

Changing Pattern in the Clinical Presentation of Pediatric Celiac Disease: A 30-Year Study

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Key Words

Celiac disease · Celiac disease, clinical presentation ·
Celiac disease, trends · Pediatric celiac disease

Abstract

Background/Aims: The incidence of celiac disease (CD) has increased in recent years due to the recognition of atypical forms and the identification of silent cases through serological screening. Our aim was to detect temporal trends in the presentation of pediatric CD in Greece. **Methods:** We reviewed the medical files of all children diagnosed with CD between 1978 and 2007 at a single academic pediatric center. Cases were classified according to the year of diagnosis. We examined demographic data, presenting symptoms, delay to diagnosis, and the prevalence of associated conditions. **Results:** During the study period, 284 new cases of CD were diagnosed. The incidence of CD was significantly increased in recent years ($p < 0.05$). We observed significant trends towards older age at diagnosis ($p < 0.001$), longer delay to diagnosis ($p < 0.05$) and decreased frequency of the classical and/or gastrointestinal predominant mode of presentation ($p < 0.001$). In recent years, diagnosis of CD was significantly more frequent due to testing of asymptomatic children with a positive family history for CD or personal his-

tory of associated conditions ($p < 0.001$). **Conclusion:** We report a changing pattern in the presentation of pediatric CD in Greece. CD is diagnosed more frequently in older children, oftentimes presents with atypical symptoms, and is increasingly detected through serological screening. CD should be considered in the presence of atypical presentations.

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Introduction

Celiac disease (CD) is an immune-mediated condition, which is characterized by an aberrant response of the small intestinal mucosal immune system towards components of gluten (and other proteins) in the food [1]. This dysregulated reaction takes place in genetically susceptible individuals. In fact, it has been accepted that CD is one of the most common genetically conferred disorders reaching a prevalence of 1% in certain Western populations [2].

Traditionally, CD has been considered a disease of childhood, manifesting during the first years of life as a gastrointestinal (GI) syndrome that consists of diarrhea, abdominal distention and failure to thrive. This concept has, however, been challenged in recent years, as it be-

came increasingly evident that, first, CD can affect individuals of any age, and second, patients may present with symptoms that once were considered highly unusual for the diagnosis of CD [3]. Among children, these non-classical forms include atypical GI findings such as abdominal pain, vomiting or constipation as well as a number of extraintestinal problems like iron deficiency, altered bone metabolism, short stature and unexplained elevation of transaminases [4, 5].

Even more important is the current understanding that CD can exist in a preclinical, asymptomatic state in the presence of typical histological lesions [6]. The identification of such 'silent' cases became possible in recent years with the development of serological tests that have high sensitivity and specificity for the diagnosis of CD. These tests detect antibodies of IgA class against tissue transglutaminase (IgA anti-tTG) or endomysium (IgA anti-EMA) [7, 8]. In pediatric clinical practice, these tests have been widely applied for the initial screening of children with atypical presentations or asymptomatic but with CD-associated conditions [9]. The latter include, among others, positive family history for CD [10, 11], or personal history for type 1 diabetes, autoimmune thyroid disease, dermatitis herpetiformis, and Down's syndrome [12–14].

In the present study we examined the clinical characteristics at presentation in a large population of Greek children diagnosed with CD at a single institution during a 30-year period. In particular, we studied whether the increasing awareness of the multiple modes of presentation of this condition has resulted in increasing rates of CD diagnosis in our area. Accordingly, we hypothesized that this increase would be attributed to a higher number of patients with atypical manifestations or detected through serological screening of asymptomatic children.

Patients and Methods

We retrospectively reviewed the files of all patients (children and adolescents, age <16 years) who were diagnosed with CD at the First Department of Pediatrics in Aghia Sophia Children's Hospital, between 1978 and 2007. All available information from the medical files was entered into a database and rendered anonymous to protect patient privacy. Data included age at diagnosis, gender, ethnicity, age at introduction of gluten and solid foods in the diet, breastfeeding, and symptoms at diagnosis. We also determined the delay to diagnosis, which we defined as the interval between the first presentation of symptoms and the definitive diagnosis of CD. Finally, personal and family histories were reviewed and the presence of any associated conditions was reported.

The diagnosis of CD was established according to the criteria proposed by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHN). Until 1990, the 'Interlaken

criteria' were applied [15]. Those included a gluten re-challenge for confirmation of the diagnosis of CD. After their publication in 1990, the revised ESPGHN criteria were adopted and a re-challenge was applied only in special situations (doubt about initial diagnosis, suboptimal response to gluten elimination from diet, children <2 years) [16]. For histological diagnosis the Crosby capsule was utilized until 1989 when it was replaced with duodenal biopsies via upper GI endoscopy. The presentation of CD was defined as classical when one or more of the following were present: diarrhea, abdominal distention, weight loss, failure to thrive, irritability, and anorexia. Atypical symptoms included abdominal pain, constipation, short stature, vomiting, and anemia. In addition, we classified as atypical the CD cases identified through screening of asymptomatic children. In the latter the reason for screening was positive family history for CD or positive personal history for a CD-related condition (usually type 1 diabetes, thyroid disease, bone disease, arthritis, dermatitis herpetiformis).

Patients were divided into three groups based on the year of diagnosis of CD: (1) group A, patients diagnosed with CD between 1978 and 1987; (2) group B, patients diagnosed with CD between 1988 and 1997, and (3) group C, patients diagnosed with CD between 1998 and 2007.

The three groups were compared for the frequency of presenting symptoms, trends towards a classical or atypical presentation, predominance of GI or extraintestinal symptoms, delay to diagnosis, and presence of associated conditions.

Statistical Analysis

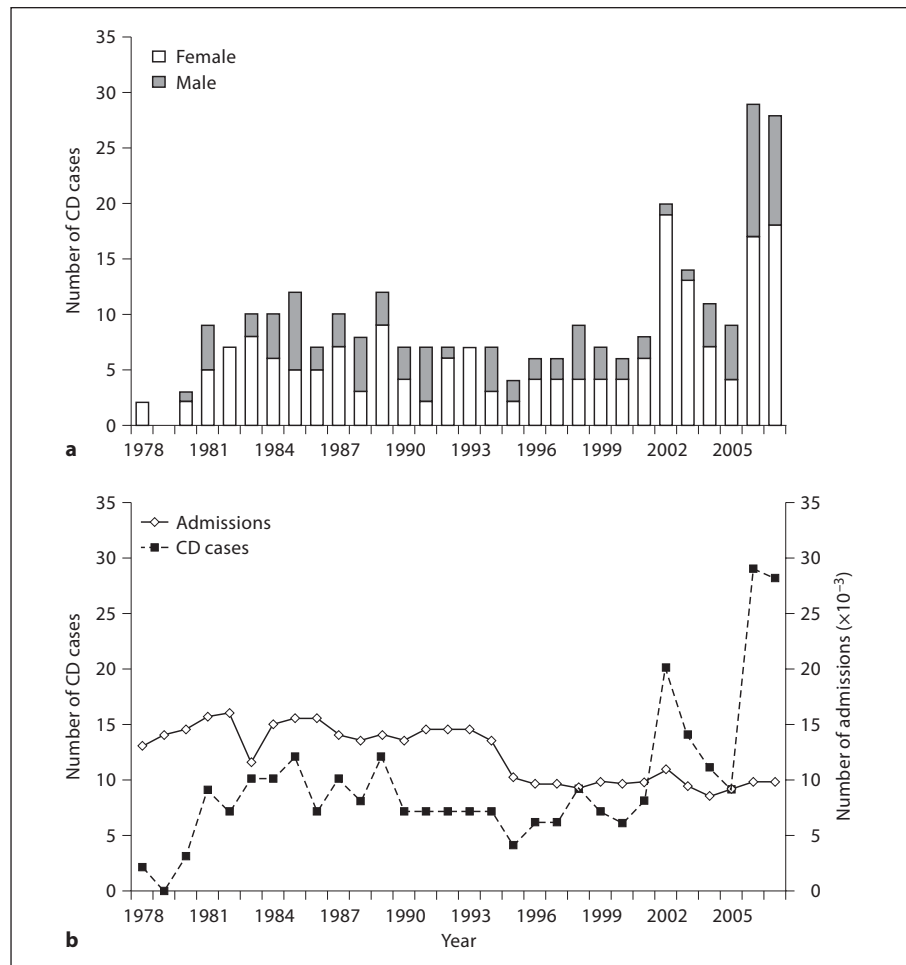
The SPSS software was used for the analysis. Continuous variables between the three groups were studied by means of one-way analysis of variance. Categorical variables were studied by corrected χ^2 test. For all comparisons an α value of <0.05 was considered significant.

Results

Increased Incidence and Trend towards Delayed Diagnosis of CD in Recent Years

During the study period (1978–2007), CD was diagnosed in 284 children. There was a significant increase in the number of patients in group C ($n = 141$) as compared with groups A ($n = 72$) and B ($n = 71$) (fig. 1). The number of new CD cases per year increased from 7.0 ± 4.02 in the first decade (1978–1987) and 7.1 ± 2.02 in the second (1988–1997) to 14.1 ± 8.6 in the third decade (1998–2007) ($p < 0.05$). There was a female predominance of cases (66%) throughout the study period (group A: 48 females/24 males, ratio 2.00; group B: 44/27, ratio 1.62; group C: 96/45, ratio 2.13) (fig. 1). The possibility existed that the increased incidence of CD in recent years was a secondary effect due to an increased number of patients seen in our hospital in general. To address this issue, we plotted the number of CD cases against the total number of patients admitted to our hospital during the same period. It is clearly shown in figure 1b that this was not the

Fig. 1. Distribution of new CD cases according to the year of diagnosis during the study period. **a** The gender of the patients is indicated. There is a higher percentage of female patients throughout the study. **b** CD cases are plotted against the total number of patients admitted to our hospital. An increase in the former along with a stability of the latter is clearly demonstrated, indicating a true increase in the incidence of CD in our area.



case as the number of children admitted declined during the third decade of the study whereas the number of patients diagnosed with CD significantly increased.

In figure 2a we show the distribution of CD cases for each group of patients according to the age at diagnosis. In group A, 78% of cases were diagnosed in the first 2 years of life and 93% before 5 years of age (fig. 2b). Similarly, 59% of cases in group B were diagnosed in the first 2 years of life and 71% before 5 years of age. In sharp contrast, after 1998 (group C) 29% of the CD patients were <2 years old whereas 48% of the cases were diagnosed after 5 years of age (fig. 2b). Therefore, it is clearly shown that in recent years (i.e. after 1998, group C) the diagnosis of CD is significantly more frequent in older children ($p < 0.001$) (fig. 2; table 1). When we analyzed female and male patients separately, we observed the same trend towards a diagnosis at a later age for both populations (data not shown). Overall, 14.1% of children had introduction of gluten before the age of 4 months. This group of chil-

dren had earlier onset of symptoms and earlier diagnosis compared to those with introduction of gluten after the age of 4 months ($p = 0.002$ and $p = 0.013$, respectively). No statistical differences concerning the type of symptoms or delay to diagnosis between the two groups were noticed.

We did not observe any differences in the mode of delivery (normal or cesarean section) or the presence of prematurity between the three groups (data not shown). There was a trend towards less breastfeeding in patients diagnosed after 1998 ($p < 0.001$). Our analysis showed that there was a significant trend towards introducing dietary gluten or solid foods in older age in patients diagnosed during the last decade of the study (table 1).

Next, we sought to determine whether there has been a change in the time between onset of symptoms and final diagnosis of CD. Our analysis clearly showed that there was a significant trend towards longer delay in diagnosis in recent years (table 1).

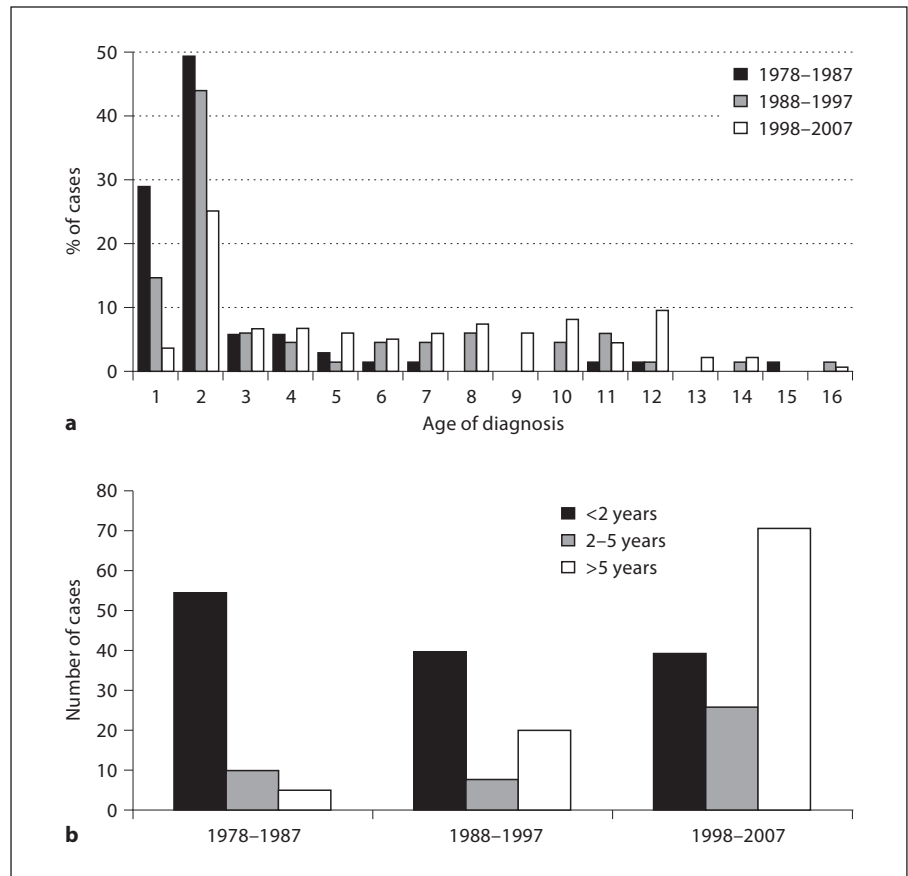


Fig. 2. Distribution of new CD cases according to the age at diagnosis during the study period. **a** The number of new cases for each year of age is indicated for the three groups of patients. **b** The number of children in each age group (<2, 2-5, >5 years) is shown. An increase in the age of diagnosis of CD in the third decade of the study is clearly demonstrated ($p < 0.001$).

Table 1. Characteristics of patients with CD

	Total (n = 284)	1978-1987 (n = 72)	1988-1997 (n = 71)	1998-2007 (n = 141)	p value
Age at diagnosis, months		25.5 ± 29.5	45.6 ± 44.7	73.2 ± 49.8	<0.001
Delay to diagnosis, months		13.3 ± 22	19.6 ± 32.7	27.3 ± 34.8	0.02
Introduction of gluten in diet, months		5.1 ± 1.1	5.8 ± 1.3	6.8 ± 1.1	<0.001
Introduction of solid food in diet, months		4.7 ± 1.2	5.2 ± 0.8	6.9 ± 1.8	<0.001
Symptoms at presentation					
Diarrhea	160 (56)	54 (75)	52 (73)	54 (38)	<0.001
Distention	137 (48)	45 (63)	38 (54)	54 (38)	0.002
Failure to thrive	158 (56)	58 (81)	48 (68)	52 (37)	<0.001
Irritability	34 (12)	17 (24)	14 (20)	3 (2)	<0.001
Anorexia	44 (15)	21 (29)	16 (23)	7 (5)	<0.001
Weight loss	71 (25)	35 (49)	24 (34)	12 (9)	<0.001
Constipation	10 (4)	4 (6)	0 (0)	6 (4)	0.157
Abdominal pain	32 (11)	4 (6)	11 (15)	17 (12)	0.158
Anemia	54 (19)	20 (28)	18 (25)	16 (11)	0.072
Vomiting	51 (18)	28 (39)	13 (18)	10 (7)	<0.001
Short stature	10 (4)	0 (0)	1 (1)	9 (6)	0.032
Asymptomatic	22 (8)	0 (0)	0 (0)	22 (16)	<0.001

Figures in parentheses are percentages.

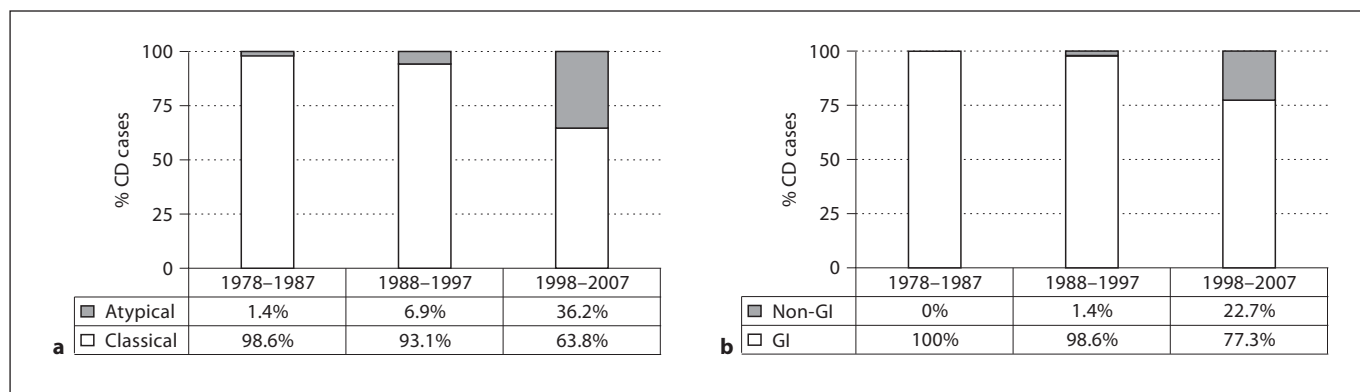


Fig. 3. Distribution of new CD cases according to symptoms present at diagnosis during the study period. **a** Classification according to the presence of classical vs. atypical symptoms. **b** Classification according to the presence of GI vs. non-GI symptoms. The number of atypical and/or non-GI presentations of pediatric CD after 1998 has significantly increased in our study ($p < 0.001$).

Clinical Trends

We examined the trends in clinical presentation of CD by comparing the frequency of several classical or atypical symptoms at diagnosis. As shown in figure 3a, there was a gradual increase in the number of cases presenting with atypical symptoms during the study. In particular, whereas less than 2 and 7% of patients had non-classical symptoms in groups A and B, respectively, the percentage rose to 36% during the last decade of the study (group C, $p < 0.001$). The same trend was observed when GI symptoms were compared with non-GI ones (including no symptoms) (fig. 3b). During the first two decades of the study, all patients presented with symptoms from the gut. In contrast, after 1998, 23% of the patients had no GI symptomatology ($p < 0.001$).

The frequency of specific symptoms present at diagnosis is shown in table 1. Overall, the classical triad of symptoms (diarrhea, abdominal distention, failure to thrive) occurred in 34.7% of children in group A, 31.0% in group B, and 15.6% in group C ($p < 0.001$). Vomiting, anemia, and irritability also were more frequent in previous than more recent years. On the other hand, patients diagnosed in more recent years had more often atypical symptoms such as abdominal pain (group A, 6%; group B, 15%; group C, 12%), and short stature (group A, 0%; group B, 1%; group C, 6%).

Identification of Asymptomatic Cases through Serological Screening

Finally, we observed that in a considerable percentage of patients in group C (16%) CD was diagnosed in completely asymptomatic individuals. There were no asymp-

Table 2. Associated conditions in patients with CD

Condition	Patients	
	n	%
Positive family history of CD	18	6.3
Positive family history of type 1 diabetes	6	2.1
Thyroid disease	2	0.7
Type 1 diabetes	9	3.2
Dermatitis herpetiformis	5	1.7
Down's syndrome	1	0.4
Bone disease	1	0.4
Arthritis	4	1.4
Pemphigoid dermatitis	1	0.4

tomatic cases in the other two groups of patients, the difference being statistically significant (table 1). Identification of CD in asymptomatic cases was achieved through initial serological screening followed by endoscopy in patients that had a known CD-relative or -associated condition. The most common CD-associated conditions in our series are shown in table 2.

Discussion

This study clearly demonstrates a rising recognition of CD in our region. Throughout a 30-year period (1978-2007) we observed a twofold increase in the annual rate of new CD cases after 1998. We did not see any differences in the initial 20 years of the study. Studies from

other countries showed that the rise in CD incidence started earlier than in ours [17, 18]. This difference may be explained by the fact that until the late 1980s (first decade of our study) our center was the only one in our geographical area that specialized in the diagnosis and management of CD. After that time more hospitals became involved in the care of such patients and this may have masked an increased incidence of CD in our center during the second decade of our study.

Throughout our study we observed a 2:1 female-to-male ratio in CD patients. Genetic or environmental factors may underlie this female predominance, which is in accordance with other studies [19, 20]. Nevertheless, we did not detect any differences between the two genders in regard to breastfeeding, prematurity, weight at birth, as well as introduction of gluten or solid food in diet (data not shown). Therefore, genetic aspects may be more relevant than environmental ones. It has recently been proposed that female sex hormones influence the response of the immune system against endogenous and environmental stimuli and divert the latter towards autoimmunity [21–26]. Nonetheless, sex hormones are not likely to be the explanation for the female preponderance of CDs in young children.

It is clear from our findings that, in recent years, the so-called ‘classical’ presentation of CD (diarrhea, abdominal distention, failure to thrive) is absent in as many as half of newly diagnosed CD cases in our country. This may have been influenced by the decreased percentage of patients <2 years of age in the last decade, as it is known that the classic presentation is usually seen between 6 and 24 months. Nevertheless, when we analyzed CD cases that were diagnosed after 1998 and were <2 years of age, we detected that patients presenting with the classical triad were less than 45%. One fourth of individuals diagnosed with CD, nowadays, do not report any GI symptomatology. In contrast, many patients in our study displayed GI symptoms that are considered highly uncharacteristic for CD, including constipation, recurrent abdominal pain, and vomiting. These data are in line with several recent studies from other countries where it is reported that, nowadays, the number of children presenting with diarrhea is lower than 50% [17, 18, 23].

In recent years, we observed an increasing number of ‘silent’ CD cases that were diagnosed through serologic screening with CD-specific autoantibodies. In our institution we introduced serological testing (originally anti-AGA, nowadays anti-EMA anti-tTG). There were two groups of children that underwent screening. First, children with a positive family history for CD are always

screened in our institution. Through this approach we identified 18 children with CD, of whom 8 had symptomatology suggestive of CD but 10 were completely asymptomatic (data not shown). Therefore, positive family history for CD should be a reason for screening, irrespective of the presence of symptoms. Second, serological screening was also performed in the presence of a CD-associated condition. A strong association between CD and type 1 diabetes was confirmed in our study [24]. Not only was CD detected in children with type 1 diabetes, but we also observed a 2% prevalence of positive family history for diabetes in children with CD. This association between the two diseases is further strengthened by the recent report that genetic predisposition to CD and type 1 diabetes share common alleles [25]. In the same line, it has been proposed that the two conditions may also share a common immunological trigger, that is the gluten present in the diet [26].

In our study, a significant delay in the diagnosis of CD was observed in recent years. This may in part be explained by the fact that CD was diagnosed at an older age in the second and third decades of the study and/or may be associated with the larger percentage of atypical and asymptomatic cases in later years. Alternatively, it may also indicate that pediatricians involved in the primary care of children are not fully aware of the atypical presentations of CD. This longer delay in diagnosis is quite opposite of what has been recently reported in adults [27]. Most probably this can be explained by the fact that in adults CD was traditionally considered a rare disease, associated with an extremely long interval between symptoms and diagnosis. Nevertheless, nowadays it has been recognized as a more common disorder and sought for more easily. In contrast, in children the classical presentation usually prompts immediate search for CD. The recent trend is therefore accounted for by the delayed evaluation of an increasing number of more atypical cases.

In conclusion, we present herein a large cohort of CD patients diagnosed in a certain geographical area over an extended period of time. Our study has the shortcomings of a single-center, retrospective study. Nevertheless, we believe that our findings clearly indicate certain clinico-epidemiological trends for pediatric CD in our area. These include diagnosis at an older age, atypical clinical presentations, and detection of a substantial number of cases through screening of asymptomatic individuals. Therefore, the diagnosis of CD should be taken into consideration when children with non-classical presentations are seen in clinical practice.

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