Clinical, Paraclinical and Histological Considerations for Coeliac Disease in Children

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Introduction: Coeliac disease is an autoimmune enteropathy caused by gluten intolerance in genetically susceptible people. Gluten is a protein found in food containing wheat, oat, barley, rye. It can start with typical (classical) gastro-intestinal symptoms, atypical symptoms or may be silent (asymptomatic).
Objectives: Evaluation of the anthropometric, clinical, paraclinical and histopatological data of children with coeliac disease hospitalised at the Pediatric Clinic I in Târgu Mureș.
Material and method: The work is based on a study conducted retrospectively during 2006-2010. From the total number of 10982 patients, 25 were admitted for malabsorption syndrome and 12 out of these, with coeliac disease. The diagnosis has been set according to anamnesis, clinical examination, serology tests, histopathological and immunohistochemical test.
Results: Eight children with coeliac disease were older than 2 years of age and 4 children younger than 2 years of age. Two-thirds of the patients showed classical symptoms and one-third an asymptomatic form. The IgA type endomysial antibodies (IgA EMA) were positive in all children. Histopathologic and immunohistochemical tests were carried out in 58.3% of the cases.
Conclusions: The classical symptoms were prevalent. Anemia, weight loss, diarrhoea and growth failure were the most frequent signs and symptoms. Type 3c according to histopathological modified Marsh-Oberhuber classification was present in the majority of the cases. Serological screening (IgA EMA) is recommended in children presenting with weight loss, ferriprive anemia that does not respond to oral iron therapy, and growth failure.

Keywords: Coeliac disease, children, classical symptoms, villous atrophy

Introduction

Coeliac disease (CD) is an autoimmune enteropathy caused by gluten intolerance in genetically susceptible people. Gluten is a protein found in food containing wheat, oat, barley, rye [1]. According to the NICE 2009 guideline, a report from 2004 including cases from north America and western Europe gives a prevalence of CD in children by biopsy of 0.5–1.6% and by serology of 0.3–1.9% [2]. The disease may start in a classical (typical) way with chronic or intermittent diarrhoea, weight loss, recurrent abdominal pain, meteorism, nausea, vomiting, anorexia, fatigability; atypical form with extra-digestive symptoms and weak digestive symptoms that require a careful anamnesis and an asymptomatic form that may show iron deficiency anemia, osteopenia and behavioural disorders [3]. Other disorders associated with this disease are type I diabetes, autoimmune thyroiditis, aphthous stomatitis, dental enamel defects, Turner syndrome, Down syndrome, autoimmune hepatitis. The prevalence of the disease is higher in diabetes patients, first-degree relatives with CD and autoimmune thyroiditis. The disease may be diagnosed at any age after starting a diet containing gluten [2]. The diagnosis is based on anamnesis, clinical criteria, serologic tests — endomysial antibodies (EMA) and/or tissue transglutaminase (tTG), histopathological exam of the duodenal biopsy, immunohistochemical exam, molecular HLA testing in unclear cases, clinical remission after withdrawal of gluten [4,5]. The histopathological changes are classified in 4 stages as per the modified Marsh-Oberhuber classification: stage 0 – prior to the infiltration; stage 1 – infiltrative (increased number of intraepithelial lymphocytes); stage 2 – infiltrative and hyperplastic crypts; stage 3 – infiltrative, hyperplastic crypts, villous atrophy; and stage 4 – total villous atrophy with hypoplastic crypts and normal number of intraepithelial lymphocytes. Stage 3 has been classified in 3 substages: a – mild, b – moderate, c – total villous atrophy [6]. The immunohistochemical exam has been performed for a better evaluation of the number and distribution of intraepithelial lymphocytes using lymphocyte marker CD3 [7]. The treatment of the disease is a lifelong exclusion of gluten [1]. The aim of this study is the evaluation of the anthropometrical, clinical, paraclinical and histopathological data of children with CD disease hospitalised at the Pediatric Clinic I in Târgu Mureş.

Material and method

The work is based on a study conducted retrospectively at the Pediatric Clinic I in Târgu Mureş during 2006–2010. The cases were evaluated based on the patient's charts. The selection criteria were patients with chronic diarrhoea, nausea, vomiting, recurrent abdominal pain, meteorism, constipation, anorexia, fatigability, weight loss, growth failure, ferriprive anemia, aphthous stomatitis, dental enamel defects. The following exams of the cases that meet these criteria were evaluated: (1) serological exam – IgA EMA (positive or negative) using indirect immunofloure-

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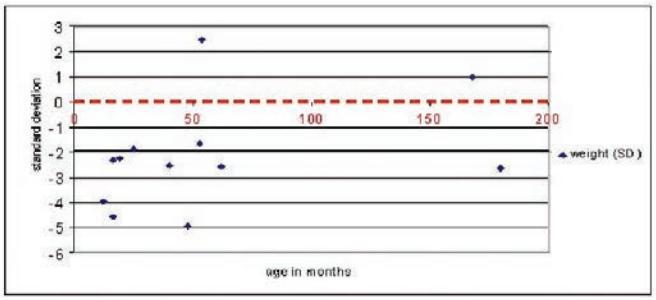

Fig. 1. Weight-for-age in standard deviations (SD)

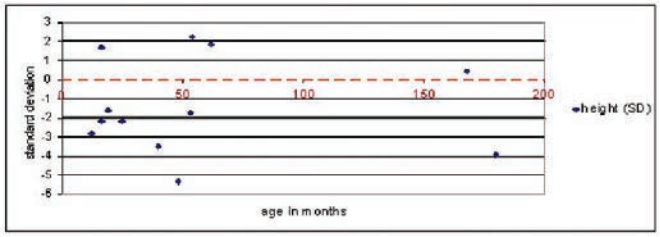

Fig. 2. Height-for-age in standard deviations (SD)

cence method; (2) other blood tests: haemoglobin, mean corpuscular volume, serum iron, protein level, serum level for Ca, Mg; (3) upper gastrointestinal endoscopy with small intestinal and gastric biopsy; (4) histopathological exam (stained with hematoxylin-eosine, PAS-alcian and Giemsa for each case). The histopathological results have been grouped as per the modified Marsh classification. (5) Immunohistochemical test to identify the positive intraepithelial lymphocytes TCD3. In the cases where endoscopy could not be performed, for objective reasons, the diagnosis has been based on the clinical features with positive serological results and clinical remission after gluten withdrawal. The data concerning breast-feeding and diversification have been taken from the patient's anamnesis included in the chart. The anthropometric data (weight, height) at the time of diagnosis have been computed with excel, growth analyser. Grubbs' test has been performed to detect outliers.

Results

From the total of 10,982 patients, 25 were hospitalised with malabsorption syndrome and 12 from these with coeliac disease. The ratio between girls and boys was 3:1. The age interval at the time of diagnosis was 1–15 years with an average of 58 months (variant: 3247, SD: 57, CV: 99). Grubbs' test revealed no aberrant values. Four (33.33%) children under 2 years of age and 8 (66.66%) over 2 years of age have been diagnosed with CD. The ratio of the patients according to the origins urban: rural was 4:7. The average length of breast-feeding was 6 months and diversification began with an average of 4 months.. The most frequent signs and symptoms the patients accused were: weight loss, anemia, diarrhoea, growth failure (Table I).

Table I. Clinical features of children with coeliac disease

Signs and Symptoms	Number of patients (%)
Weight loss	8 (66.66%)
Anemia	8 (66.66%)
Diarrhoea	7 (58.33%)
Growth failure	6 (50.00%)
Fatigability	4 (33.33%)
Recurrent abdominal pain	2 (16.66%)
Meteorism	2 (16.66%)
Nausea, vomiting	2 (16.66%)
Anorexia	2 (16.66%)
Aphthous stomatitis	2 (16.66%)
Constipation	1 (8.33%)
Dental enamel defects	1 (8.33%)

Our study showed that eight (66.66%) patients presented with classical symptoms and four (33.33%) patients had silent symptoms: iron deficiency anemia and/or weight loss, growth failure. One patient, aged 15, presented to the hospital only for weight loss and growth failure, after an endocrinological disease had been ruled out. Standard deviation (SD) for weight was below -2 SD in 8 (66.66%) children (Figure 1) and that for height in half of the children (Figure 2).

The endomysial antibodies were positive for all patients. Eight (66.66%) of them had microcytic anemia. The serum iron level was low for 5 (41.66%) children. Four (33.33%) of the patients showed hypoproteinemia and the serum level of Ca and Mg was normal in all patients. The mucosal biopsy of duodenum and stomach was performed in only 7 (58.33%) children, and for the rest of 5 (41.66%) with the age ≤2.1 years, the diagnosis has been based on the clinical picture with positive serological results and clinical remission after gluten withdrawal. Six out of 7 patients, which underwent endoscopy, showed on the mucosal biopsy of duodenum type 3c histological changes according to the modified Marsh classification. Immunohistochemical staining showed for all patients a higher amount of positive lymphocytes infiltration for CD3. One patient showed the 4th Marsh stage. Total villous atrophy was present in all patients; 5 of them had the classic form and the other two the asymptomatic form. An increase of gastric intraepithelial lymphocytes, associated with the basic disease, was found in two cases. Intraepithelial CD3 lymphocytic infiltrate was identified through a immunohistochemical test. One of these patients showed high levels of transaminases and negative serological results for other viral infections; a second patient, diagnosed at age 15, presented only for weight loss and growth failure without epigastric pain.

Discussions

Children with CD may show various clinical symptoms. These are classical, atypical or silent symptoms which need a careful anamnesis. In our study most patients, 8 (66.66%), showed classical symptoms (diarrhoea, weight loss, recurrent abdominal pain, meteorism, nausea, vomiting, anorexia, constipation, fatigue and anemia) and 4

(33.33%) patients showed silent symptoms: iron deficiency anemia and/or weight loss, growth failure. A study conducted in Italy for 19 years (1987–2006) showed a reduction of prevalence of classical symptoms from 76% during 1987–1990, to 63% during 1991–1995 and up to 44% during 2001–2006 [8]. Despite the low number of patients in our study, the frecvency of classical symptoms was higher. If a child presents with weight loss and/or growth failure the coeliac disease should also be taken into consideration, especially if it is associated with gastrointestial symptoms. The weight loss and growth failure were quite frequent 66.66% / 50.00%, respectively at diagnosis, similar to a Dutch study in 1993, where the growth disorder made up 49.7% [9]. An Italian study made in 1994 revealed the presence of hypochromic, microcytic anemia in 48.5% of children with coeliakia[10]. In our study 8 (66.66%) of the children suffered from microcytic anemia, from which 5 had ferriprive anemia. Four patients suffered from severe anemia and needed red blood cells tranfusions. The gender ratio favored the girls, 3:1, similar with the description in the literature, showing that the disease is more frequent with girls and also more severe [11,12]. The average age of diagnosis was 58 months (4.7 years), similar to that of a Spanish study done during 1991–1999 with an average age of 43.9±43.7 months [13] and the Australian study of 119 patients with an average age of 65 months [14]. In our study the number of children diagnosed under the age of 2 is higher than those over 2 years. The nutrition of infants plays an important role in the risk of coeliac disease. A prospective Swedish study indicates a lower risk for breastfed infants compared to those with discontinued breast-feeding at the time of starting the diet with gluten-containing foods. The risk to develop the disease was even lower, if breast-feeding has been continued even after the time of diversification with gluten [15]. We cannot specify in our study if the food contained gluten at the time of diversification, but we can say that the patients have been breastfed for an average of 6 months and the diversification was initiated starting with an average of 4 month. As per ESPGHAN 2008 recommendation it is prudent to avoid early (less than 4 months) and late (more than 7 months) introduction of food containing gluten and the gluten should be introduced gradually during the breast-feeding period [16]. The CD diagnose of our patients was supported in 7 (58.33%) cases by the positive IgA EMA value, by the histological modification type 3c, respectively 4 as per modified Marsh classification and the immunohistochemical test. The rest 5 (41.66%) were under 2.1 years old, the diagnosis was set by associating the clinical picture, the positive IgA EMA and the positive response to the diet treatment. Six out of 7 histopathologically tested patients showed the type 3c as per modified Marsh classification. A study conducted in 2005 investigated the variability of the histological injuries related to the CD and showed the presence of villous atrophy stage 3c in 75% of cases, all with positive serology [17]. Another study (2010) found total atrophy in 80.1% of cases [18]. Though, in most cases of our study, the total villous atrophy is associated with the classical form, there are also cases where total villous atrophy is associated with the silent form. In a large adult study there was no correlation between the clinical features and the degree of villous atrophy [19]. In our study the gastric intraepithelial lymphocytes were present in 2 cases (16.66%). Pathology reports of 304 patients with CD, described in a recent study, revealed the presence of gastric intraepithelial lymphocytes in 39 (12.8%) cases and have shown that, statistically, the patients are more likely to be diagnosed at an earlier stage and with more severe clinical, paraclinical parameters at the time of diagnosis [20]. In our study one patient had high transaminase level and the other was diagnosed later.

Conclusions

The classical symptoms were prevalent. Anemia, weight loss, chronic diarrhoea and growth failure were the most frequent signs and symptoms. Type 3c according to the histopathological modified Marsh classification was found in the majority of the cases. The total villous atrophy can be present in the classical form as well as in the silent form. The serological screening is recommended in children presenting with weight loss, iron deficiency anemia that does not respond to therapy and growth failure.

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