Chapter 8
Presentation of Celiac Disease in Children and Adults

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Celiac disease (CD) is common; however, the vast majority of people with CD are undiagnosed [1, 2]. Originally considered a malabsorptive condition of childhood [3–5], it is now diagnosed at any age [6–8]. The wide spectrum of presenting symptoms of affected individuals makes the condition challenging to diagnose in some. Symptoms vary significantly from childhood to adulthood, and, even among children, distinct trends in presentations may be seen according to age.

Terminology and Definitions

There have been several terms used to classify the presentations of CD in both childhood and adulthood. Such terms as "typical," "atypical," "classical," "nonclassical," "silent," "asymptomatic," "latent," and "potential celiac disease" have added confusion to the topic. Recently, consensus documents have attempted to bring clarity to the field [9]. When used to describe the presentation of CD, the terms "typical" and "atypical" are particularly perplexing, as they suggest the opposite of what they are intended to reflect. "Typical" symptoms are now far less common than the "atypical." In this regard the terms "classical" and "nonclassical" are preferable since they refer to the historical perception of the nature of disease presentations while not alluding to their frequency. Additionally, the term "asymptomatic" is preferred to "silent" in referring to those with CD without symptoms.

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Presenting Symptoms of Celiac Disease in Children and Adults

The majority of children with CD tend to present in one of three ways: with abdominal pain or distension, with growth issues, or through an asymptomatic presentation brought about by serological screening performed due to an associated condition or family history of CD [10–14].

Very young children commonly present with "classical," usually diarrheal, symptoms [15–18]. However, in our recent experience and as described by other authors, the classical presentation of childhood CD is no longer the most common. Children presenting with diarrhea are currently among the minority when all patients with CD are considered; only 9 % of our pediatric patients presented this way, suggesting that diarrhea and malabsorption are no longer the characteristic manifestations of this disease among young patients [10, 19, 20]. Moreover, the bulk of children with diarrheal presentations are below 2 years of age [10, 21]. In contrast, older children and adolescents more often present with nonclassical or "atypical" gastrointestinal complaints such as abdominal pain, vomiting, and constipation and extraintestinal symptoms such as arthritis, neurologic symptoms, or anemia. Some may have asymptomatic disease, diagnosed upon serological screening [11, 17] (Fig. 8.1). Screening was the mode of presentation of about 25 % of children seen in our center [19] and includes family members of adults and children previously diagnosed with CD, many of whom were asymptomatic, as well as those with associated autoimmune conditions [10].

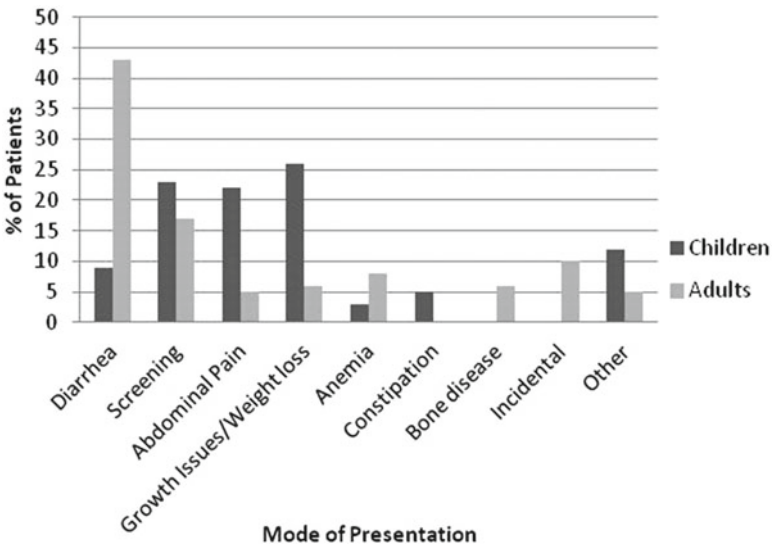

Fig. 8.1 Presenting symptoms of children and adults with CD. Adults $n = 1{,}499$, children $n = 318$

Among adults, the major mode of presentation is diarrhea, comprising about 50 % of patients [22, 23]. One potential explanation for the increase in diarrheal presentations in this group is the relative infrequency with which young adults present for routine medical care, resulting in missed opportunities to unearth subtle symptoms of CD. Diarrheal symptoms may drive many such patients to seek medical attention early. However, the elderly had a similar rate of diarrhea presentations as young adults in one study [23].

Serological screening of at-risk groups, responsible for increased detection of CD in children, is an important mode of presentation among adults as well [24]. About 10 % of those adults recently diagnosed with CD at our center presented through screening of at-risk groups (see Fig. 8.1). However, not all of those individuals detected by screening are in fact asymptomatic [25, 26].

Anemia is more frequently seen at presentation in adults compared to children [27]. Anemia as a presenting symptom of CD is mainly due to iron deficiency, though anemia due to nutritional factors and chronic disease may also be present at diagnosis of CD [28, 29].

Osteoporosis is another presentation of CD in adults. Reduced bone density is common in patients with CD [30, 31], and there is increased fracture risk [32, 33]. Bone mineral density correlated inversely with the duodenal Marsh stage in one study of Spanish adults with CD, though differences in parathyroid hormone and IGF-1 among patients with and without villous atrophy were not observed [34]. A study from the United States demonstrated an increased prevalence of CD among osteoporotic patients [35], though this was not seen in other studies from France and among postmenopausal women in Turkey [36, 37]. Low bone mineral density is commonly seen in children with CD at the time of diagnosis, and some reversal is seen upon dietary treatment [38, 39]. However, this is not typically a presenting symptom of CD in children, and this finding appears to be unrelated to other symptoms at diagnosis [40]. Early diagnosis of children with CD and early management of existing metabolic bone disease may be an important factor in preventing adult osteoporosis related to CD.

Another important mode of presentation among adults is the incidental recognition of signs of villous atrophy due to CD during endoscopy performed for any reason [41]. Upper endoscopy in adults is commonly performed for gastroesophageal reflux disease (GERD). Increasingly biopsies of the duodenum are performed at endoscopy, regardless of the appearance of the duodenal mucosa. When CD is recognized and treated in people with GERD, improvement in the reflux is frequently noted [42]. There is a reasonable argument for routine duodenal biopsies during endoscopy for adults as is the usual practice for pediatric gastroenterologists [43].

Other presentations in adults include dermatitis herpetiformis, irritable bowel syndrome, bloating, and chronic fatigue as well as a variety of neurological presentations [44]. Many of the symptoms of CD are common, frequently seen among patients attending primary care visits [45]. In a multicenter North American primary care screening study involving patients with a variety of symptoms, including

bloating, fatigue, recurrent abdominal pain, and IBS, screening for CD resulted in a 40-fold increase in the rate of CD diagnosis [46].

Recurrent episodes of abdominal pain are seen prior to diagnosis in adults and children [19, 47], but seems to occur less frequently in adults. These episodes of pain may be due to small intestinal intussusceptions that appear commonly in CD [48, 49]. Intussusceptions are more prevalent among children with CD than the general population [50].

The reason that some patients present with diarrhea and others are asymptomatic is not clear, for there is no correlation of a diarrheal presentation with severity of villous atrophy [51], nor length of bowel involved as assessed by video capsule endoscopy [52]. Neurohumoral mechanisms may be important in determining the presence of symptoms. In one study, patients with CD had increased mucosal 5-hydroxy tryptamine content and enhanced release from the upper small bowel, which correlates with postprandial dyspepsia [53].

There are geographic differences in the presentation of CD. While our institutional observations of age-related differences in disease presentation have been described by other authors as well [10, 11], greater frequencies of diarrheal presentations among children have been noted in countries such as Spain [15], India [54], and Sudan [55]. Particularly in developing countries, the malnutrition associated with CD in children may be severe, and in some cases refeeding syndrome is seen upon treatment [56]. Among adults, similar differences have been cited, with Turkish adults presenting at a younger age and more frequently with classic symptoms than American adults [57].

Childhood Factors Influencing Disease Onset and Presentation

Several factors determined during the perinatal period and infancy may impact the presentation of CD. Route of delivery seems to play a role, as there is an association between cesarean delivery and development of CD [58], especially elective cesarean section [59]. Summer birth was associated with an increased risk of CD diagnosis in children [60], as well as in adults [61]. In the latter study, however, the effect was less pronounced among adults, and the association overall did not seem to be influenced by infectious exposure [60]. Breast-feeding practices additionally appear to influence the mode of presentation. Children who were exclusively breast-fed were less likely to present with failure to thrive and short stature [62]. Breast-feeding also contributes to delaying the age of presentation of the disease [63–65]. Differences in the microbiota of the infant gut caused by genetics, methods of delivery, and infant feeding, and resulting immune alterations, may explain these observations [66–69].

The timing of gluten introduction in infancy is a subject of ongoing study. Gluten introduction either too early or too late in infancy may pose a risk of CD autoimmunity in genetically predisposed infants [70, 71]. In another study, infants appeared to be at less risk of celiac autoimmunity with delayed gluten introduction, and

differences in the microbiota were observed between infants with genetic risk for CD and those from a general pool of controls [72]. In addition, large quantities of gluten at the time of introduction were associated with a greater risk for developing CD [64].

At-Risk Individuals and Associated Conditions

The most frequently screened group is family members of individuals with CD, and this mode of presentation is important in both adults and children [25]. Several studies have shown that about 4–10 % of first-degree relatives have the disease [73]. The greatest risk is among siblings of affected individuals [74], but the risk extends to second-degree relatives as well [25, 74].

The list of conditions associated with CD is quite extensive, and there are specific individuals who are frequently screened for CD. The association between CD and type 1 diabetes in children is well described [75]. The coexistence of both diseases also occurs in adults [76, 77]. The presentation of diabetes generally precedes that of CD. While an increased prevalence of CD has been described in adults with autoimmune thyroid disease [78, 79], this association may not exist in children [80].

Children and adolescents with autoimmune liver disease, including biliary disease, have a high prevalence of CD [81, 82]. An increased prevalence of CD has additionally been identified in children with Down syndrome (7 %) [83], Turner syndrome (6.4 %) [84], and Williams syndrome (9.5 %) [85].

Other conditions that have been associated with CD include autoimmune myocarditis; idiopathic dilated cardiomyopathy; Sjögren's syndrome; IgA deficiency; Addison's disease; IgA nephropathy; sarcoidosis; primary hyperparathyroidism; alopecia areata; neurological abnormalities including epilepsy, ataxia, and neuropathy; atopy; inflammatory bowel disease; psoriasis; and chronic urticaria.

The association with CD and autoimmune disorders is great. About 30 % of adult patients with CD have one or more autoimmune disorders [86, 87], compared to about 3 % in the general population [88]. The mechanism of this prominent association is unclear. It has been suggested that the increase is associated with the duration of exposure to gluten [87]; however, this was not confirmed by other studies [89, 90]. In a study from France, however, after the diagnosis of CD, those that were strictly adherent to the gluten-free diet acquired fewer autoimmune disorders than those who were not compliant with the diet [91]. This suggests that the diet is protective against the development of autoimmune diseases. However, initiation of a gluten-free diet did not prevent progression of established autoimmune thyroid disease after the diagnosis of CD [92].

CD is also associated with infertility, in both women [93–95] and men [96]. Screening infertile women detects undiagnosed CD [97], and fertility improves after diagnosis of CD [98].

The Shifting Presentation of Celiac Disease

Most adults with CD diagnosed prior to 1980 presented with diarrhea [22]. With the advent of serological tests in the 1980s, the spectrum of clinical manifestations became apparent. Additionally, since the initial availability of sensitive and specific serological assays over the past two decades, the gap between initial presentation and diagnosis in symptomatic children has been gradually fading [99, 100]. This reduction in duration of symptoms has also been documented in adults [22]. Serological screening was an important mode of presentation among our patients, representing nearly one-quarter of all children recently diagnosed [19] and 17 % of adults diagnosed since 1990 [24].

Independent of the impact of improved screening tools, the presentation of CD is changing over time, and "classical" presentations are becoming less common. An overall decrease in the prevalence of diarrheal presentations over the past two decades, accompanied by an increase in atypical manifestations of the disease, has been well described in both adults and children [10, 16, 22, 24]. Children are being diagnosed at an older age [20, 101]. Overweight and obese children and adolescents with CD are now frequently identified [19, 102, 103]. The majority of North American children, in our series, had a normal body mass index, whereas the minority of children studied were underweight [19]. While more widespread use of serologic markers has facilitated diagnosis of CD in children [10], this alone does not entirely explain the decrease in diarrheal manifestations, as many long-term studies of adult and pediatric patients predating the use of these markers have documented this shift in clinical presentation [20, 22]. Awareness of the various manifestations of this disease is critical in rendering the diagnosis.

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