New Approaches to Celiac Disease in Children

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ABSTRACT: The celiac disease represents an important chronic digestive disorder due to the consequences of the malabsorption syndrome and the complications which may appear during adulthood. The paper focuses on recent epidemiological data, and presents both the typical and atypical disease forms and the necessity for investigating the whole range of risk groups for the diagnosis of the silent and latent forms of disease.

KEYWORDS: celiac, clinical forms, diagnosis.

INTRODUCTION

The gluten enteropathy, also known as the celiac disease or the intolerance to gluten, represents an important cause for the delay in weight and height growth and in the child evolution. Because of the presence of the malabsorption syndrome and the complications that occur when being an adult, the celiachia disease is one of the most important chronic digestive diseases in children, which was intensely studied in the last two decades. The registered progress is related to pathogeny (especially the immunologic mechanism which are involved in the disease onset), the histological changes of the small intestine, and the identification of the clinical forms both in adults and children.

DEFINITION

Classically, the celiac disease was defined as a permanent intolerance to gluten (the protein in wheat, barley, oats, and rye) which manifests through signs of global or relative malabsorption, the histological issue being the subtotal or total vilositary atrophy. A no gluten diet produces clinical and histological regress, and when the gluten is reintroduced in meals, a relapse is registered (in maximum two years).

Currently, celiachia is considered to be a genetic disorder caused by an environment factor (gliadin – a protein found within wheat gluten with a "toxic" effect against the intestinal mucosa) which produces chronic enteropathy in the individuals who are genetically predisposed (the contribution of the HLA gens was demonstrated, the sick people presenting the DQ_2 and DQ_8 molecules on the surface of the antigen presenting cells) [12,18].

EPIDEMIOLOGY

There is a great difference between the incidence and the prevalence of the celiac disease as reported to different centers around the world. The disease is subdiagnosed in the regions where the reporting is done only for the classical forms of disease (the incidence is 2-13/100000/year) [5].

The prevalence of the celiac disease in Europe is estimated to be from 1:300 to 1:5000 people [4]. In Western Ireland, the prevalence is 1:300, in Sweden 1:267, in Denmark 1:1000 [2]. In Russia, there were no epidemiology studies, the assumed incidence being 1:1000 [2]. The disease is considered extremely rare among the inhabitants of Africa, Japan, and China.

Recent studies of populational screening suggest that prevalence may be increased (1:100) and more frequent in the patients with autoimmune diseases [13]. In the 1990s, there was performed a study in Italy on 20000 students, a study which included the IgA and IgG antigliadin antibodies showed an incidence of 1:200 [19]. In the USA the prevalence is 1:333 [8], taking into consideration the unseen part of the gluten enteropathy (described by Richard Logan in 1991) which comprises the silent and atypical forms of disease. The serologic screening increased the incidence of the disease.

CLINICAL PICTURE

The gluten enteropathy is heterogeneous from the clinical point of view, presenting a very large spectrum of symptoms, especially after toddler period. The maximum frequency of the disease onset is between 6 months and 2 years for the typical forms [2]. After this period, the nutritional consequences of the malabsorption syndrome are more and more obvious.

Classically, the disease onset occurs, on average, after the age of 6 months, after the introduction of the gluten in the diet. The onset may be accelerated by an episode of intestinal or respiratory infections. After a shorter or longer period of time (weeks, months), the stools of the child become loose, fatty, accompanied by an easily installed abdominal distension, weight loss followed by the decrease of height growth. There may appear irritability, vomiting, anorexia; there are clear signs of malnutrition and malabsorption (a frail and pale child with gibbous abdomen, no muscle mass, with trophic disorders of the skin, hair and nails, which are clear signs of rickets, explained through the malabsorption of the liposoluble vitamins).

In the preschooler (2 to 7 years), the celiac disease represents the first cause of chronic diarrhea. All the children who have had an episode of diarrhea, longer than 6 weeks, should be investigated for the celiac disease (within one study [9] it was pointed out that 6.5 % of the children with more than 6 week diarrhea were diagnosed with celiac disease). The weight regress or the delay in weight gain, the abdominal distension, and the abdominal pain syndrome are good reasons to see a doctor. The symptomatology for this age group includes meteorism, anorexia, and constipation (which can replace diarrhea the older the child). Constipation is considered a part of the atypical digestive symptomatology in the preschooler and the school children.

In the case of the child over the age of 6-7 years, who lacks diagnosis and treatment, we are struck by the weight and height regress; the child presents a recurrent pain abdomen, an increase of the abdomen volume, delayed puberty with primary amenorrhea, ferriprive anemia (difficult to treat), arthralgia or sign of arthritis. The forms with delayed onset are numerous and the triggering factors are unknown.

Due to the studies and research carried out in the last two decades, there have been identified atypical forms of disease, the patients presenting non-digestive symptomatology. These forms are:

A weight and height delay with an age-related bone delay, which can be considered as a unique sign. The child's weight can be normal but with hypotrophic muscles; the child can have only a delay in weight [18]. The weight delay is considered taking into account the parents' weight, but even in the cases with short parents, some studies showed that 10% of these children were diagnosed with celiac disease [5].

Delayed puberty and primary amenorrhea in the adolescent girls, who were not diagnosed and treated; ovarian polycystosis; the unexplained infertility (or spontaneous abortion) can be the sole manifestation of the disease in women [3].

Osteopenia or arthralgia (even signs of arthritis) explained by a deficiency in calcium and the malabsorption of the vitamin D [18].

The ferriprive anemia which is reluctant to oral drug treatment can be considered a complication of the disease because of the deficiency in absorbing the alimentary iron. Recent studies [18] showed that anemia associated with low stature in the asymptomatic child (lack of digestive manifestations) can be explained through celiac disease in 6.25% of the cases (severe lesions which are typical to celiac disease, pointed out due to the intestinal biopsy).

The dermatitis herpetiformis (Duhring-Brocq disease) which is a chronic autoimmune papulovesicular dermatosis, associated to a gluten enteropathy. It appears in the child over 5 years and in the adult and it presents IgA granular, patognomonic deposits, which are found on elbows, knees, and buttocks [7,16]. In 60% of the patients with dermatitis herpetiformis, the celiac disease is diagnosed, the cutaneous lesions undergoing an amelioration process when having a no-gluten diet (there is even a dormancy state) [18]. Some authors consider that dermatitis herpetiformis and celiac disease are different phases of the same disease. According to Démaulins [6] the dermatitis herpetiformis appears between 3 and 20 years after the initial diagnosis of celiachia.

Other skin disorders which can be seen in celiachia are psoriasis and alopecia aerate.

The recurrent aphthous stomatitis is present in 5% of the celiachia cases [17].

Neuropsychic manifestations: Different studies identify some strong associations between gluten enteropathy and various neuropsychic manifestations [3]: cerebellar ataxia (2-16.7%), often accompanied by the affectation of the peripheral nerves [17], epilepsy (3.5%-5.5%), neuromuscular diseases (hypotonic syndrome). In the case of intracerebral calcifications given by the folat deficiency, celiachia must be distinguished from epilepsy [19]. Cephalea is less present, as well as the ADHD syndrome (attention deficit with hyperkinesy) whose link with gluten enteropathy led to numerous controversies. Nervous anorexia and bulimia (regarded as appetite disorders) are

an expression of the psychopathological implications of the disease [3,11].

All these forms with an atypical symptomatology have a positive serology and histological changes, characteristic to jejunum biopsy.

There were also identified other disorders (conditions) associated with the celiac disease which must be known in order to perform the serologic screening, to diagnose the silent and latent forms of disease. The autoimmune diseases are 6 times more frequent than in the rest of the population. In diabetes mellitus (intensely studied) the prevalence of the celiac disease is 2.5-8.4% [16]. Autoimmune thyroiditis is associated with gluten enteropathy in 7% of the cases [16]. Other autoimmune diseases which are associated with celiachia are LES and juvenile rheumatoid arthritis. The prevalence of different autoimmune diseases in the patients with celiachia is correlated with the duration of the toxic action of the gluten against the intestinal mucosa, reaching 35% after the age of 20 years [17]. Various genetic syndromes, such as Trisomia 21 and Turner syndrome (2-5%), and the lactose intolerance are already known associations. The IgA selective deficit is 10 to 15 times more frequent as compared to the general population (it affects 2% of the patients with celiac disease, particularly the silent forms of disease) [10,18].

Familial studies showed that among the first-degree relatives the prevalence of celiachia is 4-12% [16].

It is necessary to test the risk groups: all the sick people with diseases that can be associated with the celiac disease, the first-degree relatives of the patients with celiachia, and the patients with ferriprive anemia, unresponsive to a treatment with iron. Thus, we can detect the silent and latent forms of the disease, which represent the unseen part of the iceberg. These persons are asymptomatic but they have a positive serology and typical histological changes of vilositary atrophy (silent form) and positive serology without histological changes (latent form).

LABORATORY DIAGNOSIS (SEROLOGIC TESTING)

The serologic testing of the patients with typical or atypical symptomatology, on the one hand, and the testing used for monitoring the evolution under a glutenoprive diet, on the other hand, have been performed for more than two decades using the IgG and IgA antigliadin antibodies batching (antibodies against the alimentary proteins) The increased values of the IgG antibodies are non-specific to the celiac disease and they can indicate an allergy to the cow's milk proteins or to the egg albumin, giardiasis etc. The IgA antigliadin antibodies are more specific (specificity 95-100%), but they have a lower sensitivity (between 70 and 92%) [14].

The development of immunology led to the identification of the auto-antibodies in gluten enteropathy, the first identified antibodies being the antiendomisium ones (against a structure of the intestinal mucosa) They present a high specificity for the untreated disease, but their level slowly decrease after the introduction of the glutenoprive diet (they are not used to monitor the evolution of the disease under treatment). To determine them requires the indirect immunofluorescence technique which depends on the examiner's subjectivity. The antigens, in this method, are represented by the monkey esophagus (its use as a screening method is limited) or the human umbilical cord (this requires a rich experience of the examiner).

In the last ten years, there has been improved a batching technique for another type of auto-antibodies – the IgG and IgA tissue antitransglutaminase antibodies with high specificity and sensitivity. Nowadays, the batching of IgA tissue antitransglutaminase antibodies is considered the selection serologic method for the initial testing within a suspicion of celiac disease.

If the patient is also associated with an IgA deficiency, then the result can be falsely considered negative and it is recommended an IgG tissue antitransglutaminase antibodies batching [1].

The results of these serologic tests select the sick people who will undergo an intestinal biopsy which is highly important for deciding upon a celiac disease diagnosis. Even if the antibody level is normal, but there is a clinical suspicion regarding whether the patient is part of a risk group, it is recommended the intestinal biopsy with a histopathological examination of the harvested tissues.

THE HISTOPATHOLOGICAL EXAMINATION

In the gluten enteropathy, the changes induced by protamines (proline- and glutamine-rich) found in wheat, barley, oats and rye are diffuse at the level of the small intestine, but

very clear at the level of the duodenum and the proximal jejunum. There are harvested several fragments from the second region of the duodenum and the proximal jejunum; the histological exam which shows the decreased report between vilosities and crypts (through subtotal or total vilositary atrophy and crypt hypertrophy) determines the diagnosis of gluten enteropathy. At the epithelium level, there is a massive lymphocitary infiltration (over 25 lymphocytes for 100 epithelial cells in the duodenum and 40 lymphocytes for 100 epithelial cells in the jejunum) and in the corion there is a rich lymphoplasmocitary infiltrate. Marsh classifies these changes (in 1992) [14,15,18]:

Phases:

Marsh 0: normal aspect

Marsh 1: lymphocitary enteritis (accumulation of intra-epithelial lymphocytes)

Marsh 2: phase 1 plus cryptic hyperplasia

Marsh 3: the changes from phase 2 and vilositary atrophy which can be:

A – partial

B – subtotal

C – total

The lesions considered as Marsh 1 are non-specific, but the result must be interpreted within the clinical-biological context. All the described phases can be found in the typical, classical form of celiachia, in the silent, atypical forms, and in the course of the histological relapse which are produced after re-introducing the gluten in the diet of the diagnosed and treated patients.

The changes can influence only certain areas within the jejunal mucosa, multiple biopsies being needed. One needs the experience of the examiner and the correct orientation of the mucosa fragments.

There has not been established some correlation between the histological changes in celiachia (the Marsh phases) and the clinical data.

For clinical suspicions of celiachia, one performs the serologic examination followed by the intestinal biopsy to indicate the diagnosis. In the asymptomatic cases, which are part of the risk groups, the serologic test is necessary, while in the presence of the tissular antitransglutaminase IgA antibodies, the intestinal biopsy is performed. Once the celiachia diagnosis established and no gluten diet initiated, it is necessary the repetition of the biopsy every 1-2 years of diet when the rejuvenation of the intestinal mucosa must be total. Only then, the diagnosis is sure.

Observing a life-long, no-gluten diet ensures a rapid, favorable clinical evolution (with a significant increase in weight in children, resuming the normal rhythm of the growth in height, the relegation of the other symptoms and signs). The long-term benefit consists in avoiding intestinal complications, infertility, neuropsychic deficiency, and appearance of autoimmune diseases and decrease of the risk of malign tumors (intestinal lymphoma, intestinal adenocarcinoma, esophageal and intestinal cancer).

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