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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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