# The Many Faces of Celiac Disease

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Celiac disease (CD) is the most common food intolerance in Western populations. However, recent studies have shown that the prevalence of CD in individuals of non-European descent is similar to that of Western populations. Currently, this disorder represents a major health issue that is globally underdiagnosed. CD has a broad clinical spectrum, with signs and symptoms including iron-deficiency anemia, constipation, diarrhea, malabsorption, and weight loss. Extraintestinal manifestations have also been described, including dermatologic and neurologic disorders. To our knowledge, this case is the first report of a Middle Eastern woman with celiac enteropathy who presented with skin rash and gait ataxia. This case highlights the prevalence of CD in non-Western populations, and it illustrates the importance of considering CD in the differential diagnosis of patients with atypical gastrointestinal and neurologic symptoms.

## Case Report

A 37-year-old woman from the United Arab Emirates presented to our institution's Movement Disorder Center with a 5-year history of undiagnosed gait disturbance, imbalance, and dysarthria. She described a slowly progressive course over several years; for the last 3 years, she had used a wheelchair when traveling longer distances due to concerns about frequent falls. The patient reported moderate impairment in fine motor skills and some visual disturbances, but she denied numbness and tingling in her extremities. She admitted to increased urinary frequency and urge incontinence beginning after the onset of her gait disturbance. Initial blood laboratory analysis showed profound iron-deficiency anemia, and the patient was referred to the gastroenterology clinic for further evaluation. Except for chronic constipation and weight gain, she had no other gastrointestinal symptoms. She also reported an undiagnosed pruritic skin rash that had appeared 3 years prior to presentation. She had no other significant past medical history and no family history of any neurologic disorder. However, her parents were first cousins.

On physical examination, the patient appeared weak and unsteady on her feet. She was alert and oriented to person, place, and time. Her vitals were stable, and there was no evidence of orthostatic hypotension. She was not jaundiced. A healing, symmetric, papulovesicular rash was noted on her trunk and extremities (Figures 1 and 2). Cardiac and pulmonary examination results were normal. Her abdomen was benign, with no hepatosplenomegaly or other mass found on palpation.

Pertinent neurologic findings included prominent cerebellar oculomotor dysfunction as evidenced by saccadic pursuit, hypermetric saccades, impaired suppression of the vestibulo-ocular reflex, and mild gaze-evoked nystagmus. Her speech was consistent with cerebellar dysarthria. She had normal muscle tone with no weakness or tremor. She had 2+ symmetric reflexes and downgoing toes. Her sensation was intact to light touch, proprioception, and vibration. Rapid alternating movements were slow and dysrhythmic. There was moderate dysmetria on finger-to-nose and heel-to-shin testing. Her walk was wide-based and unsteady. Her score on the scale for the assessment and rating of ataxia was 15/40.

Neurologic work-up for sporadic ataxia, including a paraneoplastic antibody panel, was negative. Vitamin E, vitamin $B_{12}$, thyroid-stimulating hormone, rapid plasma reagin, methylmalonic acid, coenzyme $Q_{10}$, anti–glutamic acid decarboxylase 65 antibodies, and hexosaminidase levels were all within normal limits. A lumbar puncture was performed; cerebrospinal fluid revealed a normal cell count, protein content, and negative cytopathology. The patient refused genetic testing. Brain magnetic resonance imaging revealed significant cerebellar and borderline pontine atrophy (Figure 3).

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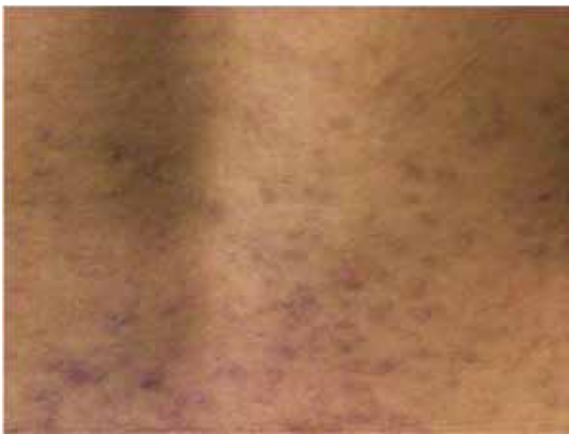
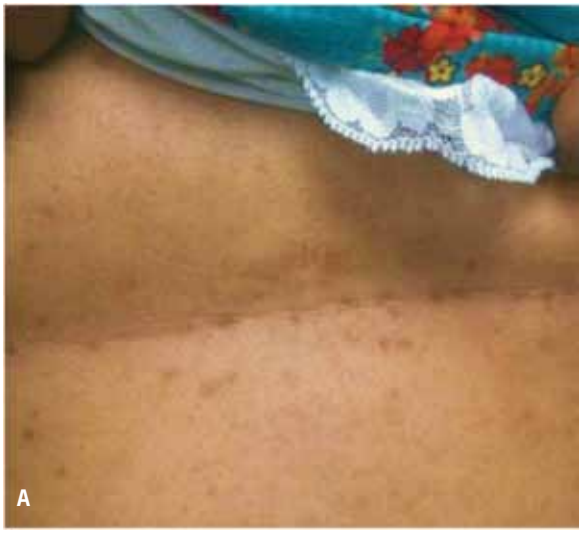


**Figure 1.** Papulovesicular eruptions with symmetrical distribution noted on the patient's back with areas of hyperpigmentation suggestive of dermatitis herpetiformis.

Blood analysis was notable for profound iron-deficiency anemia, with a hemoglobin level of 9 g/dL, mean corpuscular volume of 68 fL, and ferritin level less than 3 ng/mL. A celiac serology panel was positive: Her gliadin antibody immunoglobulin (Ig)G level was 34 mg/dL (normal, <20 mg/dL), IgA level was 59 mg/dL (normal, <20 mg/dL), endomysial IgA antibody was positive at 1:80 units (negative, <10 units), and tissue transglutaminase IgA was positive at 189 units (normal, <20 units). The patient's vitamin D level was low (16 ng/mL). Upper endoscopy revealed diffuse scalloping of the duodenal mucosa with marked flattening and mosaic appearance of the bulbar mucosa that was suggestive of CD (Figures 4 and 5). Marsh type III lesions were confirmed on histopathology and were marked by villous atrophy, prominent intraepithelial lymphocytes, and crypt hyperplasia (Figure 6). The distribution of the intermittent, pruritic, pustulovesicular rash was very suggestive of dermatitis herpetiformis. The lesions were not biopsied.

After an extensive neurologic work-up and in the absence of any pertinent family history that could suggest hereditary ataxia, the patient was diagnosed with gluten ataxia as a manifestation of biopsy-proven celiac enteropathy. The patient received nutritional education regarding a strict gluten-free diet. She was also given vitamin D and iron supplements.

On follow-up examination 6 months later, the patient had remained adherent to a gluten-free diet. She reported regular bowel movements, her anemia had improved, and she had regained her strength. She also reported resolution of her skin rash without the use of any topical agents. Although she noted improvement in her speech, she continues physical therapy for persistent but stable gait ataxia.



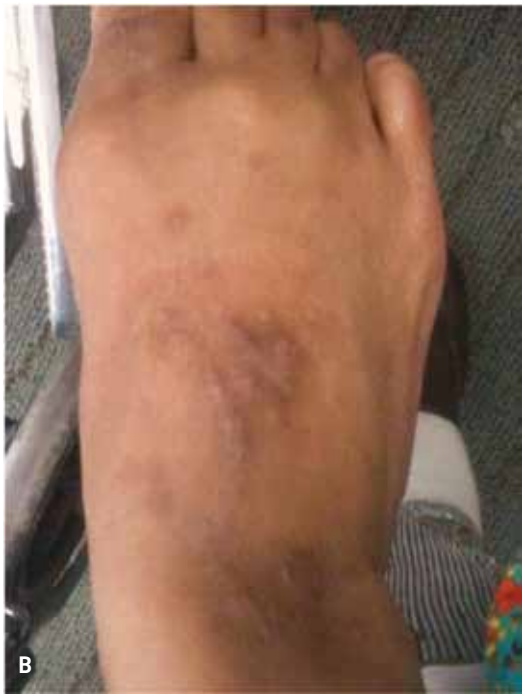




**Figure 2.** Papulovesicular eruptions noted on the abdomen **(A)** and the dorsum of the foot **(B)**, which are suggestive of dermatitis herpetiformis.

## Discussion

CD is caused by a chronic, immune-mediated response to ingested gluten and related proteins found in wheat, rye, and barley. Gluten sensitivity is strongly heritable, with 40% of the genetic load coming from major histocompatibility complex class II associations, notably haplotype HLA DQ2 (present in 90% of whites) and HLA DQ8.[1]

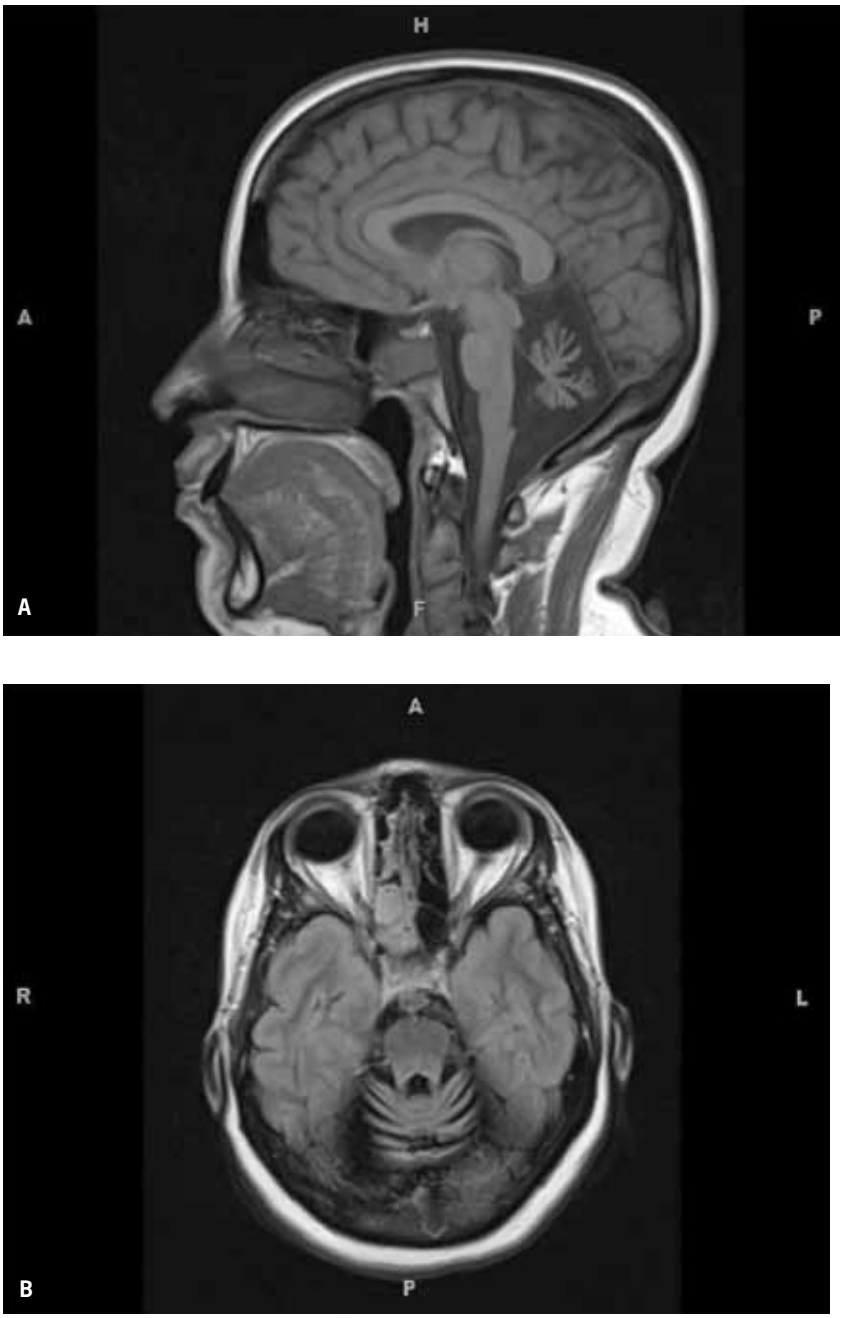



**Figure 3.** Cerebellopontine atrophy seen on a sagittal view **(A)** and axial view **(B)** of a magnetic resonance imaging scan of the brain.

In genetically susceptible individuals, this disorder leads to an inflammatory process in the proximal small bowel, which results in lymphocytic infiltration, crypt hyperplasia, and villous atrophy. Malabsorption also develops, which results in diarrhea, micronutrient deficiency, and weight loss.

CD was previously thought to be most common in individuals of European descent and rare in other populations. The Middle East is known for wheat and barley cultivation, and these grains are a major dietary staple for more than 90% of the population. It was thought that this diet conferred immune tolerance to gluten in this population. Recent studies have shown that the prevalence of CD among low-risk patients in the Middle East and North Africa is similar to the prevalence in Western populations, ranging from 0.14% to 1.17%,

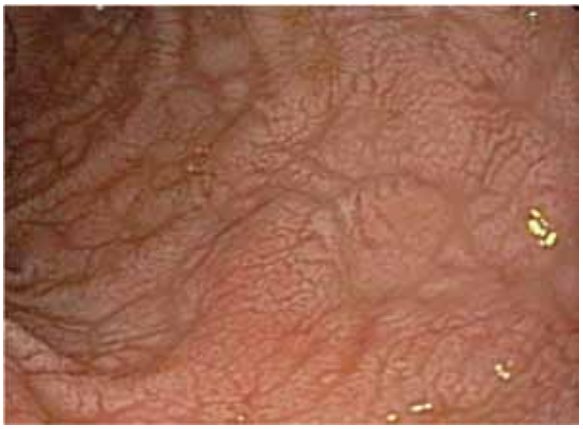


**Figure 4.** Mosaic pattern and flattening of a duodenal bulb seen on upper endoscopy.


**Figure 5.** Scalloping of duodenal folds seen on upper endoscopy.

and possibly higher in at-risk populations, ranging from 2.4% to 44%.[2,3] The Sahawari population of Arab Berber origin in Algeria has the highest world prevalence of CD, at 5.6%.[4] This high prevalence may be explained by a high frequency of HLA DQ2 and consanguinity. The exact prevalence of CD in the United Arab Emirates remains unknown.

Dermatitis herpetiformis has been widely accepted as an extraintestinal manifestation of CD for many decades. Although numerous cases of neurologic manifestations in patients with gluten enteropathy have been described since 1966, this association remains highly debated, as a mechanistic pathway has not been clearly elucidated.[5] Neurologic manifestations in patients with established gluten enteropathy have been estimated to occur in 6–10% of patients with CD. Common neurologic manifestations include gluten ataxia and peripheral neuropathy. Encephalopathy, myelopathy, epilepsy, dementia, and myopathy have also been reported.[6,7]

Gluten ataxia is described as sporadic cerebellar ataxia that occurs in the absence of other etiology, is associated with gluten sensitivity, and is demonstrated by the presence of positive serologic markers (ie, circulating antigliadin antibodies [AGAs]).[8] AGAs are antibodies to a food component, and they are known to be less sensitive and specific than anti-endomysial and anti–tissue transglutaminase antibodies for the detection of enteropathy. The prevalence of biopsy-proven CD in patients with ataxia

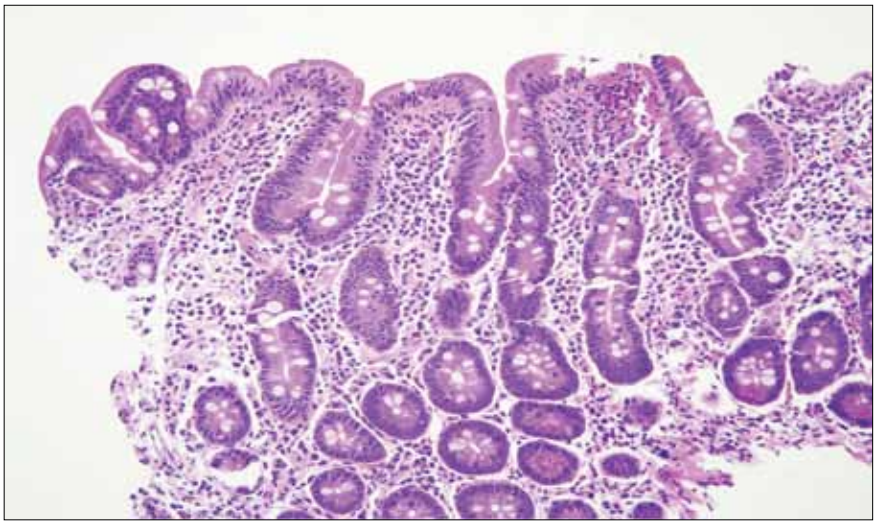


**Figure 6.** At high-power magnification, marked villous blunting, prominent intraepithelial lymphocytes, and crypt hyperplasia consistent with Marsh type III lesions were seen (hematoxylin and eosin stain).

of unknown origin ranges from 12% to 15%, whereas the prevalence of a positive AGA result in patients with ataxia of unknown origin ranges between 0% and 41%.[9-12] Some studies have failed to demonstrate a difference in the prevalence of AGAs in sporadic versus hereditary ataxia.[13-15]

Gluten ataxia has been described as having an insidious onset of predominantly gait ataxia, and it is often associated with peripheral neuropathy. Gluten ataxia affects both genders equally and has a mean age at onset of 53 years. Evidence of limb ataxia is seen in up to 90% of patients, with lower limbs affected more often than upper limbs. Gaze-evoked nystagmus and other ocular signs of cerebellar dysfunction are seen in up to 80% of cases. Bladder dysfunction is seen in up to one third of patients. Although our patient presented at a relatively young age, all of the previously mentioned symptoms were noted on presentation.

The absence of additional autonomic dysfunction and Parkinsonian findings distinguishes patients with gluten ataxia from those with a cerebellar variant of multiple system atrophy. Up to 60% of patients with gluten ataxia have evidence of cerebellar atrophy on magnetic resonance imaging, as was seen in our patient.[16] Gluten ataxia resembles dermatitis herpetiformis when gastrointestinal symptoms are not prominent, despite the presence of enteropathy. Less than 10% of patients with gluten ataxia will have gastrointestinal symptoms, and only one third will have evidence of enteropathy on biopsy.[16]

It has been suggested that the neurologic manifestations of this condition may be the result of micronutrient malabsorption. Deficiencies in vitamin $B_1$, vitamin $B_6$, vitamin $B_{12}$, vitamin E, niacin, and riboflavin can result in neurologic symptoms. More recently, the discovery of the homologous nature of certain members of the transglutaminase family—transglutaminase 2 (TG2), which is predominant in the gut; transglutaminase 3 (TG3), which is predominant in the skin; and transglutaminase 6 (TG6), which is predominant in the brain—strongly suggests an immune-mediated etiopathogenesis. The ability of TG2 to de-amidate and crosslink gluten peptides is important for gluten-dependent production of TG2 autoantibodies and development of gluten enteropathy. TG3 in skin appears to be the target autoantigen in dermatitis herpetiformis. In gluten ataxia, autoantibodies reactive to TG6 are present. Antibodies to TG6 have been found in cerebrospinal fluid, and deposits have been seen in Purkinje cells. Postmortem data from patients with neurologic symptoms have shown inflammation in the cerebellum, other parts of the central nervous system, and the peripheral nervous system.[10,17,18]

The response to a gluten-free diet has been inconsistent in terms of neurologic changes. In contrast, a significant response is seen in patients with dermatitis herpetiformis, as noted. Restriction of gluten alone has not been consistently shown to be effective in patients with gluten ataxia, nor has the efficacy of empiric vitamin replacement been proven. Intravenous steroids and immunoglobulin treatments have also been tried with varying results.[19-22]

To our knowledge, this case is the first report of gluten ataxia in a Middle Eastern patient with CD that was confirmed by serology and histology. The spectrum of gastrointestinal symptoms in CD, ranging from asymptomatic disease to significant malnutrition, renders clinical suspicion of this condition challenging. Furthermore, establishing a diagnosis in the setting of extraintestinal manifestations is difficult, as a majority of these patients will not test positive for currently available celiac serologic markers. A high index of suspicion for CD should be maintained in Western and non-Western patients who present with typical or atypical gastrointestinal symptoms, iron-deficiency anemia, and neurologic symptoms.

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# Review

## Celiac Disease: A Challenge for All Physicians

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Celiac disease is 1 of the most common genetic disorders, affecting approximately 1% of individuals worldwide.[1] In predisposed individuals, gluten ingestion precipitates chronic autoimmune responses that can manifest in a variety of ways and affect multiple organ systems. As these varied patterns can pose a diagnostic challenge, it is important that clinicians of all disciplines keep celiac disease in mind when evaluating patients. The domestication and cultivation of wheat first occurred in the Middle East, in the "fertile crescent" region stretching from modern-day Turkey to Iran.[2] The literature has increasingly noted celiac disease in this region, with reports of high prevalence coming from average-risk populations in Turkey, Egypt, Iran, Tunisia, Israel, Jordan, Lebanon, and Kuwait.[3-15]

In their case report, Asamoah and colleagues describe the diagnosis of celiac disease in a Middle Eastern woman with neurologic deficits, skin involvement, and iron-deficiency anemia.[16] The preventable cause of her ataxia was only identified 5 years after the onset of deficits that severely restricted her mobility. This case raises several important issues relating to celiac disease. First, the case underscores the geographic distribution of the condition: Although celiac disease was originally considered to be a disease of Northern Europeans, its worldwide incidence has been demonstrated. Second, the case highlights the diverse nature of celiac disease presentations. A common etiopathology likely underpins manifestations as varied as dermatitis herpetiformis (DH) and gluten ataxia. Finally, the case emphasizes the need for all physicians to have a high index of suspicion for this disease, a condition that—once considered—is easily diagnosed and can be treated.

There is increasing awareness of celiac disease among non-European populations, including those in the Middle East. The disease was considered uncommon in the developing world until the 1990s, when the introduction of serologic screening tests resulted in increased rates of diagnosis in the Middle East, India, and North Africa, where the HLA-DR3-DQ2 haplotype is prevalent and wheat consumption is quotidian.[17,18] The prevalence rates of celiac disease in North Africa and the Middle East are now thought to be similar to those of Western countries.[3,19] Average-risk groups have prevalence rates ranging from 0.14% to 1.3% as assessed by serology and 0.033% to 1.17% as assessed by biopsies, whereas prevalence rates in high-risk populations vary from 2.4% to 44%. The highest prevalence rate of celiac disease worldwide has been reported in North Africa.[20] There is evidence that the prevalence rates of celiac disease in parts of North India are comparable to those in the West; celiac disease has also been reported among South Asian immigrants in the United Kingdom.[21] A recent community-based study of 10,488 adults and children from North India reported that the overall seroprevalence of celiac disease was 1.44%, with the overall prevalence of celiac disease being 1.04%.[22] Celiac disease has also been reported in Latin America (Brazil, Argentina, and Chile, with the latter including native South American Indians).[23] In contrast, celiac disease is very uncommon among East Asians (who do not carry the requisite HLA haplotypes) and the disease is rare in sub-Saharan Africa and among African Americans.[24]

There are several issues that relate specifically to the diagnosis and management of celiac disease in individu-

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als of non-European descent. The clinical presentation of celiac disease has been reported to be similar in Western and non-Western countries, although a study comparing US and Turkish celiac disease cases found that Turkish patients presented more frequently with malabsorption symptoms of diarrhea and anemia, whereas US patients more often had atypical symptoms of fatigue, abdominal pain, and bloating.[25] Gastrointestinal complaints are the most common presenting symptoms of celiac disease in patients from the Middle East and North Africa.[3] The prevalence of celiac disease among patients with chronic diarrhea in this region has been reported to be 6.5–21%, and celiac disease has been reported to be 1 of the most common causes of chronic diarrhea. Although chronic infectious diarrheal illness and iron-deficiency anemia are highly prevalent in developing countries, a high index of suspicion for celiac disease should be maintained for patients in these areas who present with these symptoms. Similarly, short stature and failure to thrive—which are strongly associated with celiac disease in the West—should prompt investigation in developing countries despite the endemic nature of these conditions. In the past, the diagnosis of milder pathologic grades of celiac disease was problematic in the setting of widespread idiopathic enteropathy; however, the emergence of highly sensitive and specific serologic tests that can be used in conjunction with histopathology has simplified the diagnostic process.[18] Little is known regarding the prevalence of atypical or silent celiac disease outside of the West.[3]

The Middle East was the first site of widespread consumption of wheat, and wheat remains a dietary staple across the region. This reality, combined with poor availability of gluten-free supplies, can make dietary management of celiac disease a challenge.

Celiac disease is characterized by gluten-induced autoimmune injury to multiple organs, and the condition's highly varied manifestations are increasingly being understood as the result of immune-mediated attacks on homologous antigens in different tissues. Transglutaminase 2 in the intestinal mucosa has been characterized as the primary autoantigen of celiac disease; however, variants of this enzyme are found throughout the body. The patient treated by Asamoah and colleagues had DH and gluten ataxia.[16] Antibodies to transglutaminase 3 (TG3) in the skin and transglutaminase 6 in central nervous tissues both first develop in the intestine, attesting to a common underlying immune pathogenesis.[26]

DH is an intensely pruritic papulovesicular eruption that is precipitated by gluten and is a well-recognized manifestation of celiac disease. DH is a rare finding, with an estimated prevalence rate in the United States of 11.2 cases per 100,000 individuals.[27] DH is associated with silent celiac disease, in which enteropathy is demonstrable on biopsy in the absence of gastrointestinal symptoms. As such, DH may be the only presenting symptom in as many as 60% of cases, and only 10–20% of patients with DH have classic symptoms of malabsorption.[28] A significant proportion of patients with DH have mucosal biopsies that are normal or that show only very minor changes; nevertheless, increased intestinal permeability can be observed in these patients.[29] DH typically presents as pruritic papulovesicles, often excoriated, involving the elbows, knees, buttocks, and scalp. A biopsy demonstrating the presence of granular immunoglobulin (Ig)A deposits in the dermal papillary tips is diagnostic. Patients with celiac disease have elevated levels of serum anti–TG3 IgA antibodies, and those patients with DH show a trend toward still higher levels, suggesting that this autoantibody may play a role in the pathogenesis of the disease.[30] Skin lesions associated with DH respond dramatically to dapsone (diaminodiphenylsulphone) therapy even with continued gluten exposure. Nevertheless, the treatment of choice for DH is a gluten-free diet (GFD), as it may reduce or eliminate the need for medication, treats coexisting enteropathy, and reduces the risk of complications of celiac disease.[31] On average, it takes 2 years of adherence to a GFD for complete resolution of lesions, which can recur within 12 weeks after reintroduction of gluten.[32] Spontaneous remission of DH can occur; in a cohort of 86 patients, 10 patients (12%) experienced complete remission without medication or GFD.[33]

Neurologic manifestations are among the most common extraintestinal features of celiac disease. Peripheral neuropathy is most often seen, with a reported prevalence rate of 49% in an Italian study.[34] Painful paresthesias of the limbs and face are most often reported. Other neurologic findings include headache (46%), depression/anxiety (31%), ataxia (5.4%), migraines (4.4%), and epilepsy (3.3–5%).[35] Gluten ataxia is defined as a sporadic cerebellar ataxia associated with antigliadin antibodies in the absence of an alternative etiology for ataxia.[36] As described by Asamoah and colleagues, the pathogenesis of gluten ataxia appears to be immune-mediated; widespread IgA deposition has been observed in the intestines and brains of patients with gluten ataxia, but not in healthy controls.[16,37]

The management of gluten ataxia has not been rigorously addressed in the literature. Several small case series suggest a variable but generally favorable response to a GFD.[36] The only comparative study that has been conducted to date consisted of a cohort of 43 patients with gluten ataxia who self-selected to adhere to a GFD (26 patients) or a gluten-containing diet (14 patients).[38] After 1 year, the GFD group demonstrated improvement in ataxia—reflected in improved scores on several standard

ataxia tests—that was significant when compared to the non-GFD group. The use of immunosuppressants and intravenous immunoglobulin has been advised as a treatment for gluten ataxia if a strict GFD has not resulted in improvement of ataxia after 1 year or if there is significant progression.[36]

Celiac disease is an autoimmune condition triggered by an environmental precipitant that affects genetically predisposed individuals worldwide. While celiac disease continues to be underdiagnosed in the West, a low index of suspicion among physicians in the developing world has led to gross under-recognition of the disease elsewhere.[18] Celiac disease can affect multiple organ systems, and its tremendously varied clinical presentation implies that physicians of all specialties should keep this condition in mind when evaluating patients. Celiac disease is a common condition that—once considered—is easily diagnosed; unfortunately, it appears that a lack of consideration is preventing a higher rate of diagnosis.

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