specialists before the diagnosis was made. These findings are evidence that the diagnosis was not simply delayed but that the clinical disease presented later and differently, corroborating others' suggestion that breastfeeding has an altering,

if not protective, effect on the development of celiac disease.^{19,22,29}

In our study, breastfeeding appeared to be more important than whether wheat was introduced early into the diet, as the early introduction of wheat into an infant's diet was associated only with poor growth in our study. In contrast, European studies have shown the benefit of delayed and gradual introduction of gluten into the diets of infants.^{27,30-32} Interestingly, the greatest protection for children at risk for the development of celiac disease occurred when gluten was introduced, in small amounts, during the period of breastfeeding.^{22,33,34}

Those diagnosed at a younger age had more classical symptoms. Older respondents more frequently reported nonclassic symptoms such as constipation, anemia, skin problems, and learning or behavioral difficulties. Every age group reported fatigue. The incidence of associated conditions such as diabetes, thyroid disease, Downs syndrome, and epilepsy was not high in our study; however, when identified in our cohort, almost all were seen in respondents who were diagnosed as older children. This is also true for those diagnosed after screening of relatives of patients with celiac disease (6% total, 12% of children older than 5 years). In contrast, there is a considerable body of literature establishing the connection of celiac disease and other autoimmune disorders,^{4,35-38} as well as studies demonstrating the high yield of screening relatives of patients with celiac disease.^{37,39} These modes of diagnosis must not be common for children diagnosed with celiac disease in the United States.

These results suggest that the diagnosis is being missed in North American children. Further sup-

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port for this is the high number of physician visits, multiple different physicians, and long duration of symptoms before the diagnosis was made. Whereas 60% of European children are diagnosed within 6 months,²⁰ it took twice as long to diagnose the same percentage of American children in our study. This is not unique to the pediatric population, for similar findings were noted in adults with celiac disease.²¹ Additionally, parental perceptions of nonspecialist's lack of knowledge regarding celiac disease and a lack of promptness in diagnosing their children's problems can be attributed to the fact that pediatricians are not aware of the changing clinical presentations of celiac disease in the United States.

Avoidance of all gluten-containing grains or additives is the standard of care for patients with celiac disease.^{2,35,37,40} The diet is difficult for North American children and their families to adhere to, particularly for children going to school for the first time. Despite this, the majority of patients and their families have done well on the GFD and have experienced an improvement in their quality of life following its implementation. Most information about the diet is obtained neither from physicians nor dietitians, but from celiac support groups.

Celiac disease in American children is changing. Our study provides compelling evidence as to how and why this change may be occurring. Breastfeeding beyond the first 6 months and a delay in the administration of gluten-containing cereals until after 6 months of age can be protective by altering and delaying the onset of symptoms in patients with celiac disease. Additionally, our study highlights the fact that pediatricians need to have greater

awareness of the diverse presentations of celiac disease and the age dependence of symptoms to facilitate earlier diagnosis of this eminently treatable condition.

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