SOCHAL, Piotr, IWASZKO-SOCHAL, Klaudyna & SZCZEPANIAK-WÓJTOWICZ, Elżbieta. Celiac disease in children - diagnosis in light of the current 2020 ESPGHAN guidelines. Journal of Education, Health and Sport. 2023;34(1):75-83. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.34.01.006
https://apcz.umk.pl/JEHS/article/view/43723
https://zenodo.org/record/7980041

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 27.04.2023. Revised: 10.05.2023. Accepted: 29.05.2023. Published: 29.05.2023.

Celiac disease in children - diagnosis in light of the current 2020 ESPGHAN guidelines

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Abstract: Celiac disease is a chronic immune disorder of the small intestine that is triggered by the consumption of gluten in genetically predisposed individuals. The disease is difficult to diagnose and treat, and its incidence is increasing. It can have different symptoms and clinical manifestations in individuals. Diagnosis is usually based on the presence of specific antibodies and histopathological examination of biopsy specimens from the small intestine. The only effective treatment is a gluten-free diet for life. Diagnosis of celiac disease in children is mainly based on the presence of specific antibodies in the blood, such as antibodies to tissue transglutaminase (tTG), antibodies to endomysium (EMA) or deamidated gliadin peptides (DGP). In addition, genetic testing is also used in diagnosis to detect the presence of HLA DQ2 or DQ8 genes, which are often present in people with celiac disease. The final diagnosis of celiac disease is based on a combination of the results of these tests and the presence of characteristic lesions in the small intestine, which are detected during endoscopy and small bowel biopsy.

Keywords: celiac, Coeliac, ESPHGAN, coeliac disease

Abbreviations: DGP - antibodies against deaminated gliadin peptides, EMA - anti-endomysial antibodies, ESGPHAN - European Society for Paediatric Gastroenterology, Hepatology and Nutrition, URL - upper range limit, HLA - tissue compatibility antigen, IgA - immunoglobulin class A, IgG - immunoglobulin class G, TGA - tissue transglutaminase antibodies

BACKGROUND: Celiac disease is defined as "a chronic small intestinal enteropathy of immune-mediated origin preceded by dietary gluten exposure in genetically predisposed individuals" [5]. Celiac disease remains a difficult condition to treat and diagnose with despite a steady increase in knowledge of its pathophysiology, diagnosis, management and possible therapeutic options. It can occur at any age, with a variety of symptoms. The incidence is about 1% with a predominance among women [1].

The reported increase in incidence in recent decades is due to two reasons: improved recognition and an actual increase in incidence [2].

Celiac disease has historically been associated with the pediatric population, but is now increasingly being diagnosed in adults. It is caused by a genetically determined immune response to antigens, in this case, derivatives of gluten, which is broken down in the lumen of the duodenum into peptides characterized by high levels of proline and glutamine [3].

In intestinal epithelial cells, glutamine is deaminated to glutamic acid by the enzyme TGA. The products of this reaction - deaminated gliadin peptides (DGPs) show affinity for HLA DQ2 and DQ8 tissue compatibility antigens located on the surface of dendritic cells, with the help of which antigen presentation to CD4 lymphocytes occurs, thus initiating the entire inflammatory cascade [4].

Antibodies to these antigens - TGA and DPG, as well as the determination of tissue compatibility antigens have been used in the diagnosis of the disease.

The clinical manifestation of the disease varies widely. In the past, due to insufficient knowledge and diagnostic capabilities, the classical form of the disease was mainly diagnosed in children. This form, compared to others, is characterized by a significant increase in symptoms, including slowed growth rate, increased fatty diarrhea, numerous gastrointestinal complaints and enlarged abdominal girth. As the diagnosis ages, the symptoms change, moving toward a form

with constipation, features of irritable bowel syndrome, psychiatric disorders, or the less tangible consequences of nutritional deficiencies. In recent decades, there has been a shift in the clinical course toward subclinical and atypical forms with a predominance of symptoms outside the gastrointestinal tract, mainly due to greater awareness and knowledge of the disease (previously, these forms often went unrecognized).

The long-term consequences of mucosal damage and inflammation include impaired absorption of nutrients such as calcium, vitamin D, iron, vitamin B12, folic acid and zinc, leading to consequences such as osteoporosis, anemia and stunted growth, so it is important to keep in mind that any consequences of deficiencies can have their origins in coeliac disease [7,8,9,10]. The multifaceted clinical presentation of the disease leads to the distinction of several phenotypes: classical, nonclassical, potential, latent (subclinical) and refractory forms [5]. In atypical cases, diagnosis is delayed by an average of 11 years [6].

Despite ongoing research into potential cures, a restrictive gluten-free diet remains the only certain therapeutic option. Continuing to consume gluten can exacerbate clinical symptoms, further advance intestinal damage and increase the risk of future cancers, including small intestinal adenocarcinoma, esophageal cancer, melanoma and Hodgkin's lymphoma [11].

Prompt diagnosis of the disease is so important because a strict gluten-free diet can restore the normal histological architecture of the small intestine in 95% of children within two years [12], while in adult patients only 66% of cases see complete mucosal recovery after five years of diet. With the passage of time, this percentage decreases further, and no significant histologic improvement is usually achieved in patients over the age of 60 [13].

Pediatric patients following a gluten-free diet for two years show, on average, a greater increase in height and weight compared to controls, with some patients showing significant growth catch-up (an increase in percentile position on the growth curve) [14]. There is evidence of numerous benefits achieved with the diet, including improved bone mineral density [15].

Maintaining a strict gluten-free lifestyle comes with many challenges, including nutritional deficiencies, high costs associated with adhering to the diet, and social and psychological barriers.

One study proved that 32% of foods served by "gluten-free" restaurants contained gluten [16], while another study found that prices of foods labeled "gluten-free" were 242% higher [17].

The threshold for sensitivity to the amount of gluten present in food varies among individuals, but there is no objective standardized method to detect it. Therefore, a safe cutoff value for gluten contamination in food for most people has been estimated at 100 ppm (1/4 mg/kg) in gluten-free foods [18].

Due to the many difficulties in maintaining the diet, it is recommended that its effectiveness be periodically checked by determining antibody levels.

Diagnosis of celiac disease in the pediatric population in light of current guidelines

In 2020, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published updated guidelines for the diagnosis of visceral disease in the pediatric population [19].

Screening: the first step in diagnosis can be a screening test, which is carried out in two cases:
- Clinical suspicion of celiac disease (presence of specific symptoms - Table 2)
- Presence in the risk group (Table 1). Numerous studies have proven the effectiveness of screening diagnostics in at-risk groups [21,22]. It is particularly important not to stop at a single determination, but to perform it every 2-3 years [20].

Table 1 . Specific conditions that are a risk group for the development of celiac disease
First-degree relatives with celiac disease
Presence of autoimmune diseases in history
Down syndrome
Turner syndrome
Williams-Beuren syndrome
IgA deficiency

The screening test involves the simultaneous determination of two laboratory parameters:

1) Total IgA antibody level (by itself has no diagnostic significance, it is only performed to verify if the test has diagnostic value)

2) The level of antibodies to tissue transglutaminase (TGA) in the IgA class.

Further proceedings depend on the outcome of these determinations. The following scenarios are possible:

1) IgA antibody levels normal, TGA antibodies absent - celiac disease can be excluded with high probability (≥99%). In most cases, it is possible to discontinue diagnosis at this stage.

Table 2 Symptoms suggestive of clinical suspicion of celiac disease

Intestinal	**Parenteral**
recurrent, chronic diarrhea, constipation, abdominal pain enlarged abdominal circumference, feeling of abdominal distension recurrent nausea, vomiting	Weight loss Slowe growth rate Features of delayed sexual maturation, secondary absence of menstruation Chronic fatigue, Irritability Neuropathy Joint pain and features of arthritis Chronic iron deficiency anemia Bone mineralization disorders, osteoporosis Recurrent oral aphthas Dermatitis herpetiformis Tooth enamel defects Abnormal results of liver laboratory tests

2) IgA antibody level normal, TGA antibodies present>10 x URL - diagnose celiac disease regardless of the presence of symptoms, possible waiver of histopathological examination ("no-biopsy approach"), but it is advisable to perform an additional test to confirm the presence of anti-endomysial IgA EMA antibodies in a subsequent blood sample

3) IgA antibody levels normal, TGA antibodies present but <10x URL - clinical suspicion of celiac disease, but histopathological examination is indicated for confirmation.

4) IgA antibody level reduced - regardless of the level of TGA antibodies, the test is considered non-diagnostic. In this case, it is necessary to perform a test based on the presence

of antibodies in the IgG class - TGA, EMA or DGP. The performance of this test is particularly important because IgA deficiency is itself a risk factor for the development of celiac disease.

As can be seen from the above, it is possible to complete the diagnosis on the basis of screening.

Histological examination: is the next step in the diagnostic pathway, the inclusion of which is determined by the screening result described above. Specimen collection occurs during esophagogastroduodenoscopy. Patients should have a minimum of four sections taken from the distal part of the duodenum and at least one from duodenal bulb. The result is typically scored on the Marsh scale, in which scores of 0-1 are considered negative and scores above 2 are considered positive.

If a biopsy is performed, a positive result authorizes the diagnosis of the disease.

Other management is indicated in doubtful cases, which include significant discrepancies between the antibody value and the negative histopathological result, or the histopathological result itself of inconclusive value. In such cases, re-sampling of specimens for examination and referral to another, more experienced center should be considered, as well as consideration of additional tests.

In the case of significantly positive antibodies and undoubtedly negative histopathological examination, after excluding false-negative results, a potential form of celiac disease can be diagnosed. In its case, further monitoring is recommended.

Determination of the presence of HLA DQ2/DQ8 antigens: This test is not necessary for diagnosis, but can be useful in some cases. Namely, the absence of the presence of the above antigens allows you to exclude the disease with high probability, so this test is helpful in doubtful cases, among other suspected false-negative serological tests.

Summary: Celiac disease is one of the most common autoimmune diseases in the pediatric population. In its case, it is important to make the diagnosis as early as possible, because as time passes, the chance of resolving the negative effects of the disease despite the inclusion of a restrictive gluten-free diet decreases. Therefore, there is a need for standardized algorithms of management to avoid diagnostic mistakes and the associated negative consequences and unnecessary costs.

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