The coeliac iceberg : a consensus* in paediatrics

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Coeliac disease is an enteropathy occurring in both children and adults. The condition is characterised by sensitivity to gluten that results in inflammation and atrophy of the mucosa of the small intestine. The aim of this article is to review the current knowledge of the disease, to provide an estimation of the incidence of symptomatic cases occurring during childhood in Belgium and to standardise the current management (serologic screening, diagnosis, challenge test and follow-up) in our country.

Current knowledge about coeliac disease

1. *Epidemiology*

Probably because of environmental (wheat is a staple food in Europe and in North Africa) and genetic factors, most coeliac patients have a European or a North African ethnic origin. Therefore, coeliac disease (CD) is most often found in Europe, North Africa, Australia and North America. CD is not found in Blacks, Chinese, Japanese and uncommon in South East Asian populations even in those individuals immigrating to countries where CD is frequent (1). Also within Europe, a wide variation of the incidence of the disease is seen. Indeed, the current incidence of symptomatic CD varies from 0,1/1000 live births in Denmark to 3.5/1000 in Italy or in Sweden (see table 1) (2,3).

Epidemiological data have shown a decreasing incidence of CD in the British Isles (1) maybe due to a delayed introduction of gluten in the infant diet, but a stable or an increasing incidence in Sweden (4-6), in Finland (7) and in The Netherlands (8). These data also show that the classical severe malabsorption syndrome has become rare and that the disease can have an atypical presentation or even can run an asymptomatic course. Recently, it has also become apparent that CD is underdiagnosed and that symptomatic coeliac patients represent only the tip of an iceberg. In the multi-centre study conducted by Catassi in Italy (9), 17201 schoolchildren were screened for CD by serological tests (diagnosis confirmed by small bowel biopsy). CD was found in 75 children (prevalence 1/220). Among these, only 117 had been previously diagnosed. In Sardinia (10), 17/1607 schoolchildren were found to be coeliacs (prevalence 1/95). Unrecognised CD was found in 31/6127 (prevalence 1/200) in The Netherlands (11) and in 5/427 (prevalence 1/85) in Hungary (12). These studies confirm that the majority of coeliacs with CD go clinically undetected, confirming the iceberg hypothesis.

Table 1. — **Current incidence of symptomatic coeliac disease in childhood**

Country	Incidence (per live births)
Sweden	1 /285 – 350 (6, 31)
North Africa	1 / 700 (2)
Italy	1 /1000 (2)
Spain	1 / 2000 (66)
Jordan	1 / 2800 (67)
The Netherlands	1 /1850 – 3200 (8)
South West France	1 / 3500 (2)
Portugal	1/ 4000 (2)
Denmark	1/ 10000 (68)

The prevalence of coeliac disease among relatives of coeliac patients is significantly greater than in the control population, ranging from 1,9 to 12,8%, although affected relatives often manifest very mild disease or are asymptomatic (13-15).

In addition, some diseases are statistically associated with CD. Indeed, 2 to 4% of patients with insulin-dependent diabetes mellitus (16-19) or auto-immune thyroid diseases (20) are coeliac. Patients with selective IgA deficiency have a tenfold-increased risk of CD (21). The occurrence of small-bowel lymphoma was calculated to be nearly hundredfold greater in coeliac patients compared to controls (22). Other disorders like Down syndrome (23-26) are also associated with CD (see table 2 and 3).

No data were available in Belgium concerning the incidence of CD before 1995. At that time, we decided to conduct a prospective study of the incidence of CD occurring during childhood. During three years, Belgian Paediatric Gastroenterologists were contacted to collect data about new cases of CD diagnosed before the age of 18 years (table 4). Therefore, the incidence of symptomatic CD in our country appears to be low during childhood but comparable with that of neighbouring

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* This consensus was achieved between all members of the LOK/GLEM of Paediatric Gastroenterology (see below) that could be considered as co-author.

Table 2. — **Symptoms, physical signs and diseases assodated with coeliac disease** (69)

Body system	Symptoms
General systemic	Adults: fatigue, anorexia, depression, irritability, general malnutrition with or without weight loss, short stature
	Children: irritability, emotional withdrawal or excessive dependence, nausea, anorexia, malnutrition with abdominal distension, muscle wasting, vomiting and diarrhea
Skin and mucous membranes	Aphthous stomatitis (recurrent), angular cheilitis, dermatitis herpetiformis (in 5 percent of patients with coeliac disease), alopecia areata (especially alopecia universalis), melanosis (chloasma bronzium)
Skeletal system	Osteoporosis/osteopenia, dental enamel defects, arthritis or arthralgia, bone pain
Haematological system	Anaemia (iron deficiency is the most common cause), folic acid deficiency, B12 deficiency (rare), leukopenia, coagulopathy and thrombocytosis
Gastrointestinal system	Diarrhoea, constipation, lactose intolerance, nausea, vomiting, abdominal pain and bloating, pancreatitis, hepatitis, intestinal lymphoma
Immune system	Associated auto-immune diseases : diabetes mellitus type 1, thyroid disease, Sjögren's syndrome, collagen disorders, rheumatoid arthritis, liver disease, selective IgA deficiency
Reproductive system	Delayed puberty, infertility, miscarriages
Neurologic system	Seizures, with or without occipital calcifi cation, unexplained neuropathic illnesses, including ataxia and peripheral neuropathies
Other associated conditions	Down syndrome, IgA nephropathy, fibrosing alveolitis of the lung

countries like France or The Netherlands. Most children are younger than 3 years at the time of the diagnosis. This suggests that reported gluten sensitive children are only those presenting with classical symptoms.

2. *Pathogenesis*

Normally, ingested food does not elicit a local or systemic immune response. Ingestion of protein down- regulates the intestinal immune response to that protein. This phenomenon is known as oral tolerance. In patients with CD, the immune system is abnormally activated by gluten, specifically by the gliadin portion of wheat protein and by the prolamines (insoluble proteins) in rye, barley and presumably oats (27). Studies of patients with coeliac disease using molecular biology techniques demonstrate a strong association with specific HLA class 11 genotypes. More than 95 percent of patients with coeliac disease have a particular type of HLA DQ alpha and beta chain encoded by two genes, HLA-DQA1*0501 and HLA-DQB1*0201 (28). This gene is also found in about 20% of non-affected controls. Therefore, it is suspected that other genes, outside the HLA region, are also involved in CD susceptibility (29). A minority of coeliac patients have the haplotype DR4-DQ8 (DQA1*0301, DQB1*0301). Delaying ingestion of gluten through prolonged breast feeding or dietary habits may change or delay the onset of the disease and the severity of the symptoms (30,31). Exposure to certain viruses has been reported to trigger an immune response in persons genetically predisposed to coeliac disease ; this could occur with adenovirus type 12, which shares a sequence of eight to 12 amino acids with the toxic gliadin fraction (32-34). Thus, coeliac disease is a genetic, immunologically mediated, enteropathy in which intestinal mucosal villi are destroyed by cellular and/or humoral-mediated immunologic reactions to gliadin protein. Loss of the villous functions limits the ability of the small intestine to absorb nutrients, adversely affecting all systems of the body. The immune response to gluten may also occur secondarily in other bodily tissues, an example being dermatitis herpetiformis.

Table 3. — **Diseases statistically assodated with coeliac disease where coeliac disease should be excluded**

Dermatitis herpetiformis	Lymphoma
Down syndrome	Cerebral calcifications
Diabetes mellitus	Thyroid disease
Selective IgA deficiency	Arthritis

Table 4. — **Estimated inddence of reported cases of coeliac disease in childhood in Belgium**

Year	Number of new cases	Median age (range)	Incidence
1995	29	1,2 (0,7- 16,25) years	1 /4100
1996	23	2,4 (1,3-13,5)	1 /5200
1997	30	1,8 (1,0-6,7)	1 /4000

3. *Clinical presentation*

Usually, the first symptoms appear in the months following the introduction of gluten in the diet. The interval between introduction and occurrence of the first symptoms depends on the precocity of introduction of gluten containing food into the diet. Traditionally, symptoms occur between 6 months and 2 years of age (early presentation). In a minority of children, the diagnosis is not made by the age of 2 years. Because symptoms are sometimes ignored or misinterpreted or because the disease is truly symptomless (silent presentation) or atypical (atypical presentation), the diagnosis can be made at any time up to adulthood (late presentation) (35).

a) Early presentations

Within weeks or months after gluten introduction into the diet, the classical syndrome of chronic diarrhoea, failure to thrive and abdominal distension occurs. Stools become more frequent, looser, seldom greasly but sometimes also liquid and dehydration may occur during

exacerbation of the disease. In about 10% of cases, the stools are normal. Anorexia is common and one third of patient's vomit. The general condition of the child is impaired with muscle wasting. He/she is depressed or irritable and psychomotor levelopment does not progress. Weight gain is more affected than height. Blood analysis reveals multiple nutritional deficiencies (36).

b) Late presentations

Growing in age, these presentations become subtler. Decreased appetite with stagnation or limited loss of weight, abnormal stools (or constipation), dental enamel hypoplasia or isolated short stature are the most frequently reported signs of CD in this age group. A mild degree of abdominal distension, microcytic anaemia or decreased bone mineral content may lead to the diagnosis (9,37,38).

c) Atypical and silent presentations

Symptomless or atypical CD is often discovered only through systematic screening in selected populations such as first-degree relatives (27). Severe depression with suicide attempts (39-41), peripheral neuropathy (42), ataxia (43,44), epilepsy with posterior cerebral calcifications (45,46), arthritis (47-49), infertility in men and women or miscarriages (50,51) have been described. CD should always be excluded in the presence of any of these clinical features.

4. *Diagnosis*

a) Serological tests

Serological tests have greatly simplified the procedure for screening CD. Blood samples should be drawn before the patient is on a gluten-free diet and the results need to be confirmed with a small intestinal biopsy. Current screening tests include IgA, IgG antigliadin antibodies and IgA anti-endomysium antibody. Some investigators also perform IgG and IgA anti-reticulin antibodies. Anti-gliadin antibodies assays are very sensitive but lack of specificity (see table 5). On the contrary, anti-endomysium antibody test is highly specific but has a lower sensitivity (52).

Anti-endomysium antibody is an IgA type antibody. Therefore, patients with selective IgA deficiency can be missed (53). In addition, the anti- endomysium test is less sensitive in children below 2 years of age. According to a large-scale study conducted by Burgin-Wolff's group 12% of coeliac children younger than 2 years had no anti-endomysium antibodies (54). Furthermore, very large epidemiological studies have shown positive antiendomysium antibodies without intestinal mucosal atrophy in 2-3% (55, 56).

Recently, tranglutaminase has been described as a target for auto-antibodies useful for the screening of CD (57). Tissue transglutaminase is a widely expressed molecule thought to have a repair function in damaged tissues. It is normally retained in the cytoplasm and released when cells are damaged. Gliadin may act as a potent substrate for tissue transglutaminase, due to the high number of glutamine residues (58). It has been postulated that gliadin- transglutaminase complexes could initiate an immune response after an initial epithelial damaging event. Some laboratories are now running anti-transglutaminase IgA, IgG and IgM tests. More validations studies are needed as well as comparative studies with anti-endomysium antibodies in infants. For the moment it is an ongoing investigation area.

b) Intestinal biopsy

In 1990, the working group of European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) revised criteria for the diagnosis of CD59. The group confirmed the need of establishing the diagnosis with small intestinal biopsy demonstrating villous atrophy followed by a complete resolution of clinical symptoms on a gluten-free diet. A decrease in the serologic markers under gluten free diet is an additional evidence of CD. The working group questioned the previous recommendation of follow-up biopsy to confirm villous recovery. In small children, many other possible causes of enteropathy such as infective enteropathy, post enteritis enteropathy, giardiasis, cow's milk sensitive enteropathy, auto- immune enteropathy and microvillus atrophy can be confounded with CD. In a large series of 3293 patients fulfilling the ESPGAN's criteria, 155 (4,7%) had a negative challenge (60). Most of those children were younger than 2 years at the time of the diagnosis. The need for a challenge test in this age group is controversed and the opinion differs from centre to centre.

Table 5. — **Sensitivity and specificity of serological tests for the screening of coeliac disease** (52)

	Sensitivity (%)	Specificity (%)
IgG anti-gliadin	91 to 100	58 to 96
IgA " "	53 to 100	86 to 100
IgA anti-endomysium	88 to 100	Up to 100
IgG and IgA anti-reticulin	50 to 83	Up to 100

5. *The gluten free diet*

Coeliac patients have to adhere to a gluten free diet permanently. This means that their diet should exclude wheat, rye and barley. Rice and maize can be used as wheat substitutes. However, sensitive methods of detection revealed that commercial gluten free product may represent an unsuspected vehicle of small amounts of gliadin. In fact, the Codex Alimentarius defines a product as free of gluten if the total nitrogen content of the gluten containing cereal grains in a gluten free product does not exceed 50 mg/100 g (61). Although "gluten free" flours may contain up to 40-60 mg of gluten per 100 g, patients from many European countries have healed with those products.

A new discussed issue is whether oats could be allowed. Oats clearly diversifies the diet of patients with CD but oats prolamines are able, in vitro, to activate an immune response in intestinal biopsy specimens (27), while recurrence has not been observed in clinical studies conducted in adults after selective reintroduction (62). Of course, oats containing products should not be contaminated by wheat gliadin during manufacturing or packaging. Sufficient paediatric data are lacking. For this reason most paediatricians do not recommend oats consumption for the moment, at least in infants.

6. *Malignancies*

An increased risk of malignant tumors has long been noted in patients with CD (22), but not when they adhere to a strict gluten free diet (63,64). This is the strongest argument advocating for a life long exclusion diet. In particular, the risk of adenocarcinoma throughout the gastrointestinal tract is elevated, especially at the small bowell level. However, the highest risk concerns intestinal lymphomas (mainly T-cell lymphoma). It is postulated that the sensitivity to gluten increases the number of activated T-cells in the intestinal mucosa leading to a clonal T-cell lymphoma (22).

Consensus

1. *Screening*

Screening should be done when any suggestive symptom (table 6) is present and in all children (and in adults) with associated disease (table 3). CD should also be excluded in relatives of CD patients. Blood samples should be drawn before a symptomatic patient is placed on a gluten-free diet.

IgA, IgG anti-gliadin antibodies and IgA anti-endomysium antibody should be performed. Total IgA levels must be determined once in order to rule out selective IgA deficiency. Although these tests do not have 100% of sensitivity, coeliac disease is very much unlikely when they are negative (54). A confirmation of the diagnosis by a small bowel biopsy in all patients with suggestive serology is mandatory.

Because of their clinical implicaffon, serological tests should be standardised and a quality control should be organised at a nation level. In Belgium, a quality control will start in 1999 and will be organised by the Institute of Hygiene and Epidemiology once a year.

Table 6. — **Symptoms suggestive of coeliac disease**

Chronic diarrhoea	Pubertal delay
Failure to thrive	Dental enamel hypoplasia
Malabsorption	AWominal distension
Nutritional deficiency	Abdominal pain
Short stature	(Psychomotor delay) (Epilepsy)

2. *Diagnosis*

a) First biopsy

Histopathological investigation of the small bowel biopsy is the only acceptable tool to achieve a correct diagnosis of coeliac disease. The biopsy specimen can be obtained either with a forceps (during routine endoscopy) or with a Watson-Crosby capsule after adequate sedation. Histopathological evaluation of formalin fixed / paraffin embedded biopsies should comprise the villous height, the ratio between villous height and depth of the crypts, the number of mitosis in the crypts, the degree of infiltration of the lamina propria by inflammatory cells and of the surface epithelium by lymphocytes (65).

b) Follow-up

After diagnosis, regular follow-up by physical examination and serology must be done during the first year (for example 1, 3, 6 and 12 months after the diagnosis) and at least once a year thereafter.

A second biopsy to prove the normalisation of the intestinal lesions when on gluten free diet is indicated whenever the anti-gliadin or anti-endomysium antibody titers do not decrease, when the clinical evolution is not optimal or when a challenge with a glutencontaining diet is planned.

c) Challenge

In our country, the prevalence of symptomatic CD (at least with early presentation) seems low, due to a later introduction of gluten-containing food into the diet. Besides, other conditions (much more frequent in this age group) can provoke unspecific and sometimes severe changes of the intestinaí mucosa, mimicking those produced by gluten aggression, and comparable symptoms. Therefore, we believe that the challenge remains necessary to confirm the diagnosis. However, in children who were diagnosed after the age of three, a typical flat intestinal mucosa, a satisfactory clinical recovery and a normalisation of the serology when on gluten-free diet can be accepted as an unequivocal diagnosis of CD.

For the challenge, the minimal required dose of gluten is 10 grams per day, given either through an ordinary gluten-containing diet or as gluten-powder added to the gluten-free diet. Serology should be performed before the reintroduction of gluten and followed regularly through the challenge period that can last from 1 month to several years. Small bowel biopsy should be performed before the test and whenever symptoms resume or serology becomes clearly positive.

The gluten challenge is not indicated if the nutritional status of the child is not optimal and should not be performed earlier than 12 months after the diagnosis. The most suitable periods for the challenge are between 2 and 5 years of age or after the puberty in order to give clear and firm dietetic guidelines before entering in

primary school and also to optimise the growth during puberty.

Conclusion

In genetically predisposed subjects, gluten may provoke an immunologically mediated enteropathy. Many patients have a subclinical or only a mildly symptomatic disease instead of the classical presentation with chronic diarrhoea, steatorrhea, weight loss and failure to thrive. Recent epidemiological data have estimated that the real prevalence of CD varies between 1/85 and 1/250, about one-tenth only being clinically suspected. Once a firm diagnosis has been established, the cornerstone of treatment is the gluten free diet. This article gives practical guidelines and recommendations for the management of these patients during childhood.

Members of the Belgian Group of Paediatric Gastroenterology and Nutrition who have contributed to the consensus

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