Coeliac Disease in Children and Young Adults

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Introduction

Coeliac disease (CD) is an autoimmune disorder that occurs in genetically predisposed individuals who develop an immune reaction to gluten. The disease primarily affects the small intestine; however, the clinical manifestations are broad, with both intestinal and extra-intestinal symptoms [1]. CD provides a model of an immune-based disease with strong genetic and environmental risk factors. The key environmental factor responsible for the development of CD is gluten. Gluten is incompletely digested by gastric, pancreatic and brush border peptidases, leaving large peptides up to 33 amino acids long. These peptides enter the lamina propria where, in predisposed people, an adaptive immune reaction occurs, is dependent on deamidation of gliadin molecules by the enzyme tissue transglutaminase (TTG), the predominant autoantigen of CD [2]. Deamidation increases the immunogenicity of gliadin, facilitating binding to the HLA-DQ2 or HLA-DQ8 molecules on antigen presenting cells. Gliadin peptides are then presented to gliadin-reactive CD4+ cells. During this process, antibodies against TTG, gliadin and actin are made through unclear mechanism. Almost 100% of patients with CD possess specific variants of the HLA class II genes HLA-DQA1 and HLA-DQB1 encoding the alpha and beta chains making up the coeliac-associated heterodimer proteins DQ2 and DQ8 expressed on the surface of antigen presenting cells. These HLA genes and gluten ingestion are quite common in Caucasian people but CD occurs only in about 1% of the population, suggesting that other environmental factors besides gluten are probably important.

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CD Main Medical Characteristics

The recognition of the broad clinical presentation of CD has evolved during the last decades. It has shifted from the historically classic symptoms of malabsorption in childhood to non-classic symptoms, which can be present in childhood or adulthood. Classical symptoms of malabsorption seem to be more specific and include failure to thrive, weight loss and chronic diarrhoea. The more common, non-classical symptoms include iron deficiency, bloating, constipation, chronic fatigue, headache and abdominal pain [1, 2] (Table 1).

Diagnosis

If CD is suspected, total serum IgA and IgA-antibodies against transglutaminase 2 (TGA-IgA) should be measured. Deamidated gliadin peptide antibodies (DGP-IgG/IgA) should not be used for initial testing. In patients with low or undetectable total IgA concentrations, an IgG-based test (DGP or TGA) should be performed as a second step [2]. Patients with positive results should be referred to a paediatric gastroenterologist. If TGA-IgA is ≥10 times the upper limit of normal (10 × ULN), the no-biopsy diagnosis may be applied, provided endomysial antibodies (EMA-IgA) will test positive in a second blood sample. In this case, HLA DQ2-/DQ8 determination and the presence of overt symptoms are not compelling criteria [2]. In children with positive TGA-IgA but with value below 10 × ULN, an upper endoscopy should be performed in order to collect at least four biopsies specimen from the distal duodenum and one from the bulb. Discordant results between TGA-IgA and histopathology may require endoscopic re-evaluation. Patients with no or mild histological changes (Marsh-Oberhuber classification 0/1) but confirmed autoimmunity (TGA-IgA or EMA-IgA positivity) should be re-evaluated closely during follow-up.

Table 1 Symptoms and signs suggesting CD

Gastrointestinal	Chronic or intermittent diarrhoea
	Chronic constipation[a]
	Chronic abdominal pain[a]
	Distended abdomen[a]
	Recurrent nausea and vomiting
Extra-intestinal symptoms	Weight loss, failure-to-thrive, stunted growth/ short stature
	Delayed puberty, amenorrhea
	Irritability, chronic fatigue[a]
	Chronic iron-deficiency anaemia[a]
	Recurrent aphthous stomatitis
	Dermatitis herpetiformis-type rash Dental enamel defects Abnormal liver biochemistry

[a]Common symptoms

Treatment and Follow-Up of CD

The mainstay of treatment of CD remains adherence to a gluten-free diet (GFD). Improvement and resolution of symptoms typically occurs within weeks and often precedes normalization of serological markers of duodenal villous atrophy [3]. Despite its effectiveness in achieving normalization of these parameters in most patients, the GFD encounters many difficulties. Gluten-free substitute foods are substantially more expensive than their gluten containing counterparts and therefore patients with low incomes might be at particularly high risk of non-adherence to the diet [4]. The quality of information regarding the gluten-free status of food ingredients is variable in online resources, which can lead to confusion among patients. Potential gluten exposure when travelling or eating in restaurants can be a hazard and a source of concern. Social pressures, particularly in adolescence, can also be an impediment to strict adherence [5]. Uncertainty regarding the presence of gluten in trace amounts in medications and supplements is another concern. Patients with newly diagnosed CD should be referred to an expert dietitian, because the GFD requires knowledge not only of hidden sources of gluten, but also of healthy gluten-free substitute grains that provide adequate fibre and nutrients. Upon diagnosis, patients should be tested for micronutrient deficiencies, including iron, folic acid and vitamin D. Beyond the initial diagnosis period, traditional medical follow-up for coeliac patients consists of regular physician visits to evaluate health, including weight and height measurements, dietary adherence and serology (which usually normalizes within 2 year of starting the diet). Vit D status should be monitored, and possibly the study of bone mineralization should be performed when indicated.

Transition from Childhood

The Child and Adolescent Health Measurement Initiative estimates that one million US children with special health needs make the transition to adult care every year [6]. CD is one of the most common chronic disorders in childhood and children with CD and constitutes an important part of transition healthcare in the Western world. The overall prevalence of CD varies from 0.71% in the USA [7] to as high as 2.9% in certain age groups in Sweden [8]. Generally, the transition from paediatric to adult care should be a collaborative process involving patients, their parents, the physician and the dietician.

Paediatric patients with CD are usually evaluated in specialized centres by teams including paediatric gastroenterologists, dieticians and psychologists. In children, the delivery of care is mainly family-centred, whereas in adulthood responsibility becomes autonomous and dependent upon the needs of individuals. The physical, mental, psychosocial and self-control development during transition from adolescence to adulthood is therefore pivotal. Children with a chronic disease may develop autonomy later than their peers [9]. Both the family and the adolescent patient should be at the centre of transition process, and the clinician's purpose is to balance

parental authority and the adolescent's need for autonomy. To parents, this means stepping back and allowing their adolescent children to make independent decisions. The physician should start a discussion about transition when the adolescent is 12–13 years old, develop a transition plan when the child is 14–15, with the actual transfer taking place at 18 years of age [6].

Growth and Puberty

Growth impairment is a known consequence of untreated CD [10] though many children with short stature diagnosed with CD in childhood demonstrate good catch-up growth [11]. However, catch-up growth may occur more predictably for those with a delayed bone age at diagnosis and where growth velocity acceleration during the first year of treatment for CD is clear [12]. Untreated CD, or CD diagnosed after attainment of adult height, results in shorter adult height than healthy controls, particularly among men [13]. Some adolescents and young adults with CD will experience a delay in pubertal development and may continue to grow and sexually mature beyond the expected age of pubertal completion; the pathophysiology is currently poorly understood, but a hormone disregulation could be involved [14]. This may have implications for emotional maturity, sexual health and menstrual regularity. At the time when transition is planned, the paediatrician should provide data regarding the patient's history of physical development and should note to the gastroenterologist whether the patient has achieved his or her final adult height. It may be advisable to coordinate transition to an adult provider at the completion of puberty, particularly if paediatric gastroenterologist is still taking care of the patient in order to manage growth failure. A bone age X-ray may add information in cases of patient's pubertal delay, to inform growth expectations and timing of transition.

The Actual Transfer of Care

For adult gastroenterologists, CD is also often perceived as a less serious disease compared with GI cancer or IBD, and knowledge may be limited with respect to complications, diet, inheritance, extra-intestinal manifestations and how to monitor patients. The actual transfer can take many forms. In some settings, the paediatric and adult gastroenterologists see the patient at the same visit; in others, paediatric and adult gastroenterologists meet annually to discuss patients in transition. Hopefully, joint transition clinics with paediatric and adult service clinicians can be established for information delivery and generating trust in the new physician. Structured transitional models and targeted education are important and, in other chronic diseases, have been linked to improved care, better health outcome and improved health-related quality of life (QoL) [15]. One path to facilitate transition

and transfer of care is to create a 'transition document', which would allow a smooth transfer of individual medical care data. This transition document should be created by the paediatrician prior to transfer, containing details and information during follow-up such as serology, anthropometric data, comorbidities and dietary compliance.

Several issue may be discussed during the transition period. Dietary adherence and consequences of non-adherence are key components for discussion in a transition setting. In Europe, adherence to a GFD by children and adolescent varies from 44% to 97% and accidental transgression are common [16]. Adolescence report lower adherence than younger children, particularly at social events. The risk of osteoporosis and adverse pregnancy outcome may be big issues in individuals with poor adherence [17]. The implementation of a systematic transition policy in CD has been limited by a lack of clinical guidelines based on outcome-related research and clear and consistent definitions. Models of transition will eventually need to be evaluated in randomized controlled trials with clear patient outcome measures. It is crucial to know to what extent a well-structured and planned transition will influence adherence to a GFD, which in CD is imperative for restoration of health and well-being.

Sexuality and QoL

Among the extra-digestive complications associated with CD, unexplained infertility has been reported since the 1970s. The prevalence of CD among women with unexplained infertility is 2.5–3.5%, higher, although not always significantly so, than in the control population. To date, it is widely accepted that untreated CD poses a risk of miscarriage, low-birth weight babies, and a short breastfeeding period. These characteristics can be remediated by a GFD. With regard to a potential pathogenic mechanism, because CD causes malabsorption of folic acid and other nutrients, this pathway has been proposed to explain unfavourable pregnancy outcomes [18, 19].

The psychological aspects of CD should not be underestimated. The feelings of deprivation and failure, alongside the burden of an unchanging lifelong diet, remain difficult components to accept. Also in social life.

In the time of Covid 19, the scientific literature has also investigated the perceived risk of celiac patients contracting the virus.

Jamie Zhen et al. [20] conducted a survey in ten countries between March and June 2020 and collected information on demographics, diet, COVID-19 testing and perceived risk of COVID-19 in patients with CD.

Participants were recruited through various coeliac associations and via clinical visits and social media. Perception of risk was assessed by asking people whether they believed that patients with CD had a higher risk of contracting COVID-19 than the general population. Perception of COVID-19 risk was measured according to age, gender, adherence to a GFD and comorbidities such as cardiac conditions, respiratory conditions and diabetes.

10,737 patients diagnosed with celiac disease completed the survey.

Specifically, 6019 (56.1%) patients perceived themselves to be at higher risk or were unsure as to whether or not they had a higher risk of contracting COVID-19 than the non-coeliac population.

A higher percentage of patients perceived an increased risk of contracting COVID-19 compared with infections in general due to their disease. As a result, 34.8% reported taking additional precautions against COVID-19.

Members of coeliac associations were less likely to perceive an increased risk of COVID-19 than non-members (49.5% vs 57.4%). Being older, male and strict adherence to a GFD were all associated with lower perceived COVID-19 risk.

The scientific literature has also investigated other correlations.

Giorgetti et al. [21] showed that CD was more common in subjects with insulin-dependent diabetes mellitus than in normal people. The study was conducted on a group of 93 diabetic children and adolescents who had undergone determination of antigliadin and anti-endomysium antibodies. In the study, the prevalence of CD exceeded the data reported in the literature. Hence, immunological screening for CD in paediatric T1DM patients is advocated.

A recent study conducted in the US population showed the following prevalence:

- 3–6% in individuals with Type 1 diabetes,
- up to 20% in first-degree relatives of coeliac patients,
- 10–15% among symptomatic cases of sideropenic anemia and
- 1–3% among those with osteoporosis. [22].

Given the prevalence of CD and the impact on patients' lives, extensive research has been conducted in several countries on the following aspects:

1. dietary compliance
2. health status including anthropometric data (primarily BMI)
3. daily habits
4. perception of QoL and of one's mental and physical health
5. any limitations in major social activities
6. ability to find gluten-free products
7. mode of supply
8. comorbidities, including psychiatric comorbidities such as anxiety disorder and depression
9. the relationship with health professionals and
10. the level of information provided by said professionals [23].

Most of the literature has identified the following [24]:

- SMOKING: present in both sexes in 24%; 4% are occasional smokers and 72% on average are non-smokers.
- WINE, BEER AND ALCOHOL: 24% of patients of both sexes habitually drink wine, 4% of males and 24% of females say they rarely drink it; 10% of males say they drink beer and alcoholic beverages, such as aperitifs vs 9% of females who say they drink beer (gluten free) and only 3% alcoholic beverages [25].

- MEDICATION: 25% males vs. 48% females take medication.
- Only females, 16%, report taking psychotropic drugs while 12% take drugs for osteoarticular disorders (osteoporosis, rheumatic disease), 8% use anti-allergic drugs, 4% take drugs for diseases of both the nervous system (Parkinson's disease) and the respiratory system (asthma) and 16% take contraceptives. Medications against gastrointestinal disorders (reflux and colon disease) are taken by 8% of both sexes.
- GFD: It is strictly observed in 90% of females vs. 79% of males. 10% of females do not follow the diet because they state that they are not able to "hold back" on social occasions vs. 21% of males who in part report not liking the taste of foods and find it difficult to buy them [26].
- LEISURE TIME: 71% of men and 58% of women pursue a hobby. 25% on average of both sexes answered that they do not pursue any hobby (in males 21% have no hobby and 4% did not answer). 41% of patients of both sexes had a pet in their care.

A study published by Digestive Diseases and Sciences, coordinated by Randi Wolf of Columbia University in New York, 2021, showed that CD had a major/moderate impact on their dating life.

With regard to sexuality however, many patients with CD report reduced sexual potency.

Problems related to infertility and oligospermia, on the other hand, are often solved with supplements and a GFD, even though the therapy lasts for several years [27].

In some patients, low-circulating levels of testosterone and 5-dihydrotestosterone were also detected, while the plasma level of luteinizing hormone often appeared elevated. These hormonal alterations may explain, in part, the delay in pubertal development and the appearance of secondary sexual characteristics observed in male patients not receiving any treatment.

CD has also been associated with spontaneous abortions and an increased incidence of intrauterine growth retardation.

Although the pathogenetic mechanism of celiac disease has not yet been clarified, a state of general malnutrition and the deficiency of specific factors such as iron, zinc and folic acid are to be considered as one of the causes that can lead to miscarriage. Moreover, pregnancy requires a calcium intake moderately higher than normal; consequently, bone remodelling becomes more important especially in women in whom the diagnosis of CD was made in adulthood, when occult malabsorption had already reduced the body's natural stores [28].

On the other hand, data from the National Social Life, Health, and Aging Project have shown that the psychological burden of chronic disease is associated with the sexual frequency and sexual dysfunction for men ($N = 893$) and women ($N = 641$). The results indicate that CD induces lubrication problems for women and orgasm problems for men. Especially among elderly patients. [23].

The GFD and consequent proper nutrition can help sexuality. Scientific literature reports that 18% report low interest in sex, compared with 13% in the GFD group

and 11% in the "transitional" GFD group. Specifically, it is impossible to kiss someone wearing gluten-containing lipstick without getting risk of falling sick if you have celiac disease, and it is wise to ask a partner who eats gluten (or drinks beer), to brush his or her teeth before kissing. Women suffer from a wide range of reproductive disorders related to celiac disease, including an increased risk of infertility, miscarriage and other pregnancy problems. Although much less research has been done to document the reproductive health effects of celiac disease on men, the few studies available indicate that male infertility is higher among undiagnosed celiac men.

Conclusion

Every patient with CD must face a process of self-learning about his or her own life: not only from a nutritional point of view, but also in terms of intimacy, social relationships and in not being held back by the limitations of the disease. "Familiarizing oneself with CD appears to be a path of progressive growth, where every apparent difficulty (in diet, sexuality, health) can become a <difference> to be highlighted and given the proper attention so that the individual does not feel marginalized and in a state of constant underestimation of their psychophysical abilities". Consistency in diet as well as in self-care, hobbies, social relationships and interaction with peers can make the therapeutic discipline that CD imposes less painful. The communication between the specialists and the patient can contribute greatly to a more durable therapeutic contract and less risk of drop-off.

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