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Coeliac disease in children

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Although coeliac disease (CD) can present at any age, including the elderly, typical cases often manifest in early childhood. The clinical spectrum in children is wide and includes: (1) typical cases presenting early in life with signs of intestinal malabsorption (chronic diarrhea, weight loss, abdominal distention, etc); (2) atypical cases showing milder, often extra-intestinal, symptoms; (3) silent cases that are occasionally discovered because of serological screening; (4) potential/l atent cases showing isolated positivity of coeliac serology at first testing and eventually the typical intestinal damage later in life. Many CD-associated problems, which were originally described mostly in adults, can indeed be observed in children or adolescents, e.g. reduced bone mineral density, neurological problems and associated autoimmune disorders. It is instrumental that both primary pediatricians and pediatric subspecialists have a high degree of awareness and embrace a 'liberal' use of serological CD tests in order to identify these cases in a timely fashion to prevent serious complications secondary to untreated CD.

Key words: coeliac disease; clinical spectrum; epidemiology; infant feeding; growth; screening; serology.

Coeliac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Gluten is a protein component in wheat, a staple food for most populations in the world, and other cereals (rye and barley). The major predisposing genes are located on the HLA system, namely the HLA-DQ2 and/or DQ8 genotypes found in at least 98% of patients. CD is one of the most common

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lifelong disorders in Europe and in the US. This condition can manifest with a previously unsuspected range of clinical presentations. These include the typical malabsorption syndrome (chronic diarrhea, weight loss, abdominal distention) and a spectrum of symptoms potentially affecting any organ or body system (Table 1). Since CD is often atypical or even silent on clinical ground, many cases remain undiagnosed and exposed to the risk of long term complications, such as osteoporosis, infertility or cancer.[1] There is a growing interest on the social dimension of CD, since, the burden of illness related to this condition is doubtless higher than previously thought.[2] Although CD can present at any age, including the elderly, typical cases often manifest in early childhood. In 1888, Samuel Gee, having drawn attention to the disorder in a lecture delivered on 5th October 1887, at the Hospital for Sick Children, Great Ormond Street, London, produced his classical paper, *On the Coeliac Affection*.[3] Dr Gee described CD as follows: 'There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between 1 and 5 years old…. Signs of the disease are yielded by the faeces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for…'. Remarkably, he already hypothesized that foodstuff could be the trigger of the disease: 'The causes of the disease are obscure. Children who suffer from it are not all weak in constitution. Errors in diet may perhaps be a cause, but what error? Why, out of a family of children all brought up in much the same way, should one alone suffer?' to regulate the food is the main part of treatment…. The allowance of farinaceous food must be small; highly starchy food, rice, sago, corn-flour are unfit'. Despite his great clinical acumen, Dr Gee was not able to

Table 1. Clinical manifestation of CD in children.

Manifestations secondary to untreated CD	Associated diseases (or secondary to untreated CD?)	Genetic associated diseases
CD with classic symptoms	Autoimmune diseases:	Down syndrome
	Type I diabetes	
Abdominal distension	Thyroiditis	Turner syndrome
Anorexia	Sjogren's syndrome	
Chronic or recurrent diarrhea		Williams syndrome
Failure to thrive or weight loss	Neurological and psychological	IgA deficiency
Irritability	disturbances	
Muscle wasting	Ataxia	
Coeliac crisis (rare)	Autism	
	Depression	
CD with non-classic symptoms	Epilepsy with intracranial	
	Calcifications	
Arthritis		
Aphtous stomatitis	IgA nephropathy	
Constipation		
Dental enamel defects	Osteopenia/osteoporosis	
Dermatitis herpetiformis		
Hepatitis		
Iron-deficient anemia		
Pubertal delay		
Recurrent abdominal pain		
Short stature		
Vomiting		

Table 2. Histological and clinical manifestations of coeliac disease in children.

Clinical form	Histological and clinical manifestations
CD with classic symptoms	Fully expressed enteropathy Intestinal symptoms
CD with non-classic symptoms	Fully expressed enteropathy Extra-intestinal manifestations
Silent	Fully expressed enteropathy Minimal complaints or symptom-free (occasionally discovered by serological screening)
Potential	Minimal changes enteropathy or normal small intestinal mucosa Sometimes symptomatic

make the final link between gluten ingestion and coeliac disease, since, he concluded: 'Malted food is better, also rusks or bread cut thin and well toasted on both sides…:'.

CLINICAL SPECTRUM IN CHILDREN

The clinical presentation of CD in children is wide[1,4–9] (Tables 1 and 2, Figure 1).

CD with classic symptoms

This form is characterized by gastrointestinal manifestations starting between 6 and 24 months of age, after the introduction of gluten in the diet. Infants and young children typically present with impaired growth, chronic diarrhea, abdominal distention, muscle wasting and hypotonia, poor appetite and unhappy behaviour (Table 1). Within weeks to months of starting to ingest gluten, weight gain velocity decreases and finally weight loss can be observed. A coeliac crisis, characterized by explosive watery diarrhea, marked abdominal distension, dehydration, electrolyte imbalance, hypotension, and lethargy, was more commonly described at the beginning of this century, while it is now

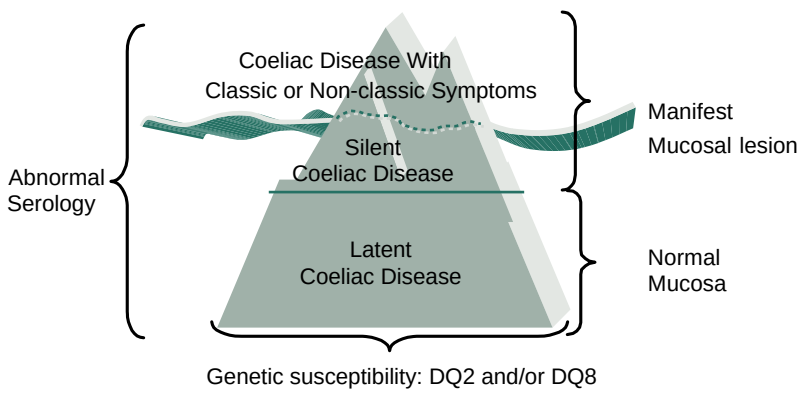

Figure 1. Clinical manifestations in children: the iceberg.

rarely observed. Despite a wide variability between countries, typical CD still represents a common presentation in the pediatric age group.

CD with non-classic symptoms

Currently, there is a general trend of delayed onset of symptomatic CD involving older children (5–7 years old). These children tend to experience unusual intestinal complaints (e.g. recurrent abdominal pain, nausea, vomiting, bloating, and constipation) or extra-intestinal manifestations (e.g. short stature, pubertal delay, iron deficiency, dental enamel defects, abnormalities in liver function test) (Table 1). Dermatitis herpetiformis, a blistering skin disease, is at present regarded as a variant of CD rarely affecting the pediatric population.

Silent CD

CD is defined silent whenever a typical gluten-sensitive enteropathy is occasionally found in a subject who is apparently healthy. Large numbers of silent cases of CD have been reported in at-risk groups (such as subjects with insulin-dependent diabetes and first-degree relatives) and in general population samples enrolled in screening programs. An in-depth clinical examination shows that many of these 'silent' cases are indeed affected with a low-grade intensity illness often associated with decreased psychophysical well-being.

Potential CD

A potential form of CD is diagnosed in subjects showing positivity of anti-endomysium antibodies (AEA) and/or anti-human tissue transglutaminase (hTTG) antibodies, the typical HLA predisposing genotype (DQ2 or DQ8), but a normal or minimally abnormal mucosal architecture (increased intraepithelial count) at the intestinal biopsy. These cases are at-risk of developing a typical CD enteropathy later in life.

Untreated CD is associated with a list of diseases and complications[1] (Table 1).

Associated conditions

An increasing number of studies show that many CD-associated problems, which were originally described mostly in adults, can indeed be observed in children or adolescents[9] (Table 1). Osteoporosis is one of the well-known complications of untreated CD. Persistent villous atrophy is associated with low bone mineral density. Several clinical and epidemiological studies have been published on the association between CD and osteoporosis. However, no conclusive data on the pathogenesis of bone involvement in CD are available yet. Bone alterations were once thought to derive from calcium and vitamin D deficiency secondary to simple intestinal malabsorption. Recently, other causes of bone metabolism impairment have been claimed, including the interaction between cytokines and local/systemic factors influencing bone formation and re-absorption. Further, there is now substantial evidence supporting the concept that a lifelong gluten free diet (GFD) is the only effective measure to restore bone metabolism to an apparent normality. In the pediatric population, a prompt enforcement of a GFD can even lead to a satisfactory recovery of the bone mass. In a group of 14 adolescents with CD, Mora et al found that bone mineral content, bone area and bone mineral

density were significantly lower in CD subjects than in controls.[10] The study also showed a complete recovery of bone density after one year of GFD and maintenance of normal bone mineral density after long-term treatment.[10] Barera and collaborators[11] reached similar conclusions by studying the body composition by dual-energy X-ray absorptiometry in 29 children and adolescents. The authors showed that an appropriate dietary treatment could reverse body-composition abnormalities quickly and the beneficial effects of gluten withdrawal are persistent. Lunt and co-investigators also obtained similar results, showing that a year of GFD in coeliac children allows a virtually complete return in body mass composition.[12] Contrary to pediatric cases, adults affected by osteoporosis secondary to CD do not experience spontaneous recovery, and there are no conclusive data on the efficacy of standard therapies for osteoporosis in reducing the fracture risk. This evidence stresses the need of a timing diagnosis as a preventive intervention to avoid CD complications.

The existence of a syndrome characterized by epilepsy, occipital calcifications and CD is widely accepted.[13] The selective involvement of the occipital region is also suggested by the study of Labate et al,[14] who found an increased prevalence of associated CD in children with partial epilepsy (no brain calcifications) with occipital (2 out of 25 cases) but not in those with centrotemporal spikes (0 out of 47).

Autism is the better-studied association between CD and behavioral disorders in pediatrics. Pavone et al evaluated 20 healthy controls and 120 patients with CD in order to identify behavioral problems and autistic features.[15] Further, the authors screened for CD 11 patients with infantile autism and 11 age- and sex-matched controls. No coeliacs were detected among the group of autistic patients and, although two of them had slightly increased levels of AGA IgG and EMA, subsequent antibodies determinations and jejunal biopsies gave normal results.[15] Moreover none of the coeliacs had a positive DSM-III-R test for infantile autism. These results, together with a growing body of literature, seem to dispute a strong association between CD and autism. Whether gluten per se has a role in causing autistic behaviour outside the contest of CD remains to be established through systematic, well-designed studies.

One of the most controversial issues concerning the clinical presentations of CD in pediatrics is the association between the disease and other autoimmune disorders. The two most accredited theories propose: (1) this association is secondary to a linkage disequilibrium of genes predisposing for both CD and the associated autoimmune disease or, (2) CD leads to the onset of other autoimmune disorders in genetically susceptible individuals. This second hypothesis is supported by the evidence that TTG seems to be only one of the autoantigens involved in gluten-dependent autoimmune reactions. Other autoantigens which are normally 'cryptic' can be unmasked and cause a self-aggressive immunological response following the gliadin-initiated inflammatory process.[16] In fact, persistent stimulation by some pro-inflammatory cytokines such as IFN-γ and TNF-α can cause further processing of autoantigens and their presentation to T-lymphocytes by macrophage-type immunocompetent cells (the so-called antigen-presenting cells). The phenomenon of antigen spreading has been described in well-defined natural models such as Type 1 diabetes, whose clinical manifestations appear after the patient has produced an autoimmune response to various autoantigens (i.e. anti-insulin, anti-beta cell, etc), and might also be present in CD. This would explain the high incidence of autoimmune diseases and the presence of a large number of organ-specific autoantibodies in a certain number of coeliacs on a gluten-containing diet. The question on the possible role of an early treatment of CD on the development of autoimmune complications is still open to debate. Ventura et al reported that children with untreated CD have higher than expected prevalence of organ-specific

autoantibodies (apparently 'gluten-dependent') which tend to disappear after starting the GFD.[17] This study provided laboratory data supporting the hypothesis that a GFD started early in life may prevent the other autoimmune diseases.[17] A recent report from Cataldo and Marino[18] suggest that the increased prevalence of autoimmune disorders is also increased in first-degree relatives of CD patients. The authors reported a 6-fold increase of autoimmune diseases among relatives, a risk that increased with age. A subgroup of these relatives were diagnosed with silent CD and their prevalence of autoimmune disorders as compared to first-degree relatives not affected by CD was significantly higher with an odd ratio of 6.3.[18] The authors concluded that first-degree relatives of CD patients have an increased risk of autoimmune disease, most likely related to unrecognized CD. On the other hand, Sategna-Guidetti et al have recently reported that the duration of gluten exposure in adult coeliacs does not correlate with the risk for autoimmune disorders.[19]

The strong association with autoimmune thyroid disease is confirmed by the study of Larizza et al, who found a 7.8% prevalence of associated CD in children with either autoimmune thyroiditis or Graves disease.[20] The average prevalence of CD among children with type I diabetes mellitus in 26 reports is 4.5% (0.97–16.4%).[21] To quote just a few European data, recent studies found a disease association in 6.3% of diabetics in Germany (205 children),[22] 6.2% in Italy (273 children),[23] 10.4% in Denmark (106 children),[24] 3.0% in Austria (403 children)[25] (33), 3.9% in Spain (177 children).[26] The reported prevalence of associated CD in diabetic children living in North America is just the same as in Europe.[27] Several regional studies showed similar results: 4.6% in Wisconsin (216 children),[28] 7.7% in British Columbia (233 children),[29] 5.1 in Calgary (236 children)[30] and 4.3% in the multicenter USA study.[7]

Several genetic disorders have been associated to CD (Table 2). Among others, Down syndrome in CD is the association that has been better studied. In a multicenter Italian study on 1202 subjects with Down syndrome, 55 coeliacs were found, with a prevalence of this disease association of 4.6%.[31] Other European studies reported a prevalence of associated CD of 6.6% in Spain ($n=284$),[32] 8% in the Netherlands ($n=137$)[33] and 3.9% in Sweden ($n=76$).[34] The situation is not different in the USA, where, the reported prevalence ranges between 3.2 and 10.3%.[35,36] In Down's children CD is not detectable on the basis of clinical findings alone and is, therefore, under-detected. Even when there are symptoms, they may be considered clinically insignificant or possibly attributed to Down's syndrome itself. Nevertheless, the reported resolution or improvement of gastrointestinal complaints on a GFD for all symptomatic patients suggest that identification and treatment can improve the quality of life for these children.[36]

PHYSICAL GROWTH AND CD

Typical cases

The poor growth observed in typical CD depends on (1) reduced food intake and (2) nutrient malabsorption. It has recently been pointed out that signs of malabsorption can also be found in cases showing minimal changes at the intestinal biopsy, due to patchy distribution of the mucosal damage.[37] Weight growth tends to normalize as soon as treatment with the gluten-free diet (GFD) is started.

Although the typical form of CD is still the most frequent presentation in the pediatric age-group, severe growth delay is less commonly seen nowadays, particularly in developed countries. Lopez-Rodriguez et al compared the incidence and the clinical features at diagnosis in Spanish coeliac children diagnosed during either the 80s (group A, $n=61$) or the 90s (group B, $n=96$). The mean weight at diagnosis was much lower in group A (-0.1 ± 1.9 deviation from the 3rd centile) than B (1.5 ± 3.6).[38] Similarly, Swedish CD children born between 1997 and 1999 were at much lower risk of presenting with suboptimal weight gain or suboptimal linear growth than patients born between 1985 and 1989 (Odds ratio of 0.02 and 0.14, respectively).[39] Increased awareness of CD among pediatricians has resulted in shorter delay from symptom onset to diagnosis and consequently to a decrease in the proportion of coeliac children who experience suboptimal growth. It is, however, well possible that changes in environmental factors, e.g. prolonged breast feeding and delayed gluten introduction, might influence both the risk of CD and the disease presentation.

On the other hand, severe growth failure, eventually leading to stunting, is still a hallmark of untreated CD in developing countries. Unsuspected high frequency of disease is increasingly reported in North Africa, Middle East and the Indian continent.[40–41] The highest frequency of CD in the world (5.6%) has been reported in the Saharawis, a population living in Western Sahara. In Saharawi children with CD the degree of stunting is pronounced, with a mean height-for-age of -2.5 ± 1.4 SD of the NCHS/WHO reference population, with 63% of subjects having values < -2 SD.[42] Treatment of CD in poor countries is hampered by the lack of diagnostic facilities and the scarcity of commercially available gluten-free food.

Atypical and screening-detected cases

It is well established that short stature can be the only presenting clinical feature of CD, an issue that has been recently reviewed.[43] In unselected cases admitted for short stature, the prevalence of CD varies from 2.9 to 8.3%, and CD is by far more common than growth hormone (GH) deficiency or any other organic disorder. The pathogenesis of CD-associated short stature is still unclear. Growth retardation has traditionally been attributed to generalized or selective malnutrition, e.g. of zinc. During active disease there can be different alterations in the insulin-like growth factor (IGF-1) system, like reduction of IGF-1 and IGF binding protein 3 (IGF-BP3), increase of IGF-BP2 and IGF-BP1. Likewise, a low response of GH secretion after stimulation that reverts to normal after starting treatment with the GFD has been reported. It is not known whether the impaired pituitary release of GH is related to malnutrition or to the action of circulating gluten peptides in the central nervous system or to an abnormal brain monoamines metabolism. Spontaneous GH secretion did not change in 12 children with CD after a 5–6 weeks standardized gluten challenge.[44] After starting the GFD a significant increase in height velocity is often noticed, especially within 1 year of gluten restriction. The target height is usually reached within 2–3 years. However, the catch up growth is not always complete, probably due to the marked acceleration in bone maturation that parallels the rapid increase in growth velocity.

In developed countries the prevalence of CD among children and adults with Type 1 diabetes (T1D) (mean 4.1%, range 0–10.4) greatly exceeds the prevalence of this condition in the general population. CD associated with diabetes is typically characterized by minor or even lacking symptoms. Cross-sectional studies on the influence of CD on growth and metabolic control in TID children showed conflicting

results. In a longitudinal study on 11 children with TID and CD vs. 22 TID controls, Amin et al found that untreated CD was associated with significantly lower body mass index (BMI) standard deviation score (SDS) (−0.2 vs. 0.7) and lower HbA_{1c} (8.9 vs. 9.8%). Introduction of a GFD led to recovery of BMI-SDS and further improvement in HbA_{1c}. In contrast to controls, in case subjects there was no deterioration in glycemic control during the pubertal years.[45] However, the issue of screening diabetic children for CD is still open to debate[46].

Not surprisingly, the overall process of physical growth is minimally compromised in cases of CD occasionally detected through serological screening of the general population. Normal weight and height data were found in screening-detected CD children in the Denver study by Hoffenberg et al.[6] In the UK Bingley et al found 54 coeliacs on 5470 children screened for CD at age seven. Subjects with positive CD serology were slightly shorter (mean z-score −0.53 vs. 0.23) and weighed less (mean z-score −0.36 vs. 0.18) than matched controls. Growth impairment equaled to about 9 months' growth and weight gain in an average child around that age.[47]

A DIFFERENT CLINICAL SPECTRUM OF PEDIATRIC CD IN THE OLD AND THE NEW CONTINENT ?

Based on recent epidemiological data,[7,48] it is now evident that the true prevalence of CD is similar in Europe and North America. It is also undisputable that less diagnoses are made in the USA, i.e. the coeliac iceberg is more submerged in that country than in Europe, a finding that is the consequence and the cause, at the same time, of poor disease awareness among health care professionals. This situation prompted the US National Institutes of Health to organize a consensus conference that confirmed these discrepancies and outlined the need to close the gap.[49] A question remains, however, unsolved: is the clinical presentation of CD different in the USA from Europe? In other words, is the proportion of early-onset, classic pediatric cases of CD lower in the USA, so providing the rationale on why more cases remain undiagnosed in that country? Unfortunately there are no epidemiological data to answer this question. The general wisdom among health care professionals in the USA has been that the typical coeliac infant with chronic diarrhea, weight loss, abdominal distension and malnutrition is less commonly seen in the USA than in Europe. However, should this be the case, differences in the distribution of causal factors (genetic predisposition and gluten intake) could hardly be claimed since available data suggest that HLA-related predisposing genes (DQ2 and DQ8) are found with the same frequency, both in the general population and patients with CD, in the American and the European populations.[50] A recent North American family-based study found no evidence for linkage or association with a set of non-HLA candidate genes, in agreement with previous European studies; likewise, there are no data to suggest that the level of gluten intake, an important trigger of disease during the first years of life, is different.

Rather, it seems likely that some early-onset cases of CD could be masked and remain undiagnosed in the USA because of the diffuse tendency in this country of the liberal use of the gluten-free diet in the symptomatic treatment of children with diarrhea or suspected food-related allergies.

INFANT DIET AND RISK OF CD AND RELATED AUTOIMMUNE DISORDERS

Can early dietary habits affect the overall frequency of CD? This old hypothesis was again put forward by Ivarsson et al by analyzing a recent 'epidemics of CD' observed in Sweden. These authors suggested that prolonged breast feeding coupled with the introduction of small amount of gluten when the infant is still breastfed, can reduce the risk of developing CD.[51] This issue has indirectly come again on stage with the simultaneous publication on the JAMA of two studies on dietary risk factors of TID, an autoimmune disease sharing pathogenic features with CD. The DAISY study followed up 1183 children born in Denver, Colorado (USA) at increased risk of type 1 diabetes, defined as either HLA genotype (HLA-DRB1*03/04, DQB8) or having a first-degree relative with type 1 diabetes. Children initially exposed to cereals between ages 0 and 3 months and at 7 months or older had increased risk of islet autoimmunity compared with those who were exposed during the fourth through sixth month (hazard ratio of 4.32 and 5.36, respectively).[52] The BABYDIAB study is a prospective German study of 1610 offspring of parents with T1D. Food supplementation with gluten-containing foods before age 3 months was associated with a 5-fold higher risk for the development of islet autoantibodies than after age 3 months. Albeit not statistically significant, a trend toward increased risk of anti-transglutaminase positivity, a specific serological marker of CD, was found in children who received gluten-containing supplements before age 3 months.[53] Although the DAISY and the BABYDIAB studies do not present conclusive evidence suggesting the need to change practice of infant weaning, further prospective studies are required to confirm and extend these findings.[54]

What is the link between the exposure to dietary gluten and the risk of developing autoimmune disorders ? A possible explanation relies on the effects of gluten peptides on the small intestinal permeability to macromolecules. Growing evidence suggests that gluten peptides specifically increase zonulin release from enterocytes.[55] Zonulin is a novel eukaryotic protein that reversibly opens the intestinal tight junctions, thereby leading to increased paracellular passage of antigenic macromolecules in the lamina propria. These early events could trigger abnormal immune reactions in the sub-epithelial environment eventually leading to autoimmune phenomena in genetically susceptible individuals.[56]

Table 3. Unresolved issues in pediatric CD.

Is CD in children and adults the same disease?
What dictates the age of onset of the disease and the type of symptoms? Age of gluten introduction? Amount of gluten?
What are the mechanisms for failure of gluten tolerance? Early gluten introduction? GI infections? Abnormal increase in intestinal permeability?
Role of breast feeding: delay onset of symptoms vs. disease prevention.
Who to screen? How to screen? When to screen?
Should asymptomatic children be always treated?
Association with other autoimmune diseases: gene segregation or cause-effect?

CONCLUSIONS

CD is a common disorder in children as well in adults. The spectrum of clinical presentations is wide, and currently extra-intestinal manifestations (e.g. anemia or short stature) are more common than the classical malabsorption symptoms. A high degree of awareness among health care professionals and a 'liberal' use of serological CD tests can help to identify many of the non-classic cases. The primary care pediatrician has therefore, a central role in this process of case-finding. Many key questions about this unique autoimmune condition remain unanswered (Table 3). The answer to some of these questions may provide a better understanding of the pathophysiological mechanisms involved in the pathogenesis of CD and, possibly of other autoimmune diseases, so paving the way to innovative treatment strategies.

Practice points

- coeliac disease (CD) is a common disorder affecting around 1% of the pediatric population in Western countries
- typical CD cases present early in life with signs of malabsorption (chronic diarrhea, weight loss, abdominal distention, etc)
- besides classical presentations, clinically atypical or even silent cases of CD are common in the pediatric age group, e.g. in children with isolated anemia, short stature, or associated disorders (type 1 diabetes, thyroiditis, Down's syndrome, etc)
- growth problems are frequently encountered in children with CD
- reduced bone mineral density is frequently found in pediatric CD but tend to normalize with treatment

Research agenda

- what dictates the age of onset of the disease and the type of symptoms? Age of gluten introduction? Amount of gluten?
- what are the mechanisms for failure of gluten tolerance? Early gluten introduction? GI infections? Abnormal increase in intestinal permeability?
- role of breast feeding: delay onset of symptoms vs. disease prevention.
- who to screen? How to screen? When to screen?
- should asymptomatic children be always treated?
- association with other autoimmune diseases: gene segregation or cause-effect?

REFERENCES

1. Fasano A & Catassi C. Current approaches to diagnosis and treatment of coeliac disease: an evolving spectrum. *Gastroenterology* 2001; **120:** 636–651.
2. American Gastroenterological Association Medical Position Statement. Coeliac sprue. *Gastroenterology* 2001; **120:** 1522–1525.
3. Gee S. On the coeliac affection. *St Bart Hosp Rep* 1890; **24:** 17–20.

4. Catassi C, Fabiani E, Ratsch IM et al. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr Suppl* 1996; **412:** 29–35.
5. Hill I, Fasano A, Schwartz R et al. The prevalence of coeliac disease in at risk groups of children in United States. *Pediatr Res* 2000; **136:** 86–90.
6. Hoffenberg EJ, MacKenzie T, Barriga KJ et al. A prospective study of the incidence of childhood coeliac disease. *J Pediatr* 2003; **143:** 308–314.
7. Fasano A, Berti I, Gerarduzzi T et al. A multicenter study on the sero-prevalence of coeliac disease in the United States among both at risk and not at risk groups. *Arch Int Med* 2003; **163:** 286–292.
8. Maki M, Mustalahati K, Kokkonen J et al. Prevalence of coeliac disease among children in Finland. *N Engl J Med* 2003; **348:** 2517–2524.
9. Catassi C & Fasano A. New developments in childhood coeliac disease. *Curr Gastroenterol Rep* 2002; **4:** 238–243.
10. Mora S, Barera G, Beccio S et al. A prospective, longitudinal study of the long-term effect ot treatment on bone density in children with coeliac disease. *J Pediatr* 2001; **139:** 516–521.
11. Barera G, Mora S, Brambilla P et al. Body composition in children with coeliac disease and the effects of a gluten-free diet: a prospective case-control study. *Am J Clin Nutr* 2000; **72:** 71–75.
12. Lunt H, Florkowski CM, Bramwell Cook H et al. Bone mineral density, Type 1 diabetes, and coeliac disease. *Diabetes Care* 2001; **24:** 791–792.
13. Gobbi G, Bouquet F, Greco L et al. Coeliac disease, epilepsy, and cerebral calcifications. *Lancet* 1992; **340:** 439–443.
14. Labate A, Gambardella A, Messina D et al. Silent coeliac disease in patients with childhood localization-related epilepsies. *Epilepsia* 2001; **42:** 1153–1155.
15. Pavone L, Fiumara A, Bottaro G et al. Autism and coeliac disease: failure to validate the hypothesis that a link might exist. *Biol Psychiatry* 1997; **42:** 72–75.
16. Fasano A & Catassi C. Current approaches to diagnosis and treatment of coeliac disease: an evolving spectrum. *Gastroenterology* 2001; **120:** 636–651.
17. Ventura A, Magazzù G & Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with coeliac disease. SIGEP Study Group for Autoimmune disorders in coeliac disease. *Gastroenterology* 1999; **117:** 297–303.
18. Cataldo F & Marino V. Increased prevalence of autoimmune diseases in first-degree relatives of patients with coeliac disease. *J Pediatr Gastroenterol Nutr* 2003; **36:** 470–473.
19. Sategna Guidetti C, Solerio E, Scaglione N et al. Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. *Gut* 2001; **49:** 502–505.
20. Larizza D, Calcaterra V, De Giacomo C et al. Coeliac disease in children with autoimmune thyroid disease. *J Pediatr* 2001; **139:** 738–740.
21. Holmes GKT. Screening for coeliac disease in type 1 diabetes. *Arch Dis Child* 2002; **87:** 495–499.
22. Spiekerkoetter U, Seissler J & Wendel U. General screening for coeliac disease is advisable in children with type 1 diabetes. *Horm Metab Res* 2002; **34:** 192–195.
23. Barera G, Bonfanti R, Viscardi M et al. Occurrence of coeliac disease after onset of type 1 diabetes: a 6-year prospective longitudinal study. *Pediatrics* 2002; **109:** 833–838.
24. Hansen D, Bennedbaek FN, Hansen LK et al. High prevalence of coeliac disease in Danish children with type 1 diabetes mellitus. *Acta Paediatr* 2001; **90:** 1238–1243.
25. Schober E, Bittmann B, Granditsch G et al. Screening by anti-endomysium antibody for coeliac disease in diabetic children and adolescents in Austria. *J Pediatr Gastroenterol Nutr* 2000; **30:** 391–396.
26. Roldan MB, Barrio R, Roy G et al. Diagnostic value of serological markers for coeliac disease in diabetic children and adolescents. *J Pediatr Endocrinol Metab* 1998; **11:** 751–756.
27. Rewers M, Liu E, Simmons J et al. Coeliac disease associated with type 1 diabetes mellitus. *Endocrinol Metab Clin North Am* 2004; **33:** 197–214.
28. Aktay AN, Lee PC, Kumar V et al. The prevalence and clinical characteristics of coeliac disease in juvenile diabetes in Wisconsin. *J Pediatr Gastroenterol Nutr* 2001; **33:** 462–465.
29. Gillett PM, Gillett HR, Israel DM et al. High prevalence of coeliac disease in patients with type 1 diabetes detected by antibodies to endomysium and tissue transglutaminase. *Can J Gastroenterol* 2001; **15:** 297–301.
30. Fraser-Reynolds KA, Butzner JD, Stephure DK et al. Use of immunoglobulin A-antiendomysial antibody to screen for coeliac disease in North American children with type 1 diabetes. *Diabetes Care* 1998; **21:** 1985–1989.

31. Bonamico M, Mariani P, Danesi HM et al. Prevalence and clinical picture of coeliac disease in Italian Down syndrome patients: a multicenter study. *J Pediatr Gastroenterol Nutr* 2001; **33:** 139–143.
32. Carnicer J, Farre C, Varea V et al. Prevalence of coeliac disease in Down's syndrome. *Eur J Gastroenterol Hepatol* 2001; **13:** 263–267.
33. Csizmadia CG, Mearin ML, Oren A et al. Accuracy and cost-effectiveness of a new strategy to screen for coeliac disease in children with Down syndrome. *J Pediatr* 2000; **137:** 756–761.
34. Hansson T, Anneren G, Sjoberg O et al. Coeliac disease in relation to immunologic serum markers, trace elements, and HLA-DR and DQ antigens in Swedish children with Down syndrome. *J Pediatr Gastroenterol Nutr* 1999; **29:** 286–292.
35. Mackey J, Treem WR, Worley G et al. Frequency of coeliac disease in individuals with Down syndrome in the United States. *Clin Pediatr* 2001; **40:** 249–252.
36. Book L, Hart A, Black J et al. Prevalence and clinical characteristics of coeliac disease in Down's syndrome in a US study. *Am J Med Gen* 2001; **98:** 70–74.
37. Bonamico M, Mariani P, Thanasi E et al. Patchy villous atrophy of the duodenum in childhood coeliac disease. *J Pediatr Gastroenterol Nutr* 2004; **38:** 204–207.
38. Lopez-Rodriguez MJ, Canal Macias ML, Lavado Garcia JM et al. Epidemiological changes in diagnosed coeliac disease in a population of Spanish children. *Acta Paediatr* 2003; **92:** 165–169.
39. Ludvigsson JF, Ansved P, Fälth-Magnusson K et al. Symptoms and signs have changed in Swedish children with coeliac disease. *J Pediatr Gastroenterol Nutr* 2003; **38:** 181–186.
40. Shahbazkhani B, Forootan M, Merat S et al. Coeliac disease presenting with symptoms of irritable bowel syndrome. *Aliment Pharmacol Ther* 2003; **18:** 231–235.
41. Patwari AK, Anand VK, Kapur G & Narayan S. Clinical and nutritional profile of children with coeliac disease. *Indian Pediatr* 2003; **40:** 337–342.
42. Rätsch IM & Catassi C. Coeliac disease: a potentially treatable health problem of Saharawi refugee children. *Bull WHO* 2001; **79:** 541–545.
43. Iughetti L, Bulgarelli S, Forese S et al. Endocrine aspects of coeliac disease. *J Pediatr Endocrinol Metab* 2003; **16:** 805–818.
44. Jansson UH, Kristiansson B, Albertsson-Wikland K & Bjarnason R. Short-term gluten challenge in children with coeliac disease does not impair spontaneous growth hormone secretion. *J Pediatr Endocrinol Metab* 2003; **16:** 771–778.
45. Amin R, Ahmed ML, Murphy N et al. A longitudinal study of the effects of a gluten-free diet on glycemic control and weight gain in subjects with type 1 diabetes and coeliac disease. *Diabetes Care* 2002; **25:** 1117–1122.
46. Freemark M & Levitsky LL. Screening for coeliac disease in children with type 1 diabetes. *Diabetes Care* 2003; **26:** 1032–1039.
47. Bingley BJ, Williams AJK, Notcross AJ et al. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. *BMJ* 2004; **328:** 322–323.
48. Hoffenberg EJ, Emery LM, Barriga KJ et al. Clinical features of children with screening-identified evidence of coeliac disease. *Pediatrics* 2004; **113:** 1254–1259.
49. National Institutes of Health Consensus Conference on Coeliac Disease: www.consensus.nih.gov.
50. Catassi C & Fasano A. Are clinical presentation and epidemiology different in the USA and Europe?. *Proceedings of the Xth International Symposium on Coeliac Disease*. UK: John Libbey Eurotext Ed, 2003, pp. 139–148.
51. Ivarsson A, Hornell O, Stenlund H & Persson A. Breast-feeding protects against coeliac disease. *Am J Clin Nutr* 2002; **75:** 914–921.
52. Norris JM, Barriga K, Klingensmith G et al. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA* 2003; **290:** 1713–1720.
53. Ziegler AG, Schmid S, Huber D et al. Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA* 2003; **290:** 1721–1728.
54. Atkinson M & Gale EAM. Infant diets and type 1 diabetes. Too early, too late, or just too complicated? *JAMA* 2003; **290:** 1771–1772.
55. Clemente MG, De Virgilis S, Kang JS et al. Early effects of gliadin on enterocyte intracellular signalling involved in intestinal barrier function. *Gut* 2003; **52:** 218–223.
56. Fasano A, Not T, Wang W et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. *Lancet* 2000; **355:** 1518–1519.