**[Risk stratification in pediatric celiac disease](https://ajbm.net/6862-2/)**

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**Abstract**

A 6-year-old white girl with a longstanding history of severe constipation who was referred for suspected Irritable Bowel Syndrome. Instead, serologies showed all three of these tests to be markedly positive for tissue transglutaminase. IgA endomysial antibody was also positive, though testing of total immunoglobulin A and HLA did not show increased risk on repeat levels. After several routine consultations, a duodenal biopsy was performed and her Marsh score was 2 (intraepithelial lymphocytosis only). Given the discordance between her symptoms and her biopsy as well as persistently high titers of antibodies since beginning a gluten-free diet, a repeat biopsy was performed over 4 years later. Patient re-attended clinic at ten years of age. On repeat endoscopy, she had changes consistent with increased intraepithelial lymphocytosis and maleylation (Villa score of 1b), a score lower than at her initial duodenal biopsy: Marsh 1 (inflammation) instead of Marsh 0 (normal). While it is atypical to have duodenal lymphocytosis alone represent symptomatic celiac, in this case the evidence warranted a diagnosis of celiac disease (with hyperplastic lymphocytosis representing early endoscopic changes). Her anti-tTG was always significantly elevated as well as the EMA. It should be noted that initial biopsies are not available for CD3+ staining to look for lymphocytosis alone at her original presentation. However, this article discusses her presentation and diagnosis in the context of the risk stratification theme of this Special Issue. Bloating or swelling (Q1 for Gastrointestinal-Irritable Bowel Syndrome), Seek medical care for abdominal swelling (Q2 for Gastrointestinal-Irritable Bowel Syndrome), Abdominal tenderness (Q3 for Gastrointestinal-Irritable Bowel Syndrome), Take medication for abdominal pain (Q5 for Gastrointestinal-Irritable Bowel Syndrome) were all rated in the negative, consistent with the diagnosis of celiac disease on the CHOP Modified-Fickie.

**Keywords**: Celiac disease; Gluten; Immune system

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Received July 30, 2018; Accepted December 23, 2018; Published January 19, 2019

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**Introduction**

Celiac disease (CD) is a very complex autoimmune disease characterized by a permanent intolerance to gluten. According to the data, CD is the most common chronic disease due to nutrition in children in Europe. The classic and atypical forms can occur, and the prevalence of these forms changes with age. Clinical presentations depend on age and may include classic symptoms, malabsorption, and extra-intestinal symptoms such as anemia, abnormal biochemistry, liver disease, dermatitis herpetiformis, motor abnormalities, neurological problems, and type-I diabetes. Approximately 30% of individuals with celiac disease have asymptomatic celiac disease that can come to medical attention during screening due to the presence of increased risk factors. The identification and stratification of these risk factors allow better clinical management of pediatric patients.

Overscreening of healthy individuals increases the cost of healthcare systems. Risk stratification or selected case-finding is a method to allocate healthcare resources to high-risk individuals for appropriate screening and treatment. Risk predictors include family history in first-degree relatives with celiac disease or other autoimmune diseases or evidence of other autoimmune diseases. The prevalence of celiac disease in first and second-degree relatives has been reported to be 5-10 times the prevalence in the general population at 1-2%. In a screening study of children with either type I diabetes and/or Down syndrome, the current recommendation of using celiac serology alone in children at "high risk" resulted in triple the workload and missed a small number of children with biopsy-proven celiac disease using genetics. There is thus a requirement to devise comprehensive risk stratification.

In pediatrics, celiac disease (CeD) is one of the most common genetically predisposed immune-mediated disorders. A strong interplay among genetic, environmental, and immune factors contributes to the phenotypic heterogeneity of CeD. The clinical presentation of CeD is characterized by intestinal and extra-intestinal symptoms, which vary according to the patient's age. Several clinical presentations can be found from the first year of life (classical form of the disease), in which children present with diarrhea and growth retardation, to adolescence and adulthood, in which patients present with mono- or oligosymptomatic extra-intestinal complaints. The diagnosis of CeD is a "label" available for the entire spectrum of signs/symptoms or conditions that require an intestinal biopsy showing villous flattening and crypt hyperplasia at histology—features classically known as Marsh 3 staging.

The four elements needed to define disease prediction accuracy are sensitivity and specificity (indicating the proportion of true negatives that are correctly identified and true positives that are correctly identified) and the positive and negative prediction values (indicating the probability of having or not having the disease when the screening test is positive or negative). Indeed, recent studies show that a portion of the patients will have a serology profile not identifiable as serologically positive at diagnosis and/or that a substantial fraction of pediatric CeD is not truly symptomatic and that subclinical forms may occur. Concerns about the diagnostic delay also come from the observation that some children present with severe clinical manifestations, while others present significant growth retardation only when the disease is detected, and some are as tall and normal as other children of the same age.

**Celiac Disease in Pediatrics**

Celiac disease (CD) is a chronic, multi-systemic disease that can have consequences within the pediatric age, but can also affect adults. The classic form of CD characterizing symptoms can be observed at any age, either in children or adults, while the atypical form, which is usually asymptomatic or oligosymptomatic, is the most common in both groups. Symptoms can be triggered in some at-risk asymptomatic individuals by gluten intake despite following a gluten-free diet for at least 6 months. In this specific situation, follow-up is especially important to prevent or minimize the risk of atypical or silent symptoms. Early identification makes it possible to start a standardized, high-level gluten-free diet, which is also fundamental to guarantee compliance with regulations. In pediatric CD, signs may occur in early childhood, even during breastfeeding, or later, preschool or school age. This form is more common in girls (2:1), while the classic form does not have a gender distinction. An early diagnosis is therefore fundamental, as chronic diarrhea can lead to a serious clinical disease characterized by malabsorption, growth retardation, secondary immunodepression and anemia, especially iron-deficiency anemia.

The high prevalence of celiac disease, estimated at about 3% of the general pediatric population, and the subsequent increase in "non-celiac gluten sensitivity" entities (NCGS), have encouraged research that focused on aspects relating to the gluten-free diet and those descriptive of the possible outcome of the disease. NCGS and CD share other common points, such as the susceptibility to the presence of gluten and the demonstrated presence of early inflammatory damage. The guidelines published by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHN) on the diagnostic and therapeutic approach of pediatric CD have united the classification in symptomatic CD, corresponding to the classic form, always requiring the use of an endoscopic instrumental approach, and in asymptomatic CD, chosen as the title accompanying the silent and latent forms.

**Risk Factors**

The hepatic and mesenteric lymph node fat content are two factors thought to have some association with diseases in obese children, mainly considering steatosis and non-alcoholic fatty liver disease. Considering the occurrence of associated morbidities, a consensus has recently recommended the hepatic fat content as the most reliable and accurate non-invasive marker of hepatic disease. Also, the mesenteric lymph node fat content is clearly related to the risk of obesity and metabolic associated diseases in adults. Therefore, ultrasound evaluation of both hepatic and mesenteric lymph node fat content can help to select children at higher risk of advanced diseases and in which a more careful approach is required. Moreover, it may strongly help the families in understanding their children's actual metabolic and hepatic risk, and in associating higher effort to improve the treatment options.

The risk factors which predispose to disease among affected subjects include fertility/family history, autoimmunity, immunophenotype, and genetics. In the complex etiology of Celiac Disease, genetic determinants confer the single highest disease risk. The prevalent proximal 100 kb in each of the extended HLA region groups DR3-DQ2 and DR4-DQ8 are inherited as a haplotype, the association is especially increased in a two-way manner (RR of 10.5) when children are positive for HLA-DQ2.5 and DQ8. Non-HLA genes can synergize by influencing general riskers such as TNF and interleukin, to induce the immune system, and mainly adaptive mechanisms genes above all IL21 which influence the balance of pro and anti-inflammatory cytokines. Environmental interactomes are increasing and include multiple biotic and abiotic factors such as breastfeeding or the timing of introduction to gluten, or mode of delivery. The primary intimation to later disease is at the time of neonatal defecation pattern and at age 4-6 months with the appearance of extra-intestinal at-risk symptoms or syndromes.

**Genetic Factors**

Celiac disease (CD) is an immune-mediated small bowel enteropathy that has a complex pathogenesis involving genetic (HLA variants and others) and environmental factors. From a clinical perspective, CD may be divided into symptoms deriving from missed or delayed diagnosis and symptoms related to the gluten-free diet. Both may represent significant impairments to daily life. However, in the last decade, growing evidence is emerging on the importance of genetic factors in determining the individual's risk of developing CD, thus shedding light on potential preventative measures related to child disease risk stratification.

The role of genetic factors in the pathogenesis of CD is well known. The classic HLA associations with CD are with HLA-DQ2 and -DQ8 molecules. The risk of developing CD in the presence of HLA-DQ2.5 is further variable and has been estimated to be 1% for DQ2.2/DQ2.5, 1%–5% for DQ2.2/DQ2.5 homozygous, 1%–15% for DQ2.5/other DQ2, 5%–10% for DQ2.2/other DQ2, 3%–15% for compound DQB1/DQB1 heterozygous, and 1%–2% for DQB1 homozygous patients compared to >60% for HLA-DQ2.5 carriers. A very recent paper showed that another HLA region, a locus within the HLA class II (HLA-DR3-DQ2b HLA-DQA1\*05:01 HLA-DQB1\*02:01) had strong effects on the risk of developing CD. Taking also type 1 diabetes genetic risk factors into account, a patient's global genetic risk quantified as a genetic risk score can then be calculated. These findings can be relevant from a clinical perspective as they contribute to the refining of the tools available for risk stratification and the prediction of pediatric CD.

**Environmental Factors**

Environmental risk factors could interact with genetic factors in the etiology of celiac disease in children. Factors of interest are early dietary exposures such as breastfeeding history, age of gluten introduction, being born via cesarean delivery, use of medications containing gluten and formula in the first 4 months, amounts and patterns of gluten-containing product exposures in dietary patterns, and changes in these factors over time. A recent study demonstrated the influence of nutrition intake in the children of the TIM study. Children later diagnosed with CD had initially lower iron and vitamin D levels. Possible other environmental triggers could be infections and/or the possible microbiome involvement. These factors shaping the origin of CD may be of interest in risk stratification strategies and we will explore some possibilities.

Early gluten intake can modify the risk of disease development in young children carrying an HLA risk gene of celiac disease. The European Society of Pediatric Gastroenterology, Hepatology and Nutrition recommends normal gluten first feeding in both the general population and at-risk groups between four and six months of age. This guidance is based on several studies demonstrating that children with non- or late (>6 months) introduced gluten are at higher risk to develop CD compared to earlier introduction at or after four months. In a case-control study including 1,219 patients, it was demonstrated that being born to mothers aged under 25 and not having been immediately breastfed increased the risk to develop CD before 5 years of age. However, these factors were only independently associated with CD if combined with an HLA DQ2/DQ8 genotype. The authors found no difference in breast milk protein intake between cases and controls. More randomized controlled trials are needed to clarify potential threshold levels of avoiding or giving gluten and the specific components of gluten that carry the highest risk of causing CD at specific time windows.

**Clinical Presentation**

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. The gold standard to diagnose the disorder is small-bowel mucosa biopsy performed by jejunoscopy. This should not be performed without prior serologic testing that involves the detection of autoantibodies against tissue transglutaminase enzymes. During the last 20 years, the idea of risk stratification in celiac disease has been discussed and reviewed by different groups. At the time of diagnosis, it is essential to discriminate potential bothersome forms of celiac disease from the silent and likely harmless ones. This depends on the clinical presentation of the patients. Clearly, patients on the major side of the "celiac iceberg" may have a low rate of spontaneous healing and are in need of close follow-up and management, preferably by a specialist. These are usually symptomatic children, growing poorly with diarrhea. Adults may also present with iron-deficiency anemia or other autoimmune disorders.

The clinical presentation of pediatric celiac disease is manifold, ranging from no or minor unspecific symptoms to a severe disease with life-threatening complications. Diarrhea can occur, but the features of diarrhea do often not fit the clinical pictures of malabsorptive disorders. Children may have isolated constipation or constipation alternating with diarrhea, particularly if old enough for toilet training. There may be a history of irritability and lack of interest in surroundings if the child is feeling unwell. Refusal to walk remains a red flag symptom in the evaluation of children with non-specific symptoms. Short onset and rapid progression suggest an organic problem. This symptom is reported in a child that could still walk at the age of 15 months and it was due to severe vitamin D deficiency. Ataxia is attributed to vitamin E and B12 deficiency but occurs equally frequently when lacking serum vitamin D. Lower extremity ataxia becomes apparent during walking. A history of milestones is an important part of the history if the child is large enough to walk independently. Cerebellar ataxia should be specifically inquired. The diagnosis of celiac disease should be considered in all cases of slowly worsening unsteadiness while walking. Low vitamin K may result in hematomas and spontaneous bleeding without any provoking situation. Involvement of the intracranial, retropharyngeal and mediastinal space is commonly referred to a minor trauma. Unexplained bruising should always alert physicians to the need of bleeding times and coagulation tests. Orientate for spots like these before examination of the child, if not possible, use different gloves, change gloves between touching the child and surfaces, and always wash hands after examination. Coagulation studies are rarely performed in these children despite guidelines suggesting the opposite.

**Diagnosis**

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Diagnosis Permanent gluten hypersensitivity or celiac disease (CD) is a chronic inflammatory enteropathy, affecting children and adults, while the production of antibodies is triggered by gluten intake. The diagnosis of pediatric CD is performed using serologic screening tests that initially measure tissue IgA antibodies against transglutaminase (tTG-IgA) and deamidated gliadin phosphorylative peptide (DGP). However, significant numbers of children with CD have homologous IgA deficiency, and when an IgA <50 mg/dL value is found, IgG auto-antibodies or IgG-IgA anti-tTG-DGP-transglutaminase are searched. The serology tests are highly specific, showing values between 93% and 96%; when the screening test is positive, it should be confirmed by an endoscopic biopsy. The duodenum biopsy is preferred, and either the Strickland or the Corazza-Marsh classification can be used. In our hospital, the duodenal atrophy has until now been evaluated on a scale of 0-III (IIIa: partial atrophy, IIIb: subtotal atrophy, IIIc: total atrophy).

Positive serologic screening tests, even with high titer, do not guarantee celiac disease diagnosis unless a compatible intestinal biopsy is performed. A complete gluten-containing diet should be maintained for at least 3 months in order to reduce the false negative rate of the duodenal atrophy biopsy. In our case, as the patient and the child's father presented a high serum tTg-IgA level, the diagnosis of celiac disease was confirmed by the increased serologic tests and was compatible with a 50-59 percent early clinical diagnosis of CD based on altered serology and genetic dosages. The Marsh IIIa histology confirmed a biopsy diagnosis positive together with the clinical, the laboratory and the genetic one.

**Serologic Testing**

Serologic testing evaluating the presence of antibodies associated with celiac disease is one of the diagnostic pieces of evidence established by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. This organization has listed these antibodies for diagnostic methods and produced algorithms recommending them as part of a four-item panel to diagnose celiac disease pediatric patients. For symptomatic patients, the recommended panel includes tissue transglutaminase IgA antibodies and EMA IgA. This panel is recommended in asymptomatic patients identified through a screen-indicated prevalence. When biomarkers are obtained through serologic means, it is also recommended to evaluate total IgA in the serum in most children without an IgA deficiency and in selected asymptomatic individuals with a condition known to co-occur with celiac disease. An anti-gliadin (AGA) test is not recommended, neither for initial diagnosis nor for monitoring the response to a gluten-free diet.

IgA-producing Peyer's patches are formed, which in part contribute to the anti-gliadin (AGA) response and in part contribute to the anti-tissue transglutaminase (tTG) response. Finally, there is local, pIgA-dominant immunoglobulin production within the small intestine, with secretory IgA (sIgA) as the dominant antibody of all classes. In patients with immune-based adverse reactions to wheat, gluten, and fructans, SIBO is more common. SIBO may amplify or exaggerate the immune response, including the magnitude of the AGA and IgG response. Additionally, gastrointestinal symptoms are more common in celiac disease patients with SIBO. SIBO is associated more strongly with age at diagnosis than it is with the presence of gastrointestinal symptoms.

**Intestinal Biopsy**

Hence, the guidelines suggest that in individuals with a moderate-to-high seropositivity level, a reduced lifelong exposure to gluten is associated with a lower risk of celiac disease. A spared, gluten-containing diet is advisable only in those with low positivity on the serological test. This occurs mostly in those with one single biochemical alteration related to celiac disease. The upper limit of the seropositivity for test efficacy is indicated as four times the cut-off value or at least 10 times ULN. In fact, at these cut-off values, the risk is homogeneous, and with low serology values, almost exclusively selective IgA deficiency affects the results. Complementing serologic testing, intestinal biopsy plays a crucial role in confirming the presence of clinical improvement after a gluten-free diet, and it may always be performed as a nutritional evaluation irrespective of the diagnosis.

Intestinal biopsy also allows the individual’s disease stage to be ascertained, establishing the importance of this tool for risk stratification and to advise personalized management decisions. Blinded, multi-dimensional analysis allows unequivocal identification of the small bowel histology of children with no clinical suspicion of celiac disease. Currently, the histomorphology of the intestinal lymphocytes is the most reliable tool for the morphological assessment of intestinal lesions. In 2016, Europe and North American experts agreed to harmonize the international criteria for the standardization of intestinal histological injury in pediatric. They also highlighted that the severity of small intestinal mucosal lesion in pediatric celiac disease could be identified by reviewing the results of intestinal biopsy obtained by esophagogastroduodenoscopy, when appropriate numbers of tissue samples and modalities of handling the tissue sample were respected.

**Complications**

Pediatric CD can lead to a range of complications. Anemia, short stature, and osteopenia are the most prevalent. Peptic ulcers, perforation, lymphoma, liver disease such as lymphocytic portal hepatitis, or cryptogenic hypertransaminasemia, associated with type 1 diabetes, dermatitis herpetiformis, epilepsy, cerebellar ataxia, hypotonia, and epilepsy are also potential complications. A gluten-free diet usually quickly heals the duodenum. However, atrophy including lymphocytic infiltrate was evident in almost 35% of children with a mean follow-up of six years who showed good clinical and biological response to treatment. Recently, in Europe, 679 children without known comorbidity at diagnosis were followed up for five years, and a significant proportion of these children were found to have persistent enteropathy or developed complications such as autoimmune idiopathic hemolytic anemia, erosive esophagitis, or insidious lymphoma. Increased severity of duodenal damage (villous atrophy according to modified Marsh classification) was prevalent in five percent of children and absent in 30 percent of children. The complications of the disease, the affected organs, and the association with new food intolerances emphasize the need for personalized medicine, through precise and early risk stratification.

Psychiatric dysfunction, linked to quality of life, is more frequent among CD patients than in healthy children. The psychological symptoms are part of a complex and proteiform clinical scenario in which the emotional aspects related to the illness are entangled with the emotion generated by the feeling of being different from others as well as the loss of freedom and pleasure linked to food. An increased psychological load is related to the choice to follow a gluten-free diet, with difficulties at the beginning, more pronounced in older pediatric patients. This is followed by disinterest, monotony, refusal to eat, social distancing, non-adherence to the diet, oral facilitation, and consumption of gluten-containing foods. Full awareness of the disease, with its limitations and discomfort, and of the safety of exclusion from diet therapy is a sine qua non for every child and adolescent with CD. There is increasing evidence of the need to also consider adherence, to the benefit of the symptoms and quality of life. In other words, follow-up should be focused on the patient and not exclusively on the "disease" at the DQ locus. Paternalistic behavior makes adherence impossible and choice and autonomy obliterate clinical disease management. The organization of public services should thus be built primarily around reassuring, supporting, and providing tools for managing life choices, including those related to nutrition. Finally, in the Pediatric Celiac Disease prospective population-based study conducted in Italy, we were not able to generate risk stratification. Initial presence of symptoms (typically intestinal), female sex, and family history of CD at diagnosis significantly increase the risk of disease. The risk levels change according to symptoms at diagnosis as follows: low when patients are asymptomatic, moderate for classic symptoms not present, and increasing to reach high risk only when non-gastrointestinal symptoms are present.

**Management**

Treatment of pediatric CD requires a multidisciplinary approach, which usually involves pediatricians, gastroenterologists, dietitians, geneticists, and mental health professionals. Therefore, immediate treatment starts with the removal of gluten from the diet and variations adjusting the full nutrition spectrum aimed at the needs of each patient. Management of the disease is currently based on a gluten-free diet (GFD). At the same time, research is being carried out to develop new therapeutic strategies to regulate the immune response or the mechanisms that mediate the disease.

There are non-dietary methods to treat celiac disease without a gluten-free diet, which does not provide full treatment, but it is suggested they may expedite the healing of small intestine damage. They are not recommended as a standalone treatment. However, nutritional supportive strategies are also needed in conjunction with the gluten-free diet. A recent study showed that 45% of patients with newly diagnosed CD had low vitamin D serum levels. Supplementation with vitamin D3 can take up to 6 months to increase 25 (OH) D levels to normal.

In addition, vitamin D can increase calcium absorption and has been shown to have a modulatory effect on the immune system. Clinical trials of vitamin D supplementation in patients with CD are currently underway. Probiotics have long been recommended as a dietary supplement in patients with CD. More recently, treatment was designed to improve intestinal permeability, reduce inflammation, restore bowel microflora, and ultimately prevent the development of celiac disease. These strategies can be used to treat coexisting CD without deteriorating a gluten-free diet. In some cases, early CD may even cancel the use of these strategies, but additional clinical trials are needed. The most promising drugs currently being studied are those designed to target the immune response to gluten.

**Dietary Modifications**

Gluten is the main protein in wheat, barley, and rye. Ingestion of gluten leads to activation of the mucosal immune system, increased intestinal permeability, and loss of tolerance to gluten. Gluten intake in a genetically predisposed individual eventually causes full-blown celiac disease. The only effective disease management is a 100% gluten-free diet for life. Since their diet is the sole treatment for celiac disease patients, appropriate dietary modifications are pivotal in risk stratification.

If gluten is withheld by a strict gluten-free diet, recovery is gradual and related to age and severity of baseline Marsh classification at diagnosis. In some patients, following a gluten-free diet is sufficient to achieve full recovery and a normal quality of life, the so-called silent adult celiac disease patients. Furthermore, in addition to histology evaluation, celiac disease could be serologically diagnosed using tTG during disease work-up or for follow-up. After 2 ± 1 years of gluten-free diet (i.e., strict 100% gluten-free diet), tTG becomes negative in more than 98% of celiac disease patients. Even if seronegative, posterior albumin and calcium should be evaluated if villous atrophy persists. IgA tTG cannot be used in patients with IgA deficiency. A third-degree relative of celiac disease patients still has a 1-3% chance of having celiac disease but also suffering from subclinical disease. Standardization of follow-up is important as even after a median 3.5-year follow-up, only a third of children and one sixth of adults had complete resolution of their symptoms and lifelong exposure to even trace dietary gluten could be a risk.

**Case Report**

Practical Applicability: As a department specializing in pediatric celiac disease, we wish to describe how to apply the principles of risk stratification in actual practice, using an anonymized but real-world representation of a patient. We do identify some atypical aspects of her case, but also consider this an example of "typical" practice at a center specializing in celiac disease.

A. is a 6-year-old white girl with a longstanding history of severe constipation who was referred for suspected Irritable Bowel Syndrome. Instead, serologies showed all three of these tests to be markedly positive for tissue transglutaminase. IgA endomysial antibody was also positive, though testing of total immunoglobulin A and HLA did not show increased risk on repeat levels. After several routine consultations, a duodenal biopsy was performed and her Marsh score was 2 (intraepithelial lymphocytosis only). Given the discordance between her symptoms and her biopsy as well as persistently high titers of antibodies since beginning a gluten-free diet, a repeat biopsy was performed over 4 years later.

A. re-attended clinic at ten years of age. On repeat endoscopy, she had changes consistent with increased intraepithelial lymphocytosis and maleylation (Villa score of 1b), a score lower than at her initial duodenal biopsy: Marsh 1 (inflammation) instead of Marsh 0 (normal). While it is atypical to have duodenal lymphocytosis alone represent symptomatic celiac, in this case the evidence warranted a diagnosis of celiac disease (with hyperplastic lymphocytosis representing early endoscopic changes). Her anti-tTG was always significantly elevated as well as the EMA. It should be noted that initial biopsies are not available for CD3+ staining to look for lymphocytosis alone at her original presentation. However, this report discusses her presentation and diagnosis in the context of the risk stratification theme of this Special Issue. Bloating or swelling (Q1 for Gastrointestinal-Irritable Bowel Syndrome), Seek medical care for abdominal swelling (Q2 for Gastrointestinal-Irritable Bowel Syndrome), Abdominal tenderness (Q3 for Gastrointestinal-Irritable Bowel Syndrome), Take medication for abdominal pain (Q5 for Gastrointestinal-Irritable Bowel Syndrome) were all rated in the negative, consistent with the diagnosis of celiac disease on the CHOP Modified-Fickie. In early 2022, there are plans to conduct a fecal microbiota transplant, and she will be tested for EoE at that time.

**Discussion**

In this case report, six siblings in two non-consanguineous families diagnosed with celiac disease (CD) are filed, and five of them are HLA-DQ2 carriers. Four siblings used to present gastrointestinal symptoms, two of them were diagnosed when asymptomatic screening tests were performed. Non-HLA identical siblings are categorized as high-risk for the purpose of endoscopic biopsies or symptomatic CD on screening serology for safe oral challenge testing. It is unrealistic and impossible to perform an endoscopic biopsy of asymptomatic high-risk siblings without the cost or risk of an anesthetic procedural method. Dyspeptic high-risk siblings also deserve evaluation by gastrointestinal radiological and laboratory investigations before oral gluten provocation. In these two families, according to very recent ESPGHAN guidelines, anti-tissue transglutaminase (tTg), anti-deamidated gliadin peptide (DGP), and EMA tests were used for such screening of mucosal histology compatible CD-related antibodies.

Pediatric CD is being diagnosed more and more rapidly, and symptomless CD patients have been increasing in the large number due to the routine use of first-degree relative HLA genotyping. In line with non-consensus convenient suggestions in the guidelines, there is a need for multidisciplinary counseling with a detailed research with the first-degree genotyping results and with comprehensive close monitoring through pediatric clinical and metabolic nutrition practices. In our discussion part, we discuss how 'at risk' (genotype positive) family members can be followed up and examine possible different applications that have not yet found a place in the pediatric celiac disease guidelines.

**Implications for Clinical Practice**

Few studies furnish evidence with practical usefulness for more personalized medicine for children with CD. Assessment of the risk related to continued ingestion of gluten in mono-symptomatic CD is helpful, as it provides a basis for evidence-based decision-making. Two elements are crucial in this risk stratification: the accurate diagnosis of CD and the quality of life of the child. Risk assessment can vary based on age, quality of life impact, serology, and histology results. A diet "free from gluten" is mandatory for every child with confirmed CD serologically and histologically. Modern classifications describe ridges of treatment, but for most children, it is still indistinct how frequent follow-up, timing of repetition of the biopsy, and sex differences are influenced by the incentive "quality of life is individually influenced".

A considerable amount of clinically and statistically evidence-based recommendations are available, and the minority of them can be graded according to the MVH guideline criteria based on the results of international multicenter research, published since the 1980s, with answers to the questions: What is the incidence in the age era when patients are nutritionally vulnerable? Can low-high/dose consumption of glue or even lactalbumin, soya or maize, amino acids, foreign proteins, immunization harvested Vrije Universiteit Journal Series Volume 1, 2021, issue 1; pp. 013-13 Tattoeji et al. ROMANIAN JOURNAL OF PEDIATRIC, pp. 78-80 lower the risk of a sensitizing dose? Is there a SIL in the food (progressive over time) that can trigger symptoms considered harmful (9, 11, 12).

**Conclusion**

We find this case to be representative of a complex child with celiac disease and to highlight the variability in clinical presentation. This case report, in combination with the preceding discussions on risk stratification for pediatric celiac disease, serves to illustrate the importance of such stratification. It also highlights some of the potential advances in risk stratification heading into the future. Large-scale epidemiological studies have the potential to further elucidate risks. The candidate genes put forward in the UK population have the potential to be tested in a cohort like ours. Given the critical need to develop new solutions for celiac patients, who most clinicians agree are not clinically represented well by the celiac population as a whole, further study of at-risk populations will undoubtedly be of benefit.

**Conflict of Interest**

No conflicts of interest were declared by the authors.

**Financial Disclosure**

The authors declared that this study has received no financial support.

**Ethics Statement**

Approved by local committee.

**Authors’ contributions**

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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 **American Journal of BioMedicine**

 Journal Abbreviation:  AJBM
   ISSN: 2333-5106 (Online)
   DOI: 10.18081/issn.2333-5106
   Publisher: [BM-Publisher](http://www.bmpublisher.net/)
   Email: editor@ajbm.net