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# The Changing Clinical Presentation of Celiac Disease

E. Lebenthal · E. Shteyer · D. Branski

Pediatric Gastroenterology, Division of Pediatrics, Hadassah University Hospitals,  
Jerusalem, Israel

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## Abstract

The incidence, the age at presentation and the features of celiac disease (CD) in children have changed considerably over the past 20 years. CD is now believed to be the most common genetically predetermined condition in humans with a prevalence of 1%. Only approximately one third of the patients presents with diarrhea while one third is diagnosed upon screening, and one fifth presents with non-specific recurrent abdominal pain. Furthermore, it is apparent that most children with CD remain undiagnosed. Another trend is the presentation later in life with atypical symptoms such as anemia, bone disorder and growth failure. The increasing number of CD-associated autoimmune disorders, like insulin-dependent diabetes mellitus, dermatitis herpetiformis, alopecia, Sjögren's syndrome, autoimmune thyroiditis, autoimmune hepatitis, and atrophic gastritis, is apparent. Currently most patients present with subtle or non-gastrointestinal manifestations at a later age. Median age at presentation of children has shifted from 4 to 8 years. Copyright © 2008 S. Karger AG, Basel

The incidence, age at presentation and the features of celiac disease (CD) in children have changed considerably over the past 20 years. In the past, CD presented most commonly either very early in life, between 9 and 24 months, or in the third or fourth decade of life [1–6]. In contrast to the equal sex ratio in children, twice

to thrice as many females were diagnosed in adulthood [6].

## Clinical Presentation – Past and Present

In the past infants and toddlers presented primarily with gastrointestinal manifestations and malabsorption characterized by diarrhea, steatorrhea, abdominal distention, wasted buttocks, hypotonia, growth failure, weight loss, anemia, anorexia, irritability, malnutrition and associated nutritional deficiencies (fat-soluble vitamins, electrolytes, etc.). Some, however, manifested with recurrent vomiting or constipation even with rectal prolapse and intussusception.

In contrast, in recent studies the gastrointestinal manifestations are less prominent at diagnosis. Only 36–42% presented with diarrhea while 26% were diagnosed upon targeted screening and 16% presented with nonspecific recurrent abdominal pain [7, 8]. Furthermore, it is apparent that most children with CD remain undiagnosed.

Another trend is the presentation later in life with atypical symptoms such as anemia, bone disorders or autoimmune diseases [6].

## Diagnosis of Celiac Disease

CD is characterized by small-intestinal mucosal injury and nutrient malabsorption. It is activated in genetically susceptible individuals by the dietary ingestion of proline- and glutamine-rich proteins that are found in wheat, rye, and barley, and are widely termed 'gluten'. Although approximately 1% of the population of the United States is affected by CD, most affected individuals remain undiagnosed [9]. This probably reflects the fact that patients with CD can manifest a spectrum of intestinal and/or extra-intestinal symptoms and, in some cases, they can be relatively asymptomatic, with their disease first being detected by antibody screening because they were identified as being at high risk of developing CD (for example, by being a family member of an affected patient). Presumed disease is best detected by serologic screening for the presence of IgA antibodies specific for tissue transglutaminase, and endomysium, this should be followed by biopsy of the mucosa of the small intestine to establish the ultimate diagnosis [9]. Immunoglobulin A deficiency is 10–15 times more common in patients with CD than in healthy subjects [10]. In such cases, immunoglobulin G (IgG) antibodies should be determined [10]. Life-threatening complications, although relatively rare, can include the development of refractory CD and enteropathy-associated T-cell lymphomas [9].

## Prevalence and Incidence

In 1998 Jenkins et al. [11] presented an incidence of CD of 1:2,500 whereas in a recent study the prevalence among screened healthcare professionals was 1:166 [12].

CD is now believed to be the most common genetically predetermined condition in humans with a childhood prevalence of 1% [13]. In the past CD was considered primarily a disorder of European and Western populations. Currently

there are more and more reports that CD is emerging as a global problem [14].

The incidence of CD in various autoimmune disorders has increased 10- to 30-fold when compared to the general population, and autoimmune disease is associated with clinically asymptomatic CD in many patients [15].

## Associated Autoimmune Diseases

The increasing number of CD-associated autoimmune diseases, like insulin-dependent diabetes mellitus, dermatitis herpetiformis, alopecia, Sjögren's syndrome, autoimmune thyroiditis, autoimmune hepatitis, atrophic gastritis and more, raises the question whether or not the changes in clinical presentation and increase in prevalence of autoimmune disorders are related to changing practices in breastfeeding, infant feeding, including time of gluten introduction into the diet, quantity of gluten consumption, and late diagnosis of CD [16]. In a recent publication, Norris et al. [17] reported a lower incidence of developing CD autoimmunity when gluten is introduced between 4 and 6 months of age while the infant is still being breastfed.

A significant protection effect on the incidence of CD was suggested by the duration of breastfeeding (exclusive breastfeeding as well as partial breastfeeding). The data do not support the influence of age at first dietary gluten exposure. On the other hand it appears to affect the age at onset of symptoms and, is associated with the appearance and increase of CD-associated autoimmune diseases [18].

On the other hand diabetes type 1 and other associated autoimmune diseases have an increased intestinal permeability [19]. In addition, diabetes type 1 patients have upregulation of zonulin, a protein that modulates intestinal permeability [20]. Zonulin upregulation seems to precede the onset of disease. There might be a possible link between increased intestinal permeability, gluten

antigens and the development of autoimmunity [20].

Another plausible cause for the increase in associated autoimmune diseases and the change in clinical manifestations can be due to a change in the incidence and prevalence of episodes of acute gastroenteritis early in life and a change in the response of the gut immune system and T cells [21]. A prospective study in children who carried CD human leukocyte antigens DQ2 and DQ8 [22] revealed that a high frequency of rotavirus infections may increase the risk of CD autoimmunity in childhood in genetically predisposed individuals [22].

Furthermore, a decrease in severe and prolonged diarrhea requiring hospitalization early in life might be a cause for the current modified symptoms, appearance and late diagnosis of CD [22].

### **The Modified Clinical Presentation**

In recent studies in children, only 36–42% had gastrointestinal manifestations (diarrhea and protuberant abdomen) at presentation [7, 8], whereas in adults the gastrointestinal manifestations were 43%. On the other hand, larger numbers present with relatively nonspecific and subtle symptoms, such as recurrent abdominal pain, anemia and even constipation [7, 8]. Target screening of high risk groups (insulin-dependent diabetes mellitus, Down's syndrome or autoimmune thyroiditis, autoimmune liver disease, etc.) reveal an increasing number of asymptomatic patients with CD.

Currently, most patients present with subtle or non-gastrointestinal manifestations at a later age [7, 8]. The median age at presentation of children shifted from 4 to 8 years [7]. Data from studies on adults with CD are similar to children [23] reporting only 43% with gastrointestinal manifestations in 1993, compared to 73% prior to 1993, and delay in the diagnosis of CD. The

Canadian Celiac Health survey [24] reported 2,681 adult patients in whom there was a mean delay in diagnosis of 11.7 years. In 40% of these patients the diagnoses prior to the ultimate diagnosis of CD were anemia (40%), stress (31%), and irritable bowel syndrome (29%), while osteoporosis and low bone density were found in a high percentage (35%) [24].

### **Disorders Associated with Celiac Disease**

Over the years there have been descriptions of many conditions associated with CD (table 1). The increasing number of associated autoimmune diseases in long-standing CD patients raises concerns about the association to the delayed and late diagnosis of CD, as well as the implementation, use and compliance with a gluten-free diet. The relationship between the increased frequency of autoimmune diseases and CD is attributed to a common genetic and immunological mechanism, as well as the presence of CD itself [25]. Gluten withdrawal does not prevent the development of autoimmune diseases [26]; however, insulin-dependent diabetes and thyroid-specific autoantibodies may disappear in patients after they start a gluten-free diet [26], suggesting a relationship between the autoimmune process and gluten exposure [27]. Improvement may occur in cardiomyopathy, thyroiditis and peripheral neuropathy on a gluten-free diet [24]. However, associated autoimmune disorders generally do not improve with a gluten-free diet [25].

Genetic diseases associated with an increased prevalence of CD, such as Down's syndrome or Turner's syndrome, are raising questions related to the genetic defects in CD that have not been explored.

### **Conclusion**

Only a small number of patients present with the 'classical' symptoms of marked weight loss,

malnutrition, and steatorrhea. In contrast, many individuals with CD manifest predominantly extra-intestinal symptoms and nonspecific findings of growth failure, unexplained iron deficiency anemia, recurrent abdominal pain, and osteoporosis, or are relatively asymptomatic like individuals identified only because they have affected family members or associated diseases.

**Table 1.** Disorders associated with celiac disease (CD) with approximate percentage of positive CD in screening

<b>Autoimmune disorders</b>	
Insulin-dependent diabetes	8–10%
Sjögren's syndrome	10%
Dermatitis herpetiformis	6–7%
Addison's disease	8%
Autoimmune hepatitis	6%
Autoimmune cholangitis	3.5%
Alopecia areata	3–4%
Connective tissue disease	2–3%
Atrophic gastritis	
<b>Syndromes</b>	
Down's syndrome	5–10%
Turner's syndrome	6%
Beckwith-Wiedemann syndrome	
<b>Neurological disorders</b>	
Neuropathy	5%
Celiac ataxia	
Intractable epilepsy and parieto-occipital calcifications	
Migraine	
<b>Liver diseases</b>	
Primary biliary cirrhosis	5–10%
Elevated transaminase levels	9%

**Table 1.** (continued)

<b>Cardiac diseases</b>	
Autoimmune myocarditis	4%
Idiopathic dilated cardiomyopathy	2–4%
Pericarditis	
<b>Endocrinological diseases</b>	
Secondary hypopituitarism	
Amenorrhea	
Hypogonadism	
<b>Bone diseases</b>	
Osteoporosis	2–7%
Bone fractures	
Enamel hypoplasia	
<b>Skin diseases</b>	
Atopic dermatitis	
Chronic urticaria	
Cutaneous vasculitis	
Psoriasis	
<b>Hematological and immunologic disorders</b>	
Iron deficiency anemia	
IgA deficiency	
Hyposplenism	
<b>Nephrological manifestations</b>	
IgA nephropathy/Henoch-Schönlein purpura	
Immune complex glomerulonephritis	
Nephrotic syndrome	
<b>Pulmonary manifestations</b>	
Autoimmune fibrosing alveolitis	
Lymphocytic interstitial pneumonia	
Desquamative interstitial pneumonitis	
<b>Gastrointestinal diseases</b>	
Crohn's disease	
Ulcerative colitis	
Microscopic colitis	
Enteropathy-associated T-cell lymphoma	
<b>Others</b>	
Aphthous stomatitis	

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David Branski, MD  
 Division of Pediatrics, Hadassah University Hospitals  
 POB 12000  
 Jerusalem 91120 (Israel)  
 Tel. +972 2 6777 543, Fax +972 2 6434 579, E-Mail branski@hadassah.org.il