International Journal of Celiac Disease, 2014, Vol. 2, No. 3, 76-85
Available online at http://pubs.sciepub.com/ijcd/2/3/8

DOI:10.12691/ijcd-2-3-8

Non-classical Celiac Disease: Often Missed

Prashant Singh[1], Govind K Makharia[2,*]

[1]Massachusetts General Hospital, Boston, USA
[2]Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, Ansari nagar, New Delhi, India
*Corresponding author: govindmakharia@gmail.com, govindmakharia@aiims.ac.in

Received September 01, 2014; Revised September 10, 2014; Accepted September 13, 2014

Abstract Celiac disease (CeD) is an immune-mediated enteropathy triggered by ingestion of gluten in genetically susceptible individuals. CeD is a global disease and estimated to affect approximately one percent of the global population. With advent of simple serological tests for the diagnosis, the number of individuals diagnosed with CeD is increasing exponentially. It was initially thought that gluten hypersensitivity in CeD is limited to small intestine only and all other features are secondary to malabsorption, but it is now recognized that the hypersensitivity to gluten is not limited to small intestine alone and may affect other organs such as skin, brain, and bones independent of intestinal involvement. CeD is now considered a multi-system disorder and their clinical presentation may be with gastrointestinal symptoms, called "classical CeD" or more often with non-gastrointestinal symptoms called "non-classical CeD". These patients may present with short stature, anemia, liver dysfunction (asymptomatic increase in transaminases, chronic liver disease, autoimmune hepatitis), cutaneous manifestations (dermatitis herpetiformis, oral ulcers), reproductive diseases (infertility, recurrent abortions), neurological manifestations (ataxia, peripheral neuropathy), and metabolic disorders (osteopenia/osteoporosis). What determines these variable phenotypes remain unclear but likely is a result of genetic as well as environmental factors. Many of these patients with non-classical CeD are likely to report to specialists other than gastroenterologists such as hematologists, endocrinologists, rheumatologists or gynecologists. Unfortunately, the awareness about non-classical presentations of CeD amongst health care professionals remains low. There is an urgent need to increase awareness among health care professionals about varied manifestations of CeD in order to decrease the burden of undiagnosed CeD.

Keywords: *short stature, anemia, autoimmune hepatitis, gluten ataxia, dermatitis herpatiformis, atypical celiac disease, cirrhosis of liver*

Cite This Article: Prashant Singh, and Govind K Makharia, "Non-classical Celiac Disease: Often Missed." *International Journal of Celiac Disease*, vol. 2, no. 3 (2014): 76-85. doi: 10.12691/ijcd-2-3-8.

1. Introduction

Celiac disease (CeD) is a chronic small intestinal immune-mediated enteropathy triggered by ingestion of a complex protein, gluten, present in cereals such as wheat barley and rye in genetically predisposed individuals. [1] Gluten undergoes deamidation by tissue transglutaminase (tTG) in small intestinal mucosa which allows it to bind to human leukocyte antigen (HLA)-DQ2 and -DQ8, subsequently triggering an inflammatory cascade leading to small intestinal mucosal damage, a hallmark of CeD [1].

It was initially thought that gluten hypersensitivity in CeD is limited to the small intestine only and all other features are secondary to malabsorption, but it is now recognized that many of the features of CeD may not be explained on the basis of malabsorption alone. [2,3,4,5] It is now recognized that the hypersensitivity to gluten is not limited to the small intestine alone and may affect other organs such as skin, brain, and bones independent of intestinal involvement. [2,3,4,5] Many patients with dermatitis herpetiformis and gluten ataxia for example have normal intestinal mucosal histology. [2,3] Since our knowledge about this disease has grown over the last few decades, CeD is now considered a multi-system disorder and therefore can have varieties of clinical manifestations including both gastrointestinal and non-gastrointestinal.

CeD was once considered to be a disease of children and cared mainly by pediatricians and not many adult patients were diagnosed to have CeD. Furthermore the spectrum of phenotypic expression of CeD is very wide and extends from completely asymptomatic to severely symptomatic disease. [1] While some patients have fully expressed disease, in others the disease is expressed in milder form. [1] In some, the disease manifests clinically in early childhood, while in others disease becomes apparent at a later age. [6,7] Furthermore, there are also circumstances when the clinical expression of disease is abrupt and explosive in a relatively asymptomatic individual, which partly may be due to either occurrence of a second hit or development of a complication.

2. Why There is so much Variation in the Expression of CeD?

While CeD occurs due to gluten peptide induced both acquired and innate immune response in a genetically susceptible individual; what decides the clinical

phenotypic expression is not well known. [8] One of the well-known factors which affect the clinical expression of the disease is HLA-DQ2 or -DQ8 homozygosity. [9,10,11,12] Other factors which may have affect on the clinical expression of the disease include time of exposure to gluten, and the amount of gluten ingestion. [13,14] While presence of HLA-haplotype explains approximately 40% of risk conferred, there is a strong likelihood of other genetic factors playing a role in the expression of the disease. [15] Based on the available evidences, it has been hypothesized that CeD is a multi-genetic disease and clinical expression of the disease is decided by a combination of major genes and minor genes, once they already have susceptible HLA- haplotype and are exposed to gluten, the last two being the essential factors.

With widespread availability of serological tests, less cumbersome diagnostic criteria and increasing awareness, CeD is being increasingly diagnosed in patients presenting with both gastrointestinal (Classical) and non-gastrointestinal (non-classical) symptoms. [16] CeD is now considered a multi-system disorder and their clinical presentation may be with gastrointestinal symptoms, called "classical CeD" or more often with non-gastrointestinal symptoms called "non-classical CeD". An expert panel has recently provided some of the relevant clinical terminologies related with CeD which can should be used in clinical and research settings [1].

Classic or typical CeD is defined as gluten induced enteropathy presenting with signs/symptoms of malabsorption (such as diarrhea or malnutrition) or a malabsorption syndrome (indicated by weight loss, steatorrhea, vitamin deficiencies and hypoalbuminemia). [1] Atypical or non-classic CeD is defined as gluten induced enteropathy presenting with signs/symptoms other than those mentioned above. [1] These patients may present with short stature, anemia, liver dysfunction (asymptomatic increase in transaminases, chronic liver disease, autoimmune hepatitis), cutaneous manifestations (dermatitis herpetiformis, oral ulcers), reproductive diseases (infertility, recurrent abortions), neurological manifestations (ataxia, peripheral neuropathy), and metabolic disorders (osteopenia/osteoporosis). [1,6,17] In addition, they could also present with gastrointestinal symptoms, which are not included in classical CeD presentation such as constipation, dyspepsia, or irritable bowel syndrome. [1] Fatigue may be one of the manifestations of CeD [18,19].

The proportion of patients with CeD who have been diagnosed in comparison to those who still remain undiagnosed is high in certain European countries such as Italy and Finland; while in other countries including United States this proportion is still lower. [20,21] It is predicted that upto 83%-95% of patients with CeD in the United States still remains undiagnosed. [22,23,24,25] In a cohort of 13,971 children from UK, using anti-endomysial antibody serology, 140 children were expected to have CeD, while only 12 children were diagnosed with CeD by age of 14 years suggesting that more than 90% of children with CeD were not diagnosed. [26] These studies suggest that the diagnosis of CeD is still not considered even in countries having excellent healthcare services. A part of this could be due to under-recognition of atypical forms of CeD. [26] In this review, we have highlighted some of the non-classical manifestations of CeD, which often are missed and the reasons of why are they missed.

3. Hematological Manifestations

Anemia is present in 12% to 69% of patients with CeD in western countries and 85%-90% of patients with CeD in India. [27,28,29,30] Iron deficiency is the commonest cause of anemia in CeD. [27,28] Several studies from North America, Europe and India have suggested that iron deficiency could be the sole manifestation of CeD even in the absence of diarrhea in them. [31,32,33,34,35] In addition, 8% to 41% of patients with CeD have vitamin B_{12} deficiency at the time of diagnosis. [30,36,37] The exact reason for deficiency of vitamin B12 is not known, it however may be due to under-secretion of gastric acid, bacterial overgrowth, and occurrence of co-existent autoimmune gastritis. Folate deficiency has also been reported in patients with CeD. [30,38] Anemia in patients with CeD has been shown to respond very well to gluten free diet (GFD) and iron/vitamin supplementation [28,30].

Conversely, approximately 5-10% of patients with chronic anemia are found to have CeD as a cause of anaemia. [33,34,38] Many of them are investigated extensively and referred as refractory anaemia before a diagnosis of CeD is made in them. The abovementioned observations suggest that CeD as a cause of anemia in clinical practice is still under-recognized and under-investigated [33].

Which patients with anemia should be screened for CeD in a resource limited setting? In developing countries such as India where anemia is far more common than developed countries; it may not be feasible to screen every anemic person for CeD. In a study from India, younger age of onset, longer duration of disease and presence of diarrhea were found to be independent predictors of CeD in patients presenting with anemia. [34] Furthermore all patients with anemia refractory to iron supplementation should also be screened for CeD [30,34].

Recent evidences suggest that CeD patients with anemia have significantly longer duration of symptoms, lower albumin levels, higher anti-tTG levels, and higher proportion have abnormal d xylose tests and severe villous atrophy in comparison to CeD patients having normal hemoglobin. [29] Thus presence of anemia in a patients with CeD denote advanced enteropathy.

It is also important to note that upto 15%-35% of patients with CeD do not have anemia. [28,29] Why some patients with CeD do not have anemia? Absorptive functions of the intestine are maintained till the intestinal mucosal damage is far advanced. In addition, human body has a large reserve of iron, folate and Vitamin B_{12}. [29] Anemia develops only when these reserves are depleted significantly. CeD should thus be considered even in patients with normal hemoglobin levels if there are other features to suspect a diagnosis [29].

The hematological manifestations of CeD are not limited to anemia but other cell lines and coagulation cascade is also affected. [30] Up to 60% of CeD patients can have thrombocytosis but only a minority of patients have thrombocytopenia. [30] Thrombocytosis is believed to occur due to presence of an active inflammatory state, iron deficiency state and hyposplenism. [30] Folate and

copper deficiencies can lead to leucopenia in a minority of patients with CeD [30].

Venous thromboembolism has been well reported in CeD and could be presenting manifestation as in several cases presenting with Budd-Chiari syndrome. [30,39,40] It is believed to be multi-factorial such as hyperhomocystenemia, deficiencies of Vitamin K dependent anti-coagulant proteins and increased levels of pro-coagulant proteins like thrombin activable fibrinolysis inhibitors. [30] On the other hand, patients with CeD might also have increased bleeding tendencies secondary to deficiencies of vitamin K dependent coagulation factors. [30] A recent study found that 18.5% of untreated CeD patients had prolongation of prothrombin time and these patients were also more likely to present with anemia and abnormal iron proteins [41].

4. Endocrinological Manifestations

Failure to gain height is a concern both for children as well as their parents. For past one decade, CeD is being increasingly recognized as an important cause of short stature all across the world. The prevalence of CeD in patients with short stature varies widely from 4.7% to 15.2% in various countries. [42,43,44,45,46] The prevalence of CeD in patients with idiopathic short stature is even higher and ranges from 21% to 48.7%. [42,47,48,49] Unlike many of the other causes of short stature such as genetic and familial short stature, which do not respond to specific therapeutic intervention; the growth velocity improves in children with CeD with institution of GFD. [45,46] A negative correlation has been shown between height at the end of 4 years of follow up and age of diagnosis of CeD. [50] A complete catch-up in height has been reported if CeD is diagnosed early. [46,51,52] It is therefore extremely important to make an early diagnosis to prevent the loss of opportunity to gain age specific height velocity.

Which patients with short stature should be screened for CeD? Patients with anemia and diarrhea have increased odds of having CeD as cause for failure to thrive. Studies have shown that a significant proportion of short stature patients with CeD may not have either anemia or diarrhea. [44] In a cohort of Indian children with short stature, 30% and 12% children with CeD did not have diarrhea and anemia, respectively. [43] Therefore, all the patients with short stature should be screened for CeD irrespective of presence of gastrointestinal or hematological manifestations. In view of high prevalence of CeD among short stature patients and low cost of celiac serological tests, celiac serological test should be included as a first line investigation in the diagnostic algorithm of short stature.

The pathogenesis of short stature in patients with CeD is not very well defined and appears to be multi-factorial. Earlier it was thought that CeD related malnutrition was the only factor responsible for short stature in these patients. There are now evidences that suggest that not all patients with CeD have gastrointestinal manifestations and/or malnutrition. Patients with CeD have been reported to have lower levels of both basal and hypoglycemia induced growth hormone levels, lower levels of insulin like growth factor (IGF)-1, IGF-2, insulin like growth factor binding protein (IGFBP)-1 and IGFBP-3. [45,46,53] Additionally, these patients might have partial insensitivity to the growth hormone. Surprisingly, introduction of GFD normalizes many imbalances in the somatotropic axis in the form of increased growth hormone sensitivity and also increased IGF-1, IGF-2 and IGFBP-1. [46,53] Concomitant hypothyroidism, hypogonadism and Turner's syndrome in these patients may also contribute to occurrence of short stature in them [46].

Association between CeD and type 1 diabetes (T1DM) and autoimmune thyroiditis is also well established. Upto 3-12% of T1DM patients have been reported to have CeD and 1.5-7.4% of patients with CeD have T1DM [54,55].

Similarly, as many as 10%-15% of patients with CeD have co-existent clinical hypothyroidism or hyperthyroidism and conversely upto 2-4% of patients with autoimmune thyroid disorders have CeD. [55] The evidences of association between other endocrinopathies such as Addison's disease, primary or secondary hyperparathyroidism, and autoimmune hypophysitis and CeD is not well established [55].

In summary, many of the patients with CeD may have endocrinopathy as the prime manifestation and therefore endocrinologists should consider CeD as a diagnostic possibility in patients with short stature, autoimmune thyroid disease and TIDM.

5. Liver Diseases

Spectrum of liver involvement in CeD ranges from asymptomatic elevation of serum transaminases to end stage liver disease. Elevated serum transaminases have been reported in 24%-54% of patients with CeD. [6,56,57] Conversely, upto 9% of the patients with chronic unexplained increase in transaminases have been reported to have CeD.[58] The response to GFD is excellent in more than two thirds of patients, the transaminases in them normalize within 6 months to one year [56,57].

CeD has also been reported to co-exist with other autoimmune liver diseases such as autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. Four to 6% of patients with autoimmune hepatitis are reported to have CeD. [57,59,60] Van-Gerven, et al in a recent study including 410 patients with autoimmune hepatitis reported 3.5% of them having sero-positive for CeD which was higher than the 0.35% prevalence of CeD in the general Dutch population. [61] Similarly, 4%-11% of patients with primary biliary cirrhosis have co-existent CeD. [57] Large population based cohorts from Sweden and Denmark have reported a standardized incidence ratio of 25-28 for primary biliary cirrhosis in patients with CeD. [62] Conversely, patients with CeD have more than three times increased odds of having primary biliary cirrhosis compared to the occurrence of primary biliary cirrhosis in the general population (0.17% vs 0.05%). [63] In another large population based cohort of 13,818 CeD patients, Ludvigsson et al have reported 4.5 times increased risk of having primary sclerosing cholangitis amongst patients with CeD in comparison to that in the general population. [64] In patients having a combination of both autoimmune liver disorders and CeD, symptoms of one might precede the other, or even may co-exist at the time of diagnosis and therefore need careful evaluation [65].

There are several levels of evidences, such as clinical observations, case series and population based cohort studies suggesting an association between CeD with chronic liver disease (CLD) or cirrhosis. [40,64,66,67] Patients with CeD are also more likely to die from liver cirrhosis than the general population. [67] Kaukinen, et al had reported reversal of hepatic dysfunction after initiation of gluten free diet (GFD) in four patients awaiting liver transplantation and eventually three of them were remitted from liver transplantation list. Furthermore, CeD was detected in 8 (4.3%) of 185 patients who underwent liver transplantation previously and later screened for CeD. [68] In a more recent prospective study, Wakim-Fleming et al reported CeD in 2.5% of 204 consecutive biopsy proven patients with liver cirrhosis. [66] They also reported improvement in liver function tests with initiation of GFD in these patients. [66] Based on the abovementioned study, in can be concluded that the prevalence of CeD in patients with cirrhosis is more than two times than that in the general population.

Which are the patients with chronic liver disease who should be investigated for presence of concomitant CeD? The reasons for suspicion of CeD in patients with cirrhosis generally are presence of chronic diarrhea, short stature and disproportionately severe anemia or iron refractory anemia in them. [40,65] Chronic diarrhea in cirrhosis might be attributed to bacterial overgrowth and intestinal mucosal edema. Similarly, anemia in cirrhotic patients could be caused by GI bleeding, hypersplenism and anemia of chronic disease. If liver disease sets in early years of life, it could itself lead to growth retardation. Therefore, most of these manifestations pointing towards presence of CeD can well be explained by cirrhosis itself and thus alternative causes for these manifestations may not be considered in a patient with cirrhosis. Because of overlapping manifestations of cirrhosis and CeD, there is a likelihood of missing the diagnosis of CeD if the main presentation of CeD is like cirrhosis unless actively considered.

The abovementioned evidences while suggest an association between CeD and spectrum of liver diseases, morphological changes that occur in the liver however is not well known except for a study by Jabobson, et al. Jacobsen, et al have reported histological changes in the liver of 37 patients with CeD having increase in serum transaminases. [69] Of 37 of these patients, 5 had normal liver on histological examination, 25 had nonspecific necro-inflammatory changes in the liver, 6 had chronic hepatitis, and one had primary sclerosing cholangitis [69].

How CeD leads to liver dysfunction is also not known. While population-based studies support an association between autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis with CeD, the exact reasons of association are not well established. While it is well known that patient having one autoimmune disease can have another autoimmune disease; therefore mere presence of two autoimmune diseases in an individual do not confirm causality. At present, there is no tissue specific marker/staining/cellular repertoire to support liver damage caused by gluten. CeD and autoimmune hepatitis are both associated with specific class II HLA molecules encoding for HLA complex genes on chromosome 6. [56,57] Novacek, however, reported significantly higher intestinal permeability in patients with CeD who had elevated serum transaminases compared with those with normal serum transaminases. [70] Tansglutaminase-2 which is central pathogenesis of CeD, has also been shown to modulate inflammation and fibrosis in chronic liver disease. [71] One of the valid requirements for establishing the association between autoimmune diseases and CeD is to demonstrate reversibility of the liver damage by GFD. Further studies are needed to better delineate the pathogenesis of liver involvement in CeD. Also, long term follow-up and paired liver biopsies in patients with coexistent CeD and liver disease, while being on strict GFD, would help in delineating the mechanisms of liver damage in patients with CeD.

6. Bone and Metabolic Disease

6.1. Osteoporosis and Osteopenia in Patients with CeD

CeD predisposes individuals of all age to low bone mineral density (BMD). Twenty six percent to 74% of adult patients with CeD have osteopenia or osteoporosis. [72,73,74,75] Similarly, children and adolescents with CeD have been found to have lower BMD in comparison to healthy children. [76] In a prospective study, Margoni, et al reported that approximately 30% of children with CeD had BMD below 2.5th percentile of the normal population at the time of diagnosis. Furthermore, the BMD z scores continued to be significantly lower than that in the general population even upto 2 years after institution of GFD [77].

6.2. CeD in Patients with Osteopenia and Osteoporosis

Conversely, 0-3.4% patients having low BMD have been found to have CeD. [78] Patients with osteomalacia and proximal myopathy both in developing as well as developed nations are also reported to have CeD [78,79].

While a few population-based cohort studies suggest that patients with CeD are not at a higher risk for fractures; another population-based large Danish cohort study has shown a higher risk of hip fracture (hazard ratio =1.4) in them.[80–84] In a general population-based cohort study that included individuals with CeD (n= 14,187) and reference individuals (n=14,187), CeD was positively associated with subsequent hip fracture (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.8–2.4) and fractures of any type (HR 1.4; 95% CI 1.3–1.5). [84] A systematic review with a meta-analysis, that pooled 20,995 CeD patients and 97,777 controls from eight studies published between 2000 and 2007, indicated that CeD patients have a 43% higher risk for fracture compared with subjects without CeD [85].

Children with CeD can attain normal peak bone mass if the diagnosis is made early and GFD is started before puberty. While some studies have shown that BMD return to normal after one year of GFD in children diagnosed with CeD, others have failed to show complete normalization by this time. [77,86,87] Similarly, GFD is considered the most rational approach for osteoporosis/ osteopenia in adult patients with CeD. Nevertheless, a

GFD rarely normalizes BMD in adulthood. [88] A recent study has shown that despite long-term strict adherence to GFD, 74% of them still had low BMD, and 24% of them having even osteoporosis. [76] Therefore, calcium and vitamin D supplementation should be considered for adult patients with CeD.

The pathophysiology of bone loss in patients with CeD is multifactorial; the two main mechanisms being malabsorption of calcium and vitamin D and release of pro-inflammatory cytokines leading to osteoclast activation.[76,88] Calcium malabsorption in CeD induces increase in parathyroid hormone secretion, which in turn, increases bone turnover and cortical bone loss.

7. Neurological Manifestations

In recent years, CeD has been associated with neurological and psychiatric disorders including peripheral neuropathy, epilepsy, dementia, cerebellar ataxia and depression. If looked carefully, approximately 23%-50% of patients with CeD have signs/symptoms of peripheral neuropathy. [89,90,91] In a large population-based registry from Sweden including 14,000 patients with CeD and 70,000 controls, Ludvigsson reported three fold higher risk of developing polyneuropathy. [92] Neuropathy in CeD generally is distal symmetric sensory neuropathy but they might also have pure motor neuropathy, mono-neuritis multiplex and autonomic neuropathy. [93] In addition, an unique terminology 'gluten related neuropathy' has been coined for individuals with otherwise sporadic peripheral neuropathy and having serologic (a positive AGA or anti-tTG Ab or AEA) evidence of gluten related disorders. [94,95] 'Gluten related neuropathy' is a slowly progressive disease occurring in people around 55 years of age. Villous enteropathy have been described in one-third of these patients. [94] While some investigators have reported improvement in neuropathic symptoms with GFD, others have failed to show any such response. [89,96] However, in a systematic study by Hadjivassiliou et al, improvement was found in sural nerve sensory action potential along with subjective improvement in neuropathic symptoms in 35 patients with gluten neuropathy, who maintained a strict GFD for atleast 1 year. Recovery remains incomplete in patients with more severe disease, thereby suggesting the importance of detecting the disease early in its course [94].

Cerebellar ataxia is another common manifestation of CeD and has been shown to be present in upto 6% of patients with biopsy proven CeD. [97] In a study by Hadijivassiliou et al, upto 41% of patients with sporadic cerebellar ataxia (54/132) were attributed to gluten ataxia. [98] One fourth of these patients with gluten ataxia were found to have CeD on the duodenal biopsy. In another study, 12 of 104 (11.5%) patients with idiopathic ataxia and negative genetic testing were reported to have a positive serological marker for CeD (AGA/AEA) in comparison to 5% of 600 healthy blood donors. [99] They also reported strong association between a positive serology and HLA-genotypes linked with CeD, suggesting gluten ataxia being a part of the gluten related disorders. [99] Gluten ataxia is now defined as presence of otherwise idiopathic sporadic ataxia in association with positive anti-gliadin antibodies (IgG or IgA or both) with or without enteropathy on the duodenal biopsy. [1] Anti-tTG-6 antibody is now being identified as a potential new serological marker for gluten ataxia. [100] Upto 60% of patients with gluten ataxia have MRI evidence of cerebellar atrophy. [95] There are now evidences that ataxia improves with initiation of GFD in such patients. Only available systematic study have reported improvement in ataxia (improvement in ataxia tests) after one year in 46 patients with gluten ataxia who strictly adhered to GFD compared to those 14 patients who refused to follow GFD. The improvement in ataxia was noticed even when these patients did not have enteropathy [101].

'Gluten encephalopathy' is a term used to describe individuals with gluten related disorder having headache and white matter changes on MRI. [95] Gluten encephalopathy may not always occur in isolation and may co-existent with other gluten-related neurological conditions. Additionally, 4.3% of patients with migraine have been reported to have CeD, which is higher than the prevalence of CeD in the general population. [102] Other less common neurological manifestations of gluten related disorders are myopathy, myelopathy, epilepsy, dementia, cognitive impairment and depression [95].

The neurological manifestations in gluten related disorders may occur because of two main reasons; malabsorption of vitamin specifically vitamin B_1, B_6, B_{12} and E deficiencies and neurological sensitivity to gluten.[93] Furthermore, it remains unclear whether these antibodies (including anti-tTG 6) are neurotoxic or are representative of an epiphenomenon [93].

8. Mucocutaneous Manifestations

Dermatitis herpetiformis (DH) is a cutaneous manifestation of small intestinal immune mediated enteropathy precipitated by exposure to dietary gluten. [1] It is characterized by clusters of pruritic papules and vesicles associated with intense pruritus, which are followed by erosions and excoriations. The typical sites for DH lesions include extensor surfaces of upper and lower extremities, elbows, knees, scalp and buttocks [103].

Skin biopsy is needed for the diagnosis. During initial phase the skin biopsies show, edema in the papillary dermis and neutrophilic infiltration along the dermal-epidermal junction. As the lesions progress, along with neutrophils, eosinophils and fibrin accumulate along dermal papillae and form micro-abscesses. On direct immunofluorescence, granular IgA deposition is seen in the dermal papillae and/or along the basement membrane and they are considered as gold standard for the diagnosis of DH. [103,104,105] Majority of these patients also have intestinal villous atrophy in patients with DH [1].

GFD is the first line of therapy for DH similar to that for CeD. [1] It takes several months before skin lesions start improving. Other drugs such as dapsone, sulfasalazine, topical potent corticosteroids and anti-histaminics should be used as symptomatic agents. [103,106] Among these, dapsone is the best tolerated and most widely used pharmacologic therapy for DH in both adults and children. [103] While the cutaneous lesions improve and become less pruritic with use of dapsone, the

lesions however reappear on discontinuation of dapsone. This is because daspone suppresses the inflammation in the skin but has no influence on the disease process. [103] Till the antigenic challenge is withdrawn, the disease process persists and therefore a GFD is the counterstone of the therapy.

Oral lesions are fairly common in CeD and include recurrent aphthous ulcerations, glossitis, angular cheilitis and burning in the mouth. [107,108] About 3%-6% of patients with oral manifestations may have underlying CeD. [108] Other less common cutaneous manifestations associated with CeD are psoriasis, urticaria, alopecia areata and necrolytic migratory erythema [108].

9. Gynecological Manifestations

CeD has been shown to be present in about 2%-3% of women presenting with infertility which is higher than the prevalence of CeD in the general population. [109,110,111] We recently conducted a meta-analysis and found that women with infertility had 3.5 times higher odds of having duodenal biopsy proven CeD in comparison to that in the control population (OR 3.5, 95% CI 1.3 9; p <.01). [112] In another metaanalysis, Tersigini et al have also shown that females with unexplained infertility have about 5 times increased odds of having CeD [113].

Several studies have also suggested unfavorable pregnancy outcomes in patients with CeD. CeD has been associated with recurrent abortions, intra-uterine growth retardation, and low birth weight (preterm and small for gestational age). [114,115,116,117] Tesergini et al in their recent meta-analysis also confirmed a significantly increased risk of miscarriage, IUGR, low birth weight and preterm delivery in patients with CeD [113].

These gynecological and obstetric manifestations in patients with CeD could partly be due to micronutrient deficiency particularly zinc, selenium, iron, folate and vitamin B_{12}. [113] In-vitro studies have shown that anti-tTG antibodies in CeD could bind to trophoblastic cells and induce their apoptosis thus leading to placental damage. [113] There is also evidence that anti-tTG antibodies could bind to endometrial endothelial cells and suppress angiogenesis affecting both implantation as well as placenta formation [113].

10. Why is Non-classical CeD Missed?

As discussed above, firstly spectrum of CeD is now changing across the world and more than half of CeD patients now present with non-classical manifestations. [6,118] It is important to realize that almost any of these non-classical manifestations can occur in absence of gastrointestinal symptoms and therefore a high index of suspicion is necessary.

Secondly, patients with non-classical manifestations do not directly present to gastroenterologists. [6] A significant number of CeD patients now present to hematologists, endocrinologists, gynecologists, neurologists and internists and family physicians because of varied manifestations described above. Despite non-classical manifestations being common in CeD, awareness about CeD in health care professionals remains low. In a national survey by Smukalla et al who interviewed 385 hematologists in the USA, only 8.6% believed that all patients with iron deficiency anemia should be screened for CeD. [119] Physicians who have recently finished their fellowship and those who see a high volume of patients with IDA are more likely to screen for CD. This might have been because of increased awareness of CeD in this sub-group of physicians [119].

Thirdly, CeD has been believed to be a disease of pediatric population. Studies have shown that CeD is not only common in adult population but also in elderly. In a recent study from India, 9% of patients with CeD were diagnosed after the age of 50 years. It is important to acknowledge that CeD can occur at any age and should be considered in appropriate clinical settings, irrespective of age [7].

11. How to Increase Knowledge about CeD

It is essential that awareness of and knowledge about CeD and its disease associations increase amongst medical practitioners. The obvious groups to target are pediatricians, family physicians, gastroenterologists and histopathologists. However, it should be emphasized that CeD may report to other medical specialists such as endocrinologists where patients present with short stature or type I diabetes, to hematologists with anemia, to rheumatologists with metabolic bone diseases, and to gynecologists with delay in menarche, secondary amenorrhea or infertility.

Currently, a due emphasis is not placed on CeD in the undergraduate and postgraduate medical curriculum. In the majority of the undergraduate and postgraduate textbooks of medicine, CeD is generally dealt with in the chapters on malabsorption and only limited information about CeD is provided. A due emphasis should be put on CeD during undergraduate and postgraduate medical education. Furthermore, a constant reminder should be provided to physicians, internists, gastroenterologists, hematologists, and endocrinologists through continuing medical education programmes. The first contact of patients with CeD are generally primary care physicians and family physicians. Empowering primary care physicians and family physicians should play key role in increasing detection of CeD.

12. How to Investigate?

All patients with suspected CeD should be screened using anti-tTG antibodies and/or anti-endomysial antibodies. Recently, point of care test have also been developed which also make it possible to screen for CeD in primary care or resource limited settings. Patients with positive serology should be referred to gastroenterologists for duodenal biopsies to confirm the diagnosis. Once the diagnosis is confirmed, patients should be started on strict and lifelong GFD.

13. Conclusions

Many of patients with non-classical CeD are likely to report to specialists other than gastroenterologists such as

hematologists, endocrinologists, rheumatologists or gynecologists. Unfortunately, the awareness about non-classical presentations of CeD amongst health care professionals remains low. There is an urgent need to increase awareness among health care professionals about varied manifestations of CeD in order to decrease the burden of undiagnosed CeD.

Table: Non-classical manifestations of Celiac disease

	Symptoms	Prevalence of CeD (%)	Type of studies	References
Hematological manifestations	Anemia	1.8-8.7%	Prospective	[30,31,32,33,34]
Endocrinological manifestations	Short stature	4.7-15.2%	Prospective	[42,43,44,45,46]
	Type 1 Diabetes	3-12%	Prospective	[54,55]
	Autoimmune thyroiditis	2-7.8%	Prospective	[55]
Liver disease	Unexplained transaminitis	9%	Prospective	[58]
	Autoimmune hepatitis	3.5-6%	Prospective	[59,60,61]
	Primary biliary cirrhosis	4-11%	Prospective	[57]
	Primary sclerosing cholangitis	1.6%	Prospective	[57]
	Chronic liver disease	2.3-4.5%	Prospective	[66,68]
Bone metabolism	Osteoporosis and osteopenia	0.8-3.4%	Prospective	[88]
Neurological manifestations	Sporadic ataxia	2-9.8%	Prospective	[98,99]
Gynecological manifestations	Infertility	2-3%	Prospective	[109,110,111]

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