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Review of celiac disease in the pediatric population

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ABSTRACT

Celiac disease (CD) is a chronic autoimmune disease triggered by the ingestion of gluten in genetically predisposed individuals, primarily those with HLA-DQ2 and HLA-DQ8 haplotypes. The global prevalence of CD ranges from 0.5% to 1%. Recent advances in diagnostic methods and raising awareness of this disorder have improved detection rates, but many cases remain undiagnosed due to the disease's multifaceted presentation. CD can manifest with a wide range of symptoms, including both gastrointestinal and extraintestinal signs. In smaller children common symptoms include mainly chronic or intermittent abdominal pain, abdominal distension, diarrhea and constipation. Older children and adolescent patients may frequently present atypical, vague symptoms such as fatigue, failure to thrive, weight loss, short stature, behavioral changes and anemia. Diagnosis involves primarily serological tests in patients presenting symptoms or in patients with high-risk of developing CD. A strict gluten-free diet is the principal treatment and it is highly effective in managing symptoms and promoting intestinal healing. In this paper, we will analyze epidemiology of CD, its pathogenesis, heterogeneous clinical presentation, the diagnostic process and treatment based on recent guidelines and literature.

Introduction

Celiac disease (CD) is a chronic, autoimmune-based enteropathy triggered by consumption of gluten in genetically susceptible individuals. The main genetic component associated with CD is the presence of human leukocyte antigen (HLA), especially HLA-DQ2 and HLA-DQ8 haplotypes [1,2]. Gluten is an aggregate of proteins known as prolamins and glutelins found in wheat, rye, barley and oat products [3]. Exposure to gluten leads to abnormal immune response in the small intestine, which induces inflammation, damage of the intestinal lining, villous atrophy and therefore impaired nutrient absorption [2].

Epidemiology

The prevalence of CD varies from 0.5% to 1% in the general population, however it depends on geographical region and ethnicity. Although CD was initially believed to affect primarily individuals with European descent, more recent studies have shown that the data from other regions and populations might have been incomplete due to under-reporting and under-diagnosing [1]. Meta-analysis from the cited paper indicates that global seroprevalence of CD is estimated to be 1.4%, whilst the global prevalence of biopsy-confirmed CD is 0.7%, with the highest prevalence in Europe (0.8%) and Oceania (0.8%), and the least prevalence in South America (0.4%) [9]. The prevalence of CD is also significant in regions like North Africa, the Middle East and India with a very high prevalence of 5,6% in the Saharawi population [6].Variations in prevalence of CD in different geographical regions indicate that the disorder cannot be solely attributed to genetic factors of HLA-DQ2 and HLA-DQ8 haplotypes. Additional environmental and genetic components are suggested to be an important factor of the onset of CD [4]. The disease is 1.5 times more prevalent in women than compered in men, and about twice as common in children compared to adults based on biopsy-confirmed diagnoses. Numerous factors could account for these differences, including variations in genetic factors (both HLA and non-HLA genes), environmental influences, the age at which gluten is first introduced, overall gluten consumption, gastrointestinal infections, the use of proton pump inhibitors and antibiotics, and the rate of cesarean sections [5]. The prevalence of CD has increased over the last 30 years and it is expected to rise due to the global adaptation to Western dietary patterns, alterations in the intestinal microbiome and rise in other autoimmune diseases [5,6,8]. The other significant reason for the rising incidence of CD is caused by the increased knowledge and awareness of physicians about this disorder, as well as more common use of specific diagnostic tests for CD. However, up to 95% celiac patients still remain undiagnosed due to the heterogeneous presentation of clinical signs and symptoms, which indicates the need for improved detection and awareness about the variety of symptoms. This enteropathy can manifest at any age, but the most common onset occurs in early childhood, after first gluten intake. The second peak is observed in the second or third decade of life [5,7]. CD tends to manifest more in children aged 0 - 4 years and there is observed a decrease in incidence with age. The study in the cited paper showed that 53.2% celiac patients presented before the age of 4 years followed by a decline in the number reaching only 3.2% celiac patients between the age of 15 and 18 years. Although CD is typically viewed as a condition that affects infants, diagnoses during later childhood are increasingly more frequent. This trend is due to a shift in clinical presentations, with the disease now more often manifesting in milder forms rather than the classic malabsorption syndrome [12]. There are particular high-risk groups of patients in which the probability of developing CD is higher than in the general population and which require regular screening. Those groups include first-degree relatives of CD patients, individuals with type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune liver diseases, selective IgA deficiency, IgA nephropathy, Down's syndrome, Turner syndrome and Williams syndrome [10].

Pathogenesis

The crucial element of CD is the presence of HLA-DQ2 and HLA-DQ8 haplotype in individuals' genotype and exposition to gluten proteins. In the population of celiac patients more than 99% are reported to have HLA-DQ2 or HLA-DQ8 on contrary to the general population where the prevalence of above-mentioned haplotypes is noted to be 40% [5]. Abnormal auto-immune reaction to gluten results in production of particular disease-specific auto-antibodies targeting transglutaminase 2 (TG2 - anti-tissue transglutaminase antibody) - an enzyme that is responsible for modifying gluten peptides. Other antibodies that play an important role in immune reaction include: AGA - anti-gliadin antibody, EMA - anti-endomysial antibody and DGP - deamidated gliadin antibody. In CD the interaction between gluten peptides, transglutaminase 2, and the antibodies leads to the complex interplay between genetic predisposition, environmental factors (such as unbalanced gut microbiome and malfunction of intestinal barrier function), and immune dysregulation which results in inflammation and damage to the intestinal lining and therefore villous atrophy and malabsorption [5,11]. Other factors, such as breastfeeding, gluten consumption patterns, antibiotic use, cow's milk protein intolerance in infancy have been considered as significant contributors to the pathogenesis of CD. Previously, it was recommended to either avoid early or late introduction of gluten in children at risk of celiac disease. The length of breastfeeding and the timing of gluten introduction to an infant appear to have no effect on the likelihood of developing CD, even in high-risk infants. Consequently, there are no specific recommendations for the timing of gluten introduction into an infant's diet [15,16].

Clinical manifestations

CD usually occurs in children after first exposure to the food products containing gluten - that is between 4 and 24 months [5]. However, over the past few decades it has been observed a shift in a delay of the median age of CD presentation and diagnosis. In the past, children were diagnosed with CD at the approximate age of 4 years old, however during the recent years it has been observed a trend in diagnosing children later, at the age of 8 years old. This is due to the evolving pattern of clinical presentation of this disease, with more and more cases presenting with atypical and vague symptoms [14]. Clinical representation varies depending on an age group of the patients, with younger children more likely to experience gastrointestinal symptoms, and the older presenting extraintestinal signs. The most common gastrointestinal (GI) symptoms are chronic or intermittent abdominal pain, abdominal distension, bloating, recurrent diarrhea, constipation, dyspepsia, nausea and vomiting, which can all vary in severity. Common extraintestinal signs are fatigue, pallor, failure to thrive, weight loss, short stature, behavioral changes, irritability, mood disturbances, chronic anemia, osteopenia, osteoporosis, delayed puberty, dental enamel defect, arthritis, amenorrhea, headache, neuropathy, increased liver enzymes and dermatitis herpetiformis [13]. CD in children is increasingly recognized as a systemic condition due to its wide range of extraintestinal manifestations. Various studies highlight the diversity in symptom presentation such as a retrospective study from Bahrain which identified the most common symptoms in children with CD as pallor, failure to thrive, abdominal distention, short stature, and chronic abdominal pain.

A prospective study from India found diarrhea, failure to thrive, and abdominal distention to be the primary symptoms, with abdominal pain, vomiting, and constipation being less frequent. In Saudi Arabia, research showed that chronic abdominal pain was the most common symptom, followed by poor weight gain. Furthermore, recurrent mild abdominal pain is noted as a common complaint among patients diagnosed through screening procedures. These studies emphasize the importance for healthcare providers to recognize the varied presentations of CD. Awareness of both gastrointestinal and extraintestinal symptoms is crucial for early and accurate diagnosis, ensuring comprehensive care for affected children [12].

Clinical types of celiac disease

Typical form of celiac disease

It is a form of CD that presents with the prevalence of gastrointestinal symptoms. Individuals are tested positively for celiac antibodies, HLA-DQ2/-DQ8 haplotypes and intestinal biopsy image corresponds with the image of villous atrophy.

Atypical celiac disease

It is a form of CD that presents mainly with the extra-intestinal symptoms. Individuals are tested positively for celiac antibodies, HLA-DQ2/-DQ8 haplotypes and intestinal biopsy image corresponds with the image of villous atrophy.

Seronegative celiac disease

It is a less common form of CD, estimated to occur in 5-10% of all celiac patients cases. It is characterized by the presence of symptoms attributed to CD, signs of impaired absorption and the image of intestinal villous atrophy with concurrent lack of celiac antibodies in blood tests. Seronegative CD (SNCD) can be confirmed by noticing an improvement in both symptoms and intestinal histological image after 1 year of starting a gluten-free diet [5]. In a study focused on Brazilian patients with SNCD, all cases studied showed clinical symptoms characteristic for CD, diagnostically confirmed by histological findings of the duodenal mucosa and HLA-DQ2 and/or HLA-DQ8 positivity. Dual-X densitometry revealed bone mineral density abnormalities in SNCD patients, with two women having osteopenia and two men having osteoporosis, all cases with low vitamin D levels. That indicates the need for monitoring and managing bone health in CD individuals. Family history of CD was reported in 40% of the SNCD cases studied, suggesting a potential predisposition to the condition and highlighting the necessity of considering genetic factors in the diagnostic process. A significant delay in the diagnosis of SNCD was observed, ranging from 1 to 19 years. Relatively efficient recognition and diagnostic process is vital for the proper management of CD to prevent long-term complications. The limited data on SNCD highlight the need for further research in this area to better understand its pathogenesis and clinical presentation [17].

Silent celiac disease

It is a form of CD where individuals do not present noticeable signs and symptoms of the disease, however they are positive for celiac antibodies and HLA-DQ2/-DQ8 haplotypes. Despite the lack of symptoms, silent CD can still cause inflammatory reactions in small intestine mucosa leading to villous atrophy and malabsorption. Some of the studies showed that silent form of CD can be more common, which suggests that a major part of individuals may suffer from CD while not being aware of it. That indicates an important role of screening tests in the population in order to diagnose individuals without obvious symptoms and signs [18].

Potential celiac disease

It is a form of CD characterized by the presence of positive CD serology tests and HLA-DQ2 and/or HLA-DQ8 haplotypes, however the image of small intestinal mucosa architecture is normal and not compatible with typical CD histopathological picture [19]. In Marsh classification score the image of mucosa in intestinal biopsy corresponds to score 0 or 1 [5]. In potential celiac disease (PCD) levels of celiac antibodies, especially antibodies targeting transglutaminase 2 TGA2, are usually lower than in typical CD and may vary over time or even disappear. There is reported a lower prevalence of HLA-DQ2 and a higher prevalence of HLA-DQ8 in patients with PCD, compared to the typical CD population [5]. Individuals with PCD may or may not exhibit typical symptoms of CD, thus, this type of CD poses a significant challenge in diagnosis. There is a reported higher risk of PCD evolution into a symptomatic form of CD, strictly influenced by the risk factors [19].

Refractory celiac disease

It is a condition with persistent villous atrophy despite a strict gluten-free diet. In all cases, dietary adherence should be thoroughly examined. Studies have reported adjunctive therapy in management of refractory celiac disease (RCD) which consists of steroids, mesalamine and biological therapies targeting particular molecules involved in the immune response and inflammation. The effectiveness of adjunctive therapies in RCD is an area of ongoing research, highlighting the need for further studies to evaluate their efficacy and safety [20]. RCD has been reported to cause further complications such as collagenous sprue, intestinal lymphoma and ulcerative jejunoileitis [5]. According to ESPGHAN guidelines from 2022 it is suggested to thoroughly explore alternative explanations for what seems like "refractory CD" in children. This includes assessing for accidental gluten consumption and investigating other potential concurrent conditions, such as Crohn’s disease, autoimmune enteropathy, small-bowel bacterial overgrowth, cow’s milk protein allergy, and pancreatic insufficiency [26].

Diagnosis

CD may pose a challenge to diagnose due to its heterogeneous presentation: broad range of gastrointestinal and extraintestinal symptoms that can occur at any age, clinical spectrum that includes both symptomatic and silent cases. It is advised to perform serologic tests in case of occurrence of unexplained chronic or intermittent diarrhea, chronic abdominal pain, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, recurrent nausea, recurrent vomiting, abdominal distension, chronic constipation not responding to usual treatment, neuropathy, irritability, arthritis, osteopenia, osteoporosis, dental enamel defects, iron deficiency anemia, recurrent aphthous stomatitis and abnormal liver enzyme elevations. Moreover, CD should be investigated in groups of patients with high risk of developing CD: first-degree relatives of CD patients, individuals with type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune liver diseases, selective IgA deficiency, IgA nephropathy, Down's syndrome, Turner syndrome and Williams syndrome, even if they are asymptomatic. CD diagnosis in children involves a combination of symptom assessment, clinical examination, serological tests, genetic markers (HLA-DQ2 and/or HLA-DQ8), and histopathology of the duodenal mucosa. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines from 2020 provide a structured approach for diagnosing CD:

1. Initial Screening:
    - TGA-IgA: The first-line screening test for suspected CD in children.
    - Total IgA: To rule out selective IgA deficiency, which can affect test accuracy.

If IgA levels are normal for age, TGA-IgA test is used regardless of age. All serological tests should be performed while the patient is on a gluten-containing diet. If a patient has been following a gluten-free diet for a long time or has recently started one before testing, there is a risk of false negative results. To ensure accurate results, patients should consume gluten-containing foods prior to testing. If the patient has been on a gluten-free diet before the serological tests, a gluten challenge is recommended, involving a daily intake of 3-7.5 grams of gluten (about two slices of bread) for 2 weeks [5].

2. Case of IgA Deficiency:
    - If total IgA is low, an IgG-based test (such as DGP, EMA, or TGA) is recommended.

3. Biopsy:
    - If TGA-IgA is positive but below 10 times the upper limit of normal (ULN), a biopsy is required.
    - Obtain at least four biopsies from the distal duodenum and at least one from the duodenal bulb while the patient is on a gluten-containing diet.

In CD, the key histological indicators that confirm the diagnosis are intraepithelial lymphocytosis and mucosal architectural alterations such as villous atrophy and crypt hyperplasia [21]. Biopsies are analyzed using the modified Marsh classification system, which helps diagnose CD by evaluating the extent of intestinal damage.

The system includes several stages, each representing different levels of damage:

- Marsh I: Indicates an increase in intraepithelial lymphocytes in the small intestine lining, marking an early phase of CD where immune response starts affecting the intestine.
- Marsh II: Shows not only an elevated number of lymphocytes but also damage to the intestinal lining surface, known as crypt hyperplasia, reflecting more significant immune-mediated changes.
- Marsh III: This stage is divided into three subcategories - a, b, and c - each representing varying degrees of villous atrophy, from partial to complete, signifying severe damage to the intestinal lining [22].

4. No-Biopsy Approach:
    - For children with TGA-IgA ≥10 times ULN, a biopsy can be omitted if an EMA-IgA test from a second blood sample is positive.
    - This approach should be discussed with the family and the patient. It is reported that it can reduce the need for endoscopy by 30-50% [5].
    - The no-biopsy approach is valid regardless of the presence of symptoms.

5. HLA Testing:
    - Not required in patients with positive TGA-IgA.
    - Negative HLA-DQ2 and/or HLA-DQ8 virtually exclude CD, but a positive result does not confirm CD on its own.

In summary, ESPGHAN guidelines from 2020 emphasize the use of serological testing of combination of TGA-IgA and total IgA as a primary diagnostic tool, with biopsies reserved for cases where serology is not definitive (level of TGA-IgA <10 ULN). The no-biopsy approach is a viable option for patients with high levels of TGA-IgA (>10 ULN) and positive EMA test, simplifying the diagnostic process and reducing the need for invasive procedures. HLA-DQ2/8 analysis is not advised, even if the patient shows no symptoms. CD is diagnosed when serological tests for CD are positive and the biopsy results are consistent with the disease. The 2020 guidelines from ESPGHAN clarify that neither HLA-DQ2/8 analysis nor the presence of clinical symptoms are mandatory for diagnosing CD [5,23].

Treatment

A lifelong gluten-free diet (GFD) is the recommended treatment for individuals with CD. This diet requires the complete elimination of gluten-containing foods, including those with gluten proteins from wheat, barley, rye, oats and similar grains. To support consumers following a gluten-free diet, the Food and Drug Administration (FDA) implemented a gluten-free labeling regulation. This rule defines the legal standards for labeling products as "gluten-free," "free of gluten," "without gluten," or "no gluten." Under this regulation, a product can be labeled gluten-free if it contains less than 20 parts per million (ppm) of gluten, considering possible contamination during manufacturing. Extensive studies have confirmed that a strict gluten-free diet (GFD) is highly effective. It can restore the small bowel structure in 95% of children within two years. This improvement in the bowel architecture also alleviates symptoms associated with malabsorption, such as diarrhea, steatorrhea, and weight loss.

Research has also shown significant gains in bone mineral density after one year on the diet, though complete reversal of osteopenia was not achieved. According to Soliman et al., children on a GFD for two years exhibit growth in height and weight that is comparable to age-matched peers, with some experiencing substantial catch-up growth. Kurppa et al. found that the GFD leads to similar improvements in mucosal architecture, reduction of intestinal inflammation, antibody levels, and symptom relief, whether the patient has mild enteropathy or severe villous atrophy. Additionally, a study on patients with borderline enteropathy, who do not meet the full criteria for CD, showed that a GFD significantly restored mucosal structure and improved clinical symptoms within 8 - 12 months, in contrast to controls [24].

Compliance with a gluten-free diet (GFD) among children with CD shows considerable variation, with only 58.7% adhering strictly to the diet and 3.5% not following it at all. This highlights the challenges in maintaining diet adherence. The differences between those who follow the diet and those who do not stress the importance of close monitoring and follow-up to prevent complications and improve long-term outcomes. Although the GFD effectively alleviates clinical symptoms, non-compliance can negatively affect the long-term health and prognosis of children with CD as they reach adulthood [25].

Follow-up guidelines

According to the ESPGHAN guidelines from 2022, the first follow-up visit should be scheduled 3 to 6 months after the initial diagnosis. Subsequent visits should occur every 6 months until tissue transglutaminase antibody (TGA) levels return to normal, after which visits can be spaced every 12 to 24 months.

During follow-up, evaluations should include:

- Gastrointestinal and extraintestinal symptoms.
- Growth parameters and measurements.
- IgA-TGA levels. For patients with IgA deficiency, use IgG-based tests. IgA sufficient patients should avoid IgG-based and RIA-based IgA-TGA tests.
- A complete blood count and assessments of micronutrient levels (such as hemoglobin, iron, vitamin B12, and vitamin D), along with ALT levels. Address any abnormalities and ensure they are corrected; persistent issues require further investigation.
- Thyroid disease screening may be considered based on clinical evaluation, including TSH, thyroxine, and possibly autoantibodies.
- Routine bone density screening is not advised.
- For immunized patients, HBV antibody levels may be checked, and boosters given if needed.

Since no single standard method exists, adherence to the GFD should be assessed through a combination of symptom reviews, dietary interviews, questionnaires and lab tests [26]. Recent studies have indicated that gluten intake can be detected using immunogenic peptide tests in stool and urine. For these tests to be sensitive, it appears that a daily gluten intake of over 50 mg is required for stool tests and more than 25 mg for urine tests. However, the routine application of these tests remains uncertain, and further research is needed to confirm their effectiveness and utility in everyday practice [5].

For prepubertal or pubertal children, if significant catch-up growth in height is not seen within a year of starting the GFD despite strict adherence, additional assessments and consultation with a pediatric endocrinologist are recommended to explore other causes of short stature. A lactose-reduced diet should only be tried for patients with symptoms suggesting lactose intolerance despite following the GFD. Children with anemia due to iron, folate, or vitamin B12 deficiencies should receive supplements in addition to the GFD to ensure prompt improvement, as delays could affect development and growth. Routine small-bowel biopsies are not recommended for monitoring mucosal healing; they should only be considered if there are specific clinical concerns, such as doubts about the diagnosis or potential additional conditions. For suspected "refractory CD," investigate other causes such as inadvertent gluten ingestion or other enteropathies thoroughly. HLA typing may be used before a gluten challenge if the diagnosis is uncertain. Duodenal biopsies may be considered for new symptoms, increased CD antibody levels, or persistent serological positivity on a case-by-case basis. Finally, a structured transition to adult care is recommended for adolescents, including a transition history of the patient detailing diagnosis, follow-up, growth data, comorbidities, and dietary adherence [26].

Complications

Possible, but rather rare complications of CD include collagenous sprue, ulcerative jejunoileitis, RCD, enteropathy-associated T-cell lymphoma, small bowel adenocarcinoma, hyposplenism, and cavitating mesenteric lymph node syndrome [27]. Complications typically arise in patients who are diagnosed late or who do not strictly adhere to a gluten-free diet [5].

Conclusion

CD is a complex autoimmune disorder with significant genetic and environmental components. The disease is driven primarily by genetic predisposition to HLA-DQ2 and HLA-DQ8 haplotypes and is triggered by gluten ingestion. Clinical manifestations are diverse, ranging from typical gastrointestinal symptoms to a variety of extraintestinal signs. Screening diagnosis involves a serological testing for TGA-IgA and total IgA levels in individuals with unexplained chronic or intermittent diarrhea, chronic abdominal pain, failure to thrive, weight loss, delayed puberty, short stature, amenorrhea, recurrent nausea, recurrent vomiting, abdominal distension, chronic constipation not responding to usual treatment, neuropathy, irritability, arthritis, osteopenia, osteoporosis, dental enamel defects, iron deficiency anemia, recurrent aphthous stomatitis and abnormal liver enzyme elevations. CD should be also thoroughly investigated in groups of patients with high risk of developing CD. Advances in diagnostic criteria and awareness have improved detection rates, although many cases remain undiagnosed. The crucial part of the treatment is a lifelong, strict gluten-free diet, which is highly effective in alleviating symptoms and promoting intestinal healing. However, adherence to this diet can be challenging and demanding diligent follow-up. Overall, managing CD requires a comprehensive approach, including accurate diagnosis, effective treatment, and persistent monitoring. Ongoing research is crucial for elucidating the precise interactions between genetic and environmental factors in CD.

Advances in identifying predictive biomarkers and developing targeted interventions will be key in formulating effective primary prevention strategies. Continued research and education are crucial for improving patient outcomes and understanding the full spectrum of this multifaceted disorder.

Disclosure

Author's Contribution

Conceptualization: AS
Methodology: MG
Software: MŁ
Check: MW
Formel Analysis: MG and MŁ
Investigation: AS and MW
Resources: MW and MŁ
Data Curation: AS and MG
Writing-Rough preparation: AS
Writing-Review and Editing: MW
Visualization: MG
Supervision: MW and MŁ
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