

Diagnostic challenges in children with celiac disease. A five-year experience with new guidelines in a General Pediatrics Department

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ABSTRACT

Background. The clinical characteristics of patients with celiac disease cover a wide range of signs and symptoms. Our study aimed to describe the main clinical features and investigations performed on our celiac patients diagnosed in the past five years.

Material and methods. We collected data from medical records of patients aged 0 to 18 years diagnosed with celiac disease. We included in the analysis patients newly diagnosed with celiac disease, in our department, between January 2017 and August 2022.

Results. In this period, 30 children were diagnosed with celiac disease in our general pediatrics department. The mean age at diagnosis \pm standard deviation was 6.3 ± 4.2 years (median age=4.3 years). The period between onset of symptoms ranged between 3 months to 5 years (median=6 months). Twenty children (66%) had features of classical celiac disease. Thirteen/30 patients (43.3%) were found to have iron deficiency anemia at diagnosis. In 23/30 (76%) of the children, the values of the IgA-TGA were more than 10 times the upper limit of the normal values. Nineteen children were diagnosed between 2017 and 2019. Fifteen of these 19 patients (79%) were diagnosed based on positive levels of antibodies and duodenal biopsy samples showing Marsh 2 or 3 features, and 4/19 (21%) based on positive IgA-TGA and AEM and a genetic test showing HLA DQ2 and/or DQ8.

Conclusions. Classical celiac disease remains the predominant phenotype in our patients. Adherence to new guidelines allowed in the past 2 years a diagnosis without histological examination of biopsy fragments in most of the patients.

Keywords: celiac disease, children, antitissue transglutaminase, duodenal biopsy

INTRODUCTION

Celiac disease is an autoimmune disorder triggered by gluten and other related prolamines in genetically susceptible individuals. In some parts of the world, recent data show an increase in the incidence and prevalence of this disease [1-3].

In recent years, celiac disease has been the subject of several guidelines. Recommendations regard-

ing the diagnosis of this disease changed as new and more reliable non-invasive methods emerged. The clinical spectrum of patients with celiac disease has shifted from a classical description to non-classical or non-specific signs and symptoms [4,5]. More than that, recent studies show differences in clinical pictures in different age groups [6,7].

Guidelines over the years have reconsidered the diagnostic criteria in celiac patients [8,9]. The in-

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crease in the awareness of this pathology and the availability of accessible and feasible tests contribute to diagnosing celiac disease before the appearance of severe complications.

The diagnosis of celiac disease is based on the clinical symptoms (gastrointestinal and/or extraintestinal), celiac disease-specific antibodies, histological features of the duodenal biopsy (villous atrophy and crypt hyperplasia) and HLA testing showing HLA-DQ2 and/or HLA-DQ8, in a patient who is on a gluten-containing diet [8]. The 2012 ESPGHAN guideline recommended omitting the duodenal biopsy in children who present symptoms of celiac disease, have high titers of antibodies [more than 10 times the upper limit of the normal values for IgA antibodies against tissue-transglutaminase (TGA) and positive anti-endomysial antibodies (EMA)] and HLA-DQ2 and/or HLA-DQ8 [8]. The 2020 ESPGHAN guideline recommends omitting even the HLA typing in patients with high titers of celiac disease-specific antibodies (IgA-TGA and EMA) [9].

In 2013 the Oslo classification recommends the use of the terms classical celiac disease for patients presenting with diarrhea, malnutrition and signs and symptoms of malabsorption, and the term non-classical celiac disease for patients who do not have signs or symptoms of malabsorption [10].

In this study, the **objectives** were to find which were the main features of the clinical picture of our celiac patients, in different age groups, in the past 5 years, what is the diagnostic delay between the onset of symptoms and the diagnosis, and which investigation methods were used for establishing the final diagnosis.

MATERIALS AND METHODS

Collected data

In this study, we collected data from medical records of patients aged 0 to 18 years diagnosed with celiac disease in the past 5 years. It is a descriptive, retrospective study focusing on the clinical data of celiac patients at diagnosis and investigations needed for diagnosis. We included in the analysis patients newly diagnosed with celiac disease, in our department, between January 2017 and August 2022. We defined classical celiac disease in patients who presented with diarrhea, weight loss/failure to thrive, growth stunt, abdominal distension, anemia, edema, hypoalbuminemia, and non-classical disease in patients with other symptoms (abdominal pain, constipation, fatigue, decreased appetite etc.). We excluded the patients diagnosed in other departments and were referred to our department for a second opinion or other purposes. We also excluded from the study children with silent, latent or potential celiac disease.

The clinical data that were collected are: year of diagnosis, gender, age at diagnosis, signs and symptoms, duration from onset of symptoms until final diagnosis, height and weight, associated autoimmune diseases, and family medical history.

The investigations that were followed are: IgA-TGA, IgA-EMA, hemoglobin level, vitamin D, ferritin, and albumin serum levels, liver enzymes, thyroid hormones and anti-thyroid peroxidase antibodies, upper digestive endoscopy and results of the histological examination of biopsy fragments, and HLA type.

The study has been approved by the Ethics Committee of “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca (AVZ 45/31st of March 2023).

Statistical analysis

Results were expressed as mean \pm SD, median, or percentage. The t test was used for comparisons between groups, a value of less than 0.05 being considered statistically significant.

RESULTS

We included 30 newly diagnosed children with celiac disease in this study out of a total of 63 celiac disease patients who were evaluated in our department in the past 5 years. Patients, who were not included in the study, were either diagnosed before the study period or were diagnosed in other medical units and were sent to our department for other reasons. The study group included 19 girls (63%) and 11 boys (37%). The age range of the patients was 1 year 11 months and 17 years and 2 months. The mean age at diagnosis \pm standard deviation (SD) was 6.3 ± 4.2 years (median age=4.3 years). The period between onset of symptoms ranged between 3 months to 5 years (median=6 months). In 10/30 patients (33%) the diagnostic delay was longer than 1 year and in 5/30 patients (16%) longer than 2 years.

In Figure 1, we illustrate the number of patients diagnosed each year.

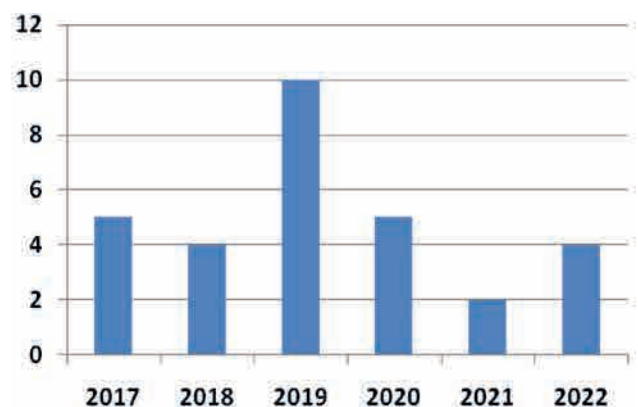


FIGURE 1. Number of patients diagnosed with celiac disease each year

In Figure 2, we illustrate the distribution of children with celiac disease in different age groups at which the diagnosis had been made. Most children were between 2 and 4 years [9/30 (30%)]. Seven children were aged between 4 and 6 years at diagnosis (23%), and the same number of patients was over 8 years, 3 of these over 15 years of age.

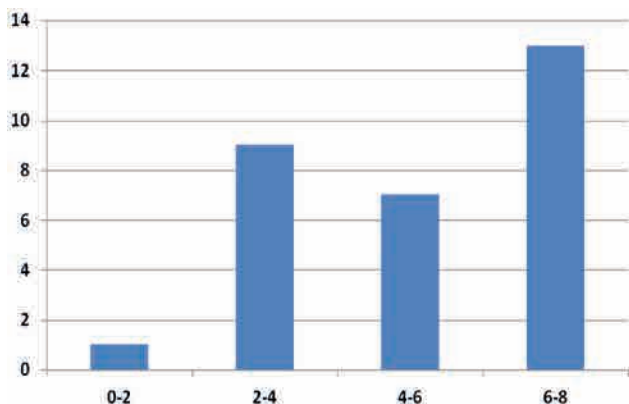


FIGURE 2. Number of patients distributed in age groups at diagnosis

In Table 1, we summarize the symptoms and signs that were described in the children included in the study group, and figure 3 depicts the clinical features in children under and over 6 years of age. There were 17/30 (57%) children under 6 years of age and 13/30 (43%) children over the age of 6 years.

TABLE 1. Clinical features of patients with celiac disease

Clinical features of patients with celiac disease	Number of patients (%)
Abdominal pain	7/30 (23)
Abdominal distention	4/30 (13)
Vomiting	3/30 (10)
Decreased appetite	4/30 (13)
Pallor	5/30 (16)
Fatigue	2/30 (6)
Diarrhea	7/30 (23)
Constipation	8/30 (26)
Weight loss/failure to thrive	9/30 (30)
Malnutrition	3/30 (10)
Growth stunt	1/30 (3)
First grade family members with celiac disease	5/30 (16)
Family medical history of other autoimmune diseases	9/30 (30)

Data regarding family members with celiac disease or other autoimmune diseases were included in table 1. Two children diagnosed with celiac disease had been previously diagnosed with type I diabetes mellitus. One of the patients diagnosed with type I diabetes mellitus also had vitiligo. Also, two children were diagnosed with autoimmune thyroiditis. One patient, a 9 years old boy, was diagnosed with autism.

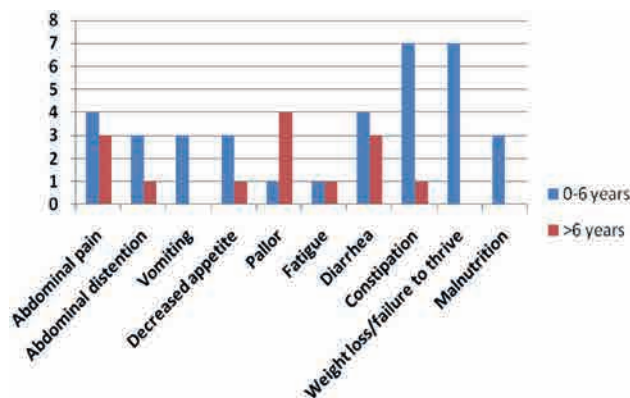


FIGURE 3. Clinical features in children under and over 6 years of age

Twenty children (66%) had features of classical celiac disease. In Table 2 we present the characteristics of patients with classical and non-classical celiac disease.

There were no statistically significant differences between the age at diagnosis or the duration of symptoms of children with classical (with or without diarrhea) and non-classical celiac disease (abdominal or nonspecific symptoms) ($p>0.05$).

Thirteen/30 patients (43.3%) were found to have iron deficiency anemia at diagnosis; in 3 of them, the diagnosis was suspected after the treatment with iron was started, but there was no response. The serum level of 25-OH Vitamin D was measured in 8/30 (26%) patients at the initial evaluation and in 5/8 celiac children an insufficient level was found. Serum albumin was within normal ranges in all the patients. Two patients had slightly increased values of liver enzymes.

IgA-TGA was determined in all the patients. All the children included in the study group had normal levels of total IgA. In 23/30 (76%) of the children, the values of the IgA-TGA were more than 10 times the upper limit of the normal values. All 30 patients had positive AEM antibodies.

Nineteen children were diagnosed between 2017 and 2019. Four of them (21%) were diagnosed based on positive IgA-TGA and AEM and a genetic test showing HLA DQ2 and/or DQ8. Fifteen of these 19 patients (79%) were diagnosed based on positive levels of antibodies and duodenal biopsy samples showing Marsh 2 or 3 features. Between 2020 and 2022, 8/11 children with celiac disease were diagnosed based on the levels of IgA-TGA (more than 10 fold the normal values). In the other 3 children, the diagnosis was based on the positive antibodies and biopsy samples showing Marsh 3 changes. Only in one of these 3 children the level of the IgA-TGA was lower than 10 fold the normal values. Figures 4 and 5 depict histopathology changes in a duodenal biopsy sample in one of the celiac patients.

TABLE 2. Number of patients, age at diagnosis, and duration of symptoms before diagnosis in different celiac disease phenotypes

	Classical celiac disease		Non-classical celiac disease	
	Malabsorption with diarrhea	Malabsorption without diarrhea	Abdominal symptoms	Nonspecific symptoms*
Number of patients (%)	7/20 (35)	13/20 (65)	8/10 (80)	2/10 (20)
Age at diagnosis (years) (median)	4.5	4.3	4.2	10.1
Duration of symptoms until diagnosis (months) (median)	6	6	7,5	3
Number of patients with diagnostic delay of >1 year	1	5	4	0

*Patients with nonspecific symptoms had fatigue and decreased appetite and no other symptoms

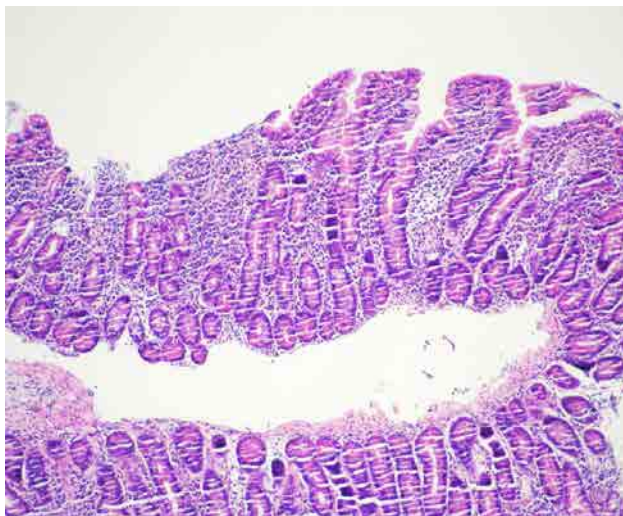


FIGURE 4. Haematoxylin-eosin x 100. Villous atrophy, crypt hyperplasia, increased intraepithelial lymphocytosis

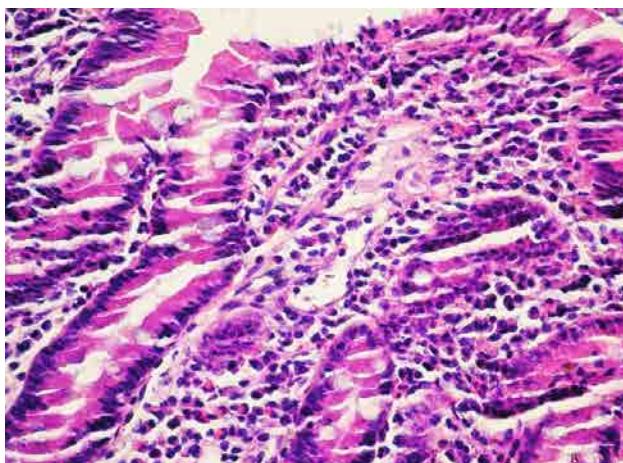


FIGURE 5. Detail x400. Stromal plasmacytosis and abundant exocytosis

DISCUSSION

We report in this study clinical characteristics and results of investigations in patients investigated in our General Pediatrics Department in the last 5 years. Features consistent with the description of

classical celiac disease were found in 66% of our patients. Weight loss or failure to thrive and malnutrition, some of the defining features of classical celiac disease, were only found in children younger than 6 years, while pallor and anemia refractory to treatment with iron were features found in children over the age of 6. Growth stunted was described in one patient, a 7 years and 6 months old boy.

Diarrhea or constipation were described in an almost equal number of patients (23 and 26%, respectively), while the rest of the patients had no changes in the intestinal transit (51%). Riznik et al. study reports a comparable percentage of patients with classical celiac disease, 67.2% [11]. Khatib et al. found that abdominal pain was the most common symptom in celiac patients (52.7%) [4]. In our study the number of patients describing this symptom was much lower (23%). Constipation was in their study the second most frequent clinical feature [4].

We diagnosed an almost equal number of children before and after the age of 6. One third of the patients were between 2 and 4 years of age at diagnosis. Our study group did not include patients under the age of 1. In the study published by Khatib et al., no children under the age of 1 were diagnosed with celiac disease either [4]. Riznik et al. report in Central European countries [11] a median age at diagnosis higher (7 years) than our patients' (4.3 years). Non-specific symptoms were described in a small number of patients, with a median age at diagnosis of 10 years of age.

The mean period between onset of symptoms and diagnosis in our patients was 6 months. We found no differences in the duration of symptoms until diagnosis, regardless of the celiac disease phenotype. A mean period of 6 months between onset of symptoms and diagnosis has also been reported in a recent study from 5 Central European countries [11]. The rate of children with diagnostic delays longer than 1 year and 2 years was higher in our study (33% and 16%, respectively) than in Riznik

and colleagues (26.7% and 12%, respectively) [11]. In patients with celiac disease, long diagnostic delays affect children's body mass [11]. Studies in adults have reported a delay in diagnosis of 3.5 years in patients with non-gastrointestinal symptoms, recommending screening patients with anemia, low bone mineral density, and thyroid diseases [12].

The study performed by Risnik and colleagues [11] in Central European countries analyzed the duration of diagnosis made only by Pediatric Gastroenterologists. A study conducted by the same team [13] showed that the knowledge about celiac disease among health care professionals is not satisfactory and can lead to long diagnostic delays.

Iron deficiency anemia was diagnosed in almost half of our patients. In 3 of them iron deficiency anemia not responding to treatment was the main reason why these patients were investigated for celiac disease. Reduced duodenal mucosal surface area and impaired iron uptake is the main cause in celiac patients [14], but studies have also shown a reduced expression of iron regulatory proteins [15,16].

Serum levels of Vitamin D were measured at diagnosis in a small number of our patients (26%). This is an important parameter that needs to be monitored [17].

The most common autoimmune diseases associated in childhood with celiac disease are type I diabetes mellitus and autoimmune thyroiditis [7]. In our group of patients, there were 2 diagnosed with type I diabetes mellitus and 2 with autoimmune thyroiditis. All these patients had been diagnosed with these autoimmune diseases before being diagnosed with celiac disease. All these patients were symptomatic but had non-classical features (abdominal pain, fatigue, decreased appetite).

Celiac disease has a strong genetic heritability. Four of our patients were first-grade relatives of patients with celiac disease. They all had symptoms. Almost one-third of our patients had a family mem-

ber diagnosed with an autoimmune disease. A recent study of children screened for celiac disease due to the diagnosis of celiac disease found that even though most of them were asymptomatic, the histological changes were severe, underlining the importance of screening [18].

Since the guideline issued by ESPGHAN in 2012, studies showed that an accurate diagnosis of celiac disease is possible without biopsy and HLA analysis [19,20]. Even though the number of patients diagnosed between 2017 and 2019 cannot be compared with those diagnosed after 2020, we were able to decrease the number of biopsies needed for a precise diagnosis in a significant percentage.

It is hard to draw conclusions regarding the number of cases diagnosed each year, considering the conditions imposed by the restrictions that came with the COVID-19 pandemic. In these circumstances, many patients and parents were reluctant to seek medical advice in the hospitals so the diagnosis may have been postponed. A recent study on children with celiac disease diagnosed during the COVID-19 pandemic showed an increase in the number of patients associating type 1 diabetes mellitus [21].

The study's strength is that it gathered cases in a General Pediatrics Department from Pediatricians with different fields of interest, not only Pediatric Gastroenterologists. Our study is a retrospective one and includes a small number of cases. This limits considerably the statistical analysis that can be performed.

CONCLUSIONS

Classical celiac disease remains the predominant phenotype in our patients. Most patients were diagnosed between 2 and 4 years of age. Adherence to new guidelines allowed in the past 2 years a diagnosis without histological examination of biopsy fragments in most of the patients.

Conflict of interest: none declared

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