

THE MULTIPLE FACES OF CELIAC DISEASE IN CHILDREN AND TEENAGERS - AN UPDATED REPORT

Oana ROȘU¹, Georgiana GÂLCĂ², Oana TIMOFTE², Gheorghe G. BĂLAN²,
Georgeta SINIȚCHI³, Laura ION⁴

¹Resident, „St. Mary” Children’s Emergency Hospital, Iași, Romania

²Univ. Assist. PhD Student, „Gr.T. Popa” University of Medicine and Pharmacy, Iași, Romania

³Prof. PhD, „Apollonia” University of Iași; „Atopia” Medical Center, Iași, Romania

⁴Assist. Prof. PhD, „Titu Maiorescu” University of Bucharest, Romania

Corresponding author: Oana Timofte; e-mail: oanatimo@yahoo.com

Abstract

Celiac disease (CD) is an autoimmune disorder occurring in genetically susceptible individuals, being characterized by inflammatory injury of the small intestine mucosa after ingestion of wheat gluten or related barley or rye products. The condition can develop at any age, although symptoms are most likely to appear during early childhood, between 9 and 18 months. Clinical presentation includes a family history and a range of symptoms such as recurrent abdominal pains, diarrhea, vomiting, bloating and flatulence, iron-deficiency anemia, weight loss, asthenia, and failure to thrive. The standard diagnostic criteria of CD require a clinical context, together with new serologic tests for antibodies against tissue transglutaminase and deamidated gliadin peptide, and especially characteristic histologic findings in small bowel biopsies (the gold standard for diagnosis). Gluten-free diet is the cornerstone therapy of CD. Although safe and effective, this method is not ideal: it is of limited nutritional value, expensive, and compliance or life quality problems are described in many countries. Consequently, alternative therapeutic strategies were developed to decrease the immunogenicity and to prevent the absorption of gluten-containing grains, together with strategies to limit T-cell migration or re-establish mucosal homeostasis. Celiac disease can appear in various associations, with atypical clinical presentation, requiring careful and early diagnosis for introducing the gluten-free diet as soon as possible, and for reducing the rate of subsequent complications.

Keywords: celiac disease, childhood, gluten-free diet.

1. BACKGROUND

Celiac disease (CD) is an immune-mediated systemic disorder of the gastrointestinal tract triggered by exposure to dietary gluten and similar alcohol-soluble proteins (prolamins) in generally susceptible individuals. Even though the condition can occur at any age, its consecrated wide perception refers to cases occurring in

genetically predisposed children and adolescents [1]. Whichever the age, CD can be manifested with gastrointestinal features, malabsorption, iron deficiency and anemia, but also with extra-digestive manifestations; asymptomatic forms can also be described at variable frequency. Among the peculiar clinical aspects of this disease, mention should be also made of its association with several autoimmune diseases: type 1 *diabetes mellitus*, and thyroiditis. Thus, CD remains a challenging diagnosis, with clinical features not clearly related to digestive pathology and accurate diagnosis, depending on the findings about the characteristic, even if not specific modifications evidenced in serologic tests, *i.e.* IgA endomysial antibody and IgA tissue transglutaminase antibody, that requires endoscopic duodenal biopsy. Currently, the gluten-free diet remains the main course of CD therapy, while concurrently evaluating novel prospects of non-dietary therapeutic opportunities [2,3].

2. EPIDEMIOLOGY

Epidemiological studies conducted in Europe have indicated a prevalence of childhood CD of approximately 0.3 – 2.4% (mean 1%). The prevalence of this condition appears to be higher in girls than in boys. CD is also common in the United States, South America, Middle East, Northern India and Northern Africa. At the same time, many cases would remain undiagnosed without active serologic screening. CD is extremely rare in China, Japan, and most of Africa. However,

recent studies showed a decrease in the number of cases in children, by excluding gluten from the diet of many countries [4].

3. PATHOGENESIS

The pathogenesis of CD develops by an interplay of genetic and autoimmune factors, together with an environmental element, namely the ingestion of gluten. Genetically predisposed individuals are those who carry the HLA alleles DQ2, DQ8 or both. Moreover, the condition is 10 times more likely to occur in first-degree relatives and 30 times more frequent in twins than in the general population. The enzyme tissue transglutaminase or type 2 transglutaminase (TTG or TG2) was identified as the autoantigen against which the abnormal immune response is directed. TTG progressively increases its immunogenicity, generating autoantibody responses (mainly type A immunoglobulin), which can exacerbate the inflammatory process. At the same time, the ingestion of gluten is the single major environmental factor triggering CD in this autoimmune process. Gluten is a protein component of wheat, barley and rye that contains proteins called prolamins, which vary amongst the different types of grain: gliadin in wheat, hordein in barley, and secalin in rye. Prolamin is resistant to degradation by gastric, pancreatic and intestinal brush border proteases, it crosses the epithelial barrier and promotes an inflammatory reaction resulting in flattening of the villi and crypt hyperplasia. The risk of developing CD is also enhanced by certain viral infections, such as rotavirus and adenovirus; the increased rates of births through elective Cesarean delivery and changes in infant feeding practices were discussed recently [5-7].

4. CLINICAL PICTURE AND DIAGNOSIS

The clinical suspicion of CD should be raised if the patient presents with a family history of CD in first and second-degree relatives, medical history of type I *diabetes mellitus*, thyroid dysfunction, autoimmune hepatitis or osteoporosis. In some cases, children show no symptoms, however, in clinically significant

observations, they may present with chronic and recurrent diarrhea, poor appetite, a bloated or painful abdomen, and weight loss or difficulty in gaining weight. These symptoms can begin at any age, if an individual eats gluten-containing foods. In older children, constipation or diarrhea may occur together with steatorrhea, meteorism, and flatulence. The patients may also have shorter than expected height. In some cases, the child does not have any of these common symptoms but has iron deficiency anemia, skin rashes (*dermatitis herpetiformis*: itchy, fluid-filled skin blisters - mainly seen in teenagers and adults) or changes in teeth (dental enamel hypoplasia, delayed tooth eruption). Children with CD are also at risk for rickets caused by vitamin D malabsorption.

Even though numerous cases of pediatric CD are asymptomatic or the presenting signs and symptoms are not necessarily related to the gastrointestinal tract, it is important to discern among the various forms of the disease and their clinical features. Accordingly, 5 main forms of the disease has been described, *i.e.* typical (some with delayed onset), atypical (extra-intestinal), silent, potential and latent CD [8]. In the typical form, children present symptoms and signs of malabsorption, *i.e.* anorexia, chronic diarrhea, constipation, vomiting, recurrent abdominal pain, bloating, failure to thrive and muscle wasting. These features appear between 6 and 24 months of age. Constipation is a frequent condition encountered in pediatric age, its growing incidence ranging from 3% to 25%, with the vast majority of cases meeting the criteria of functional constipation, while up to 10% of the patients show conditions that cause secondary constipation, such as hypothyroidism, Hirschsprung's disease, celiac disease, etc [9-11]. The celiac crisis is characterized by severe watery diarrhea, important abdominal distension, severe dehydration with hypokalemia and hypotension, together with impairment of the general condition. Atypical forms describe none or few digestive features, except for the presence of malaise, fatigue or anemia due to iron deficiency, inadequate weight and height gain or delayed puberty.

In teenagers and young adults, the most common form of presentation is anemia. These two main varieties are illustrated in the so-called Logan's "celiac iceberg" that depicts the relation between HLA status, duodenal morphology and clinical expression. Children diagnosed with typical CD are thought to represent the top of the iceberg, in that they are the obvious, visible patients. The point in using this model is that the remaining, much larger "submerged" part of the iceberg by far accounts for up to ten times more frequent atypical and silent forms of the disease. A vast number of conditions under this last category remains undiagnosed, and thus carrying the risk of long-term complications. There is evidence that the less clinically evident conditions are much more frequent than the clinically overt ones [12,13]. Silent forms do not present with clinical complaints, but duodenal mucosal changes are consistent with CD. Potential forms include patients with positive serology, normal mucosal serology that may or may not be symptomatic and which have a genetic compatibility with celiac disease. Latent forms include two categories: a) patients with previous CD diagnosis who responded to gluten-free diet and presented a normal histology or only intraepithelial lymphocyte increase; b) individuals with normal intestinal mucosa under diet including gluten and who will subsequently develop CD [14]. Nonresponsive and refractory CD can also be added to these varieties, to be therefore considered rather as a certain complication of the disorder. Nonresponsive CD is due mainly to contamination of the diet with gluten, together with additional conditions such as bacterial intestinal overgrowth, colitis, irritable bowel syndrome or pancreatic malfunction. Refractory CD is currently defined by persistent features of malabsorption after 12 months of gluten exclusion, with ongoing intestinal villous atrophy [15]. Many CD-associated conditions described mostly in adults can indeed be observed in children. These comorbidities are numerous and diverse, yet also treatable with an adequate diet. Type 1 *diabetes mellitus* is the most frequent autoimmune association (3 - 5% of CD) and usually precedes the onset of CD. Concurrently, autoimmune thyroiditis causing hypothyroidism is significantly more frequent in

CD, as CD was found at an increased rate in patients with autoimmune thyroid disease (Grave's disease and Hashimoto's thyroiditis) [16-19]. Many researches focused on the prevalence of celiac disease autoimmunity or tissue transglutaminase autoantibodies amongst patients with type 1 diabetes and autoimmune thyroid disease; associations of these three conditions with rare diseases, such as insulinoma, have also been described. Severe complications of diabetes - *i.e.* diabetic foot - now benefit from new therapeutic approaches [20-23]. Several liver conditions have been associated with CD, *i.e.* isolated cytotoxicity, sclerosing cholangitis, and autoimmune hepatitis or cirrhosis; patients with elevated transaminase levels of unclear etiology may have silent celiac disease. Other autoimmune disorders coexisting with CD include psoriasis, Addison's disease, systemic *lupus erythematosus*, Sjogren's syndrome, hypoparathyroidism, dermatomyositis, scleroderma, ulcerative colitis, Crohn's disease, myasthenia gravis, etc. Down's, Williams's and Turner's syndromes are also some frequently associated conditions which require systematic screening for CD [24-26]. Various psychological symptoms and mental disorders have been reported in CD: anxiety, depression and a moderately increased risk of suicide [27-29]. Moreover, alcohol use disorders are associated with a greater incidence of certain comorbidities in patients with celiac disease; therefore, prevention of alcohol abuse is indicated in them [30-32]. Certain common complications of CD can be developed when the disease is not recognized or treated. These include osteoporosis, iron deficiency and other nutritional deficiencies and growth retardation in children. There are also issues related to subfertility, infertility, repeated miscarriages and intrauterine growth retardation; the need for screening pregnant women for celiac disease was discussed recently. Pathology: Although CD is associated with certain macroscopic endoscopic features like scalloping, it is the histologic pattern with actual diagnostic value. It includes a large spectrum of intestinal abnormalities, ranging from an increasing number of intraepithelial lymphocytes to crypt hyperplasia lengthening and various degrees of villous atrophy. The histologic features of CD consist of a combination of flattened

mucosa with villous atrophy, increased intraepithelial lymphocytes, crypt hyperplasia, enterocytic damage and increase in mononuclear cells. Well-directed biopsies must be obtained from the duodenal bulb, which is the location

most severely affected by these lesions. The pathology changes of CD were categorized by Marsh classification in 1992. (Table 1)

Table 1. Classification of pathologic modifications in CD [33]

Marsh classification	Pathologic modifications
Marsh stage 0	normal mucosa;
Marsh stage 1	increased number of intraepithelial lymphocytes (exceeding 20 per 100);
Marsh stage 2	hyperplastic lesion (type 1 plus crypt hyperplasia)
Marsh stage 3	destructive lesion (type 2 plus villous atrophy)
Marsh stage 4	hypoplastic lesion seen in T cell lymphoma

In 2005, Corazza and Villanacci proposed a new simplified classification of CD, by dividing this condition into non-atrophic and atrophic cases [34]. Villous atrophy is more common in children younger than 3 years with untreated CD, but in older children (as well as in adults) it is common to find minor intestinal lesions and normal villi [35].

Overall diagnosis of CD requires a complete patient history with focused clinical examination, followed by serologic tests and endoscopy with biopsy. All tests should be performed before the initiation of the gluten-free diet. The initial detection of possible CD can be achieved using simple and accurate serologic tests, *i.e.* anti-tissue transglutaminase type-2 (TG2), endomysial antibodies (EMA) and deamidated gliadin peptide antibodies (DGPs). They should be done as first step in patients with a case history and symptoms suggestive of CD or in those with CD-associated diseases. The positivity for anti-TG2 CD is associated with a high probability for CD in children and adolescents. However, in children younger than 2 years, anti-TG2 sensitivity may be less than optimal; therefore, the use of deamidated gliadin peptides (DGPs) was proposed for this age group [7]. CD is also associated with some human leukocyte antigen (HLA) allele specificities, namely HLA DQ2 (in 90-95% of cases) and HLA DQ8 (5% of cases). Genetic testing for HLA-DQ2 and HLA-DQ8 is a useful tool to exclude CD or to make it very unlikely in the case of a negative test result for both. In terms of screening, measurement of IgA

anti-TG2 is the method of choice. Patients with positive test results should be referred for endoscopic duodenal biopsy, the gold standard diagnostic test. Macroscopic changes include scalloping or nodularity of the mucosa and sparse duodenal folds; at least 4 biopsies should be obtained, and duodenal bulb biopsy is mandatory. According to ESPGHAN, biopsy can be avoided in selected cases with typical gastrointestinal signs, compatible HLA status, more than 10-fold higher IgA anti-TG2 levels, and positive anti-endomysium (EMA). Other investigations are the D-xylose test - which is modified - and steatorrhea - which can be 7-50 g/day. Barium meal may evidence a dilated jejunum and flattening of mucosal contour [35-37].

5. TREATMENT

No ideal curative treatment of CD exists. The treatment of choice is a gluten-free diet, which is often necessary on a lifelong basis. The gluten-free diet (GFD) requires complete elimination of the gluten protein found in wheat, barley and rye. An experienced nutritionist can provide patients with a solid education on the foods to avoid, as well as the alternatives they have for improving compliance with GFD. A lactose-free diet is included in the initial phases of the dietary treatment; it should be adopted on a short-term basis, because clinically significant lactose malabsorption or intolerance is rather exceptional. Nutritional troubles occurring in CD - *i.e.*, loss of small intestine's absorptive capacity, pancreatic insufficiency, and restrictive

dietary practice determining iron deficiency anemia and fat-soluble vitamin deficiencies – must also be monitored and corrected. Likewise, a number of experimental novel therapeutic trials were proposed. Such attempts included the use of gluten products with low immunogenicity, oral enzyme to detoxify ingested gluten, TTG enzyme blockage, regulatory cytokines, proinflammatory cytokine blockage, anti-adhesion molecule therapy or gluten peptide vaccination [38,39]. Approximately 95% of the children with CD who follow a GFD show clinical and serological improvement within a few weeks. However, patient compliance with dietary treatment is often discouraging. Therefore, symptomatic and serologic assessment must be permanently monitored at regular intervals, depending on the severity and clinical evolution of cases. Patients and families may need frequent dietary education and compliance verification. *Families should engage with the medical team, as well as with the other actors participating in child's social life (teachers, trainers, etc.)* [40]. Although the complete disappearance of the villous atrophy is rare, in most of the cases, initiation of diet leads to remission of symptoms; specific serologic negativity is obtained within up to 12-18 months, especially in patients with particularly elevated initial levels of anti-TTG. Treatment effectiveness in children is dependent on the strict compliance with the diet; clinical surveillance and monitoring of IgA TTG antibody is useful. Alternative treatment modalities focus on changes of the dietary components, enzymatic degradation of gluten, inhibition of intestinal permeability, and modulation of the immune response. Refractory CD may require corticoids and immune modulators, such as azathioprine, 6-mercaptopurine and cyclosporine. Recurrences and refractory CD cases must be reconsidered in terms of etiology and pathogeny; serology, endoscopic biopsy and aggressive treatment with corticoids and immune modulators are necessary [41,42].

6. PROGNOSTIC AND COMPLICATIONS

If adequately treated through a completely gluten-free diet, CD has an excellent prognosis – in 95% of cases the patient having a normal life. Alternatively, failure to introduce a strict

diet or suboptimal compliance lead to further evolution and occurrence of complications, including osteopenia/osteoporosis, anemia, refractory CD, and gastrointestinal malignancies (enteropathy-associated T-cell lymphoma) [43-45]. The long-term prognosis may also be affected by various visual disturbances, such as reduction of visual fields, loss of rapid flicker and color sensitivity, and severe deficits in acuity; other authors described decreases in retinal nerve fiber, anterior chamber shallowing, and qualitative and quantitative reduction in tears. All these will cause different stages of amblyopia or low-vision, and the affected children will have social difficulties in terms of school integration [46,47].

7. CONCLUSIONS

CD is an archetypal intestinal chronic inflammatory and autoimmune disorder in genetically susceptible individuals, currently believed to affect about 1% of the general population. There are also peculiar aspects in terms of epidemiology, clinical presentation, associated diseases and treatment in pediatric compared to adult population. Clinical manifestations vary from asymptomatic patients to severe forms of malabsorption syndromes and increased risk of specific complications. CD is therefore a clinical “chameleon” considering the fact that the children can be completely asymptomatic or just present with subtle and atypical features, but the disease can also severely affect any organ or tissue. Diagnostic strategies include various serologic tests preceding video capsule endoscopy and duodenal endoscopy with biopsy (deemed the gold standard in this respect). A GFD remains the cornerstone of treatment for childhood CD, but compliance problems are rather common.

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