

Neurological manifestations, diagnosis, and treatment of celiac disease: A comprehensive review

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Abstract

Celiac disease or gluten sensitivity may initially present as one or more neurological signs and/or symptoms. On the other hand, it may be associated with or complicated by neurological manifestations. Neurological presentations are rare in children but as many as 36% of adult patients present with neurological changes. With severe malnutrition after progression of celiac disease, different vitamin deficiencies may develop. Such problems can in turn overlap with previous neurological abnormalities including ataxia, epilepsy, neuropathy, dementia, and cognitive disorders. In this study, we aimed to review the neurological aspects of celiac disease. Early diagnosis and treatment could prevent related disability in patients with celiac disease.

Introduction

Celiac disease, also called gluten-sensitive enteropathy or nontropical sprue, is a common cause of malabsorption.¹ Allergic response to the cereal grain protein (gluten) causes small intestine inflammation and results in malabsorption.² In fact, celiac disease is an

autoimmune inflammatory condition that affects small intestine. Reports in 1950s suggested the prevalence of celiac disease in Europe to range from 1 in 8000 to 1 in 4000 people.¹ However, new investigations based on small intestine biopsy have shown higher prevalence of 1 in 500 to 1 in 300 people in most countries.¹ The prevalence of celiac disease in the United States is as high as 1 in 113 people.^{1,3} Although celiac disease is classically a disorder among children, it has also been reported among 40-50 year-old individuals. In addition, women are affected twice more than men.²

The etiology of celiac disease is not clearly known. Many factors, such as environmental, genetic, and immunologic factors, are involved in the pathology of celiac disease. Gliadin, a part of gluten present in rye, wheat, and barley, is an environmental factor associated with celiac disease.¹ The immunologic component in the pathogenesis of celiac disease involves both innate and adaptive responses. The most important genes associated with susceptibility to celiac disease are human leukocyte antigen (HLA)-DQ2 and HLA-DQ8.^{3,4} Absence of this relationship fundamentally excludes the diagnosis of celiac disease.¹ HLA typing for both DQ2 and DQ8 may be useful in patients with equivocal small intestine biopsy.^{5,6}

Serum antibodies [anti-gliadin immunoglobulin A (IgA) antibody, IgA anti-endomysial antibody, and IgA antibodies to tissue transglutaminase (tTG)] are present in celiac disease. Due to high specificity (90-95%) and high sensitivity (90-95%), antibody studies are frequently used to identify patients with celiac disease.^{1,7}

Clinical Manifestation

Celiac disease resembles an iceberg phenomenon. Few patients present with classical signs and symptoms primarily to celiac disease or secondary to vitamin deficiencies and nutrient malabsorption. A bigger group of individuals have some manifestations that are not related to gastrointestinal malabsorption, e.g. osteopenia, anemia, and neurologic complications. This type of disease is called atypical celiac disease. Most patients are asymptomatic and diagnosed by serologic investigation and histopathological studies. This type of disease is referred to as silent celiac disease.¹

Although gluten-sensitivity is classically a disease of infants, celiac disease often presents in later, especially in the second and fifth, decades of life.⁸ Consequently, well-known features of a child with life threatening malabsorption is replaced by an atypical or silent celiac disease in adults.⁸ Patients may experience typical gastroenterological manifestations such as steatorrhea, flatulence, bulky stool, and weight loss or complications of severe malnutrition such as anemia and metabolic disorder. They may also have atypical manifestations without gastrointestinal symptoms that present with folate or iron deficiency.⁹ Therefore, asymptomatic relatives of patients with celiac disease have to be screened by serologic or small bowel biopsy studies.¹ On the other hand, there has been a shift from fewer patients who present with typical gastroenterological manifestations to more patients with silent or atypical disease.⁹ Neurological presentations are rare in children but as many as 36% of adult patients present with neurological changes.²

Neurological Manifestations

In the beginning of last century, neurological abnormalities caused by celiac disease were defined as peripheral neuritis in two patients affected by the disease.¹⁰ Ataxia and lower extremity paresthesia were described in 1925.¹¹ From 1964 to 2000, 83 patients (35%) with celiac disease developed ataxia and peripheral neuropathy.¹² The incidence of neurological manifestations related to celiac disease has been estimated to be 6-10%.¹³ Other neurological manifestations are epilepsy, cognitive disorders, dementia, tremor, myelopathy, neuropathy, brainstem encephalitis, progressive leukoencephalopathy, vasculitis, occipital calcification, anxiety/depression, and myoclonic syndrome. They also include neuromuscular manifestation such as peripheral

polyneuropathy, mononeuropathy multiplex, dermatomyositis, polymyositis, and inclusion body myositis.²

Ataxia

Ataxia is one of the most frequent neurological abnormalities in celiac disease.^{2,7} Its predominant clinical manifestations include dysarthria, dysphonia, pyramidal signs, abnormal movements of eyes, and progressive ataxia of gait. Ataxia related to celiac disease is not often associated with typical gastrointestinal symptoms or malabsorption signs.⁷ Hadjivassiliou et al. reported the presence of IgA anti-gliadin antibodies in 41% of patients with idiopathic celiac disease.⁸ In established cases of celiac disease based on small intestine biopsy, gait ataxia, that is often associated with neuropathy, occurs.¹⁴ Ataxia in celiac disease often lacks particular clinical features of distinguishable types of ataxia (cerebellar and sensory ataxia).¹⁵ However, in many patients with ataxia, cerebellar involvement may occur in the presence of low level of vitamin E.^{16,17} Moreover, evidence suggests the possible role of genetics in celiac disease associated with ataxia and neurodegenerative disorders such as Huntington's disease and spinocerebellar degeneration.¹⁸ There is an immune-mediated progressive ataxia associated with anti-gliadin and anti-endomysium antibodies and HLA DQB1*0201 haplotype. In some patients, small intestine biopsy reveals villus atrophy consistent with gluten-sensitive enteropathy.¹⁹ Although the exact etiology of celiac-associated ataxia is not known, gluten toxicity per se and vitamin E deficiency are considered for further investigation.²⁰ Effective treatment by vitamin E supplements in some patients with celiac disease and ataxia supports the mentioned hypothesis.^{20,21}

Ataxia may be developed as a pancerebellar syndrome due to presentation of enteropathy associated T cell lymphoma and lymphomatous metastases to the cerebellum. This diagnosis should be kept in mind for patients with celiac disease-related enteropathies before relating cerebellar findings to different vitamin or other nutritional deficiencies or an associated autoimmune mechanism.²¹

Neuropathy

Another neurological manifestation of celiac disease is peripheral neuropathy. Some studies have reported that up to 50% of patients with celiac disease may develop a form of peripheral neuropathy.²² Subclinical peripheral neuropathy in celiac patients without electrophysiological changes is demonstrated by lower pain threshold and reduced heat and touch sensations.²³ In some tertiary

referral centers, peripheral neuropathy due to biopsy proved celiac disease was found in 2.5% of all patients who were evaluated for neuropathy.²⁴ Since vitamin deficiency is rare in peripheral neuropathy, it cannot have a significant role in describing the etiology of disease in celiac patients. The role of direct gluten toxicity is not significant, either.²⁴

Normal nerve conduction while there are permanent and severe pain and sensory loss are evidences for small-fiber involvement and could be considered as early findings in celiac neuropathy.²⁴ Presence of many symptoms in favor of peripheral neuropathy while results of electro-diagnostic studies are normal, show peripheral neuropathy is restricted to small neurologic fiber alone in which electro-diagnostic study is not sensitive enough to detect abnormalities of small fiber.²⁵ The predominant manifestation of peripheral neuropathy in physical examination celiac patients is sensory neuropathy with variable involvement of large and small fibers.²⁵ Since peripheral neuropathy may precede the diagnosis of biopsy-proven celiac disease, celiac disease should be considered especially in patients with symmetrical distal form of sensory neuropathy.^{26,27} Another neuropathic manifestation of celiac disease is a rapidly progressing syndrome like acute inflammatory demyelinating polyneuropathy, mononeuritis multiplex, pure motor neuropathy, autonomic dysfunction, and Guillain-Barre-like syndrome.²⁷ Electrodiagnostic studies and biopsy samples from skin or sural nerve may be abnormal and autoantibodies against gangliosides may be detected.^{28,29} A rare manifestation of neuropathy is associated with lymphoma in complicated and prolonged celiac disease. It may occur directly or indirectly as a paraneoplastic involvement.³⁰

Headache

An association between celiac disease and migraine headaches was not established when compared to general population. However, results of functional imaging studies such as single photon emission computed tomography (SPECT) were in favor of migraine, and a gluten free diet may lead to an improvement in the migraine in these patients.³¹

Impaired Cognitive Function

Dementia in the form of memory impairment could be presented in celiac disease. It develops as acalculia, confusion, amnesia, and personality disorder.^{32,33} Alzheimer's dementia was reported in three of seven elderly patients with celiac disease who had been diagnosed after 60 years of age. However, the etiology and specific treatment of this complication were not known clearly.³⁴ In another report, some isolated cases of dementia in celiac patients have been described.³⁵

Psychiatric Manifestations

Relationships between celiac disease and psychiatric

disorders such as anxiety and depression have been described especially when celiac disease initiates after 60 years of age. In one patient with schizophrenic disorder and changes in brain imaging (hypoperfusion of the left frontal lobe by SPECT scanning), dramatic response was reported after starting gluten free diet. Therefore, gluten toxicity was suggested to be responsible in the pathogenesis of celiac disease. It was hence supposed that gluten toxicity could have also played a role in the associated psychosis.³⁶

Epilepsy

The incidence of epilepsy (seizure disorder) in patients with celiac disease has been reported as high as 5.5%. Since many patients are asymptomatic, the valid prevalence of epilepsy associated with celiac disease could be higher.³⁷ Screening studies have revealed the prevalence of celiac disease among patients with epilepsy to be 1 in 127 to 1 in 40 people.³⁷

The most common form of epilepsy in celiac disease is complex partial type. However, generalized seizures may also occur. In 1970, a peculiar syndrome of celiac disease, epilepsy, and cerebral calcifications has been described in children and adults.^{38,39} Calcification pattern in this state is bilateral and localized in the parieto-occipital area. It is in fact similar to calcifications in Sturge-Weber syndrome.⁴⁰ Central nervous system folate deficiency secondary to malabsorption caused by celiac disease was described as the possible etiology of this syndrome.³⁸ Interestingly, patients with epilepsy and cerebral calcifications without histologic evidence of celiac disease were noted to have the same HLA phenotype as those with celiac disease. This suggests a genetic linkage between celiac disease and this calcifying angiodyplasia.²⁹

Myoclonic Syndrome

A myoclonic syndrome, often accompanied by ataxia, may occur in celiac disease. This situation occurs in presence of normal levels of vitamins E and B12.⁴¹ These patients have gastrointestinal symptoms such as abdominal pain, chronic diarrhea in different degrees, and action or reflex myoclonus.⁴² Myoclonus may present as focal, multifocal, or generalized convulsions. It starts with polyspike discharges on electroencephalogram (EEG). Jerky movements will develop after discharges. In addition, opsoclonus-myoclonus has been described in a child with celiac disease.⁴³

Vitamin Deficiency Syndromes

Vitamin deficiency secondary to malabsorption in celiac disease can cause abnormal neurological findings.⁴⁴ For the presence of neurologic manifestations secondary to celiac disease, severe

and extensive involvement of small intestine, especially its proximal part, is necessary.⁴⁴ Thiamin (vitamin B1) deficiency due to celiac disease per se is rare but was reported in the presence of concomitant alcohol abuse or substance dependence.⁴⁴ Wernicke-Korsakoff syndrome results in thiamin deficiency. In addition, anything that encourages glucose metabolism will exacerbate an existing clinical or sub-clinical thiamine deficiency.⁴⁵ On the other hand, thiamine deficiency may lead to beriberi which in turn leads to a sensory axonal neuropathy and may be presented by burning feet and cardiac failure.⁴⁶ The main absorptive site for vitamin B12 is the distal part of the small intestine. Since this site is not usually involved in celiac disease, vitamin B12 deficiency is generally uncommon in uncomplicated celiac disease. However, vitamin B12 deficiency has been reported in celiac patients due to pancreatic involvement and bacterial overgrowth that had altered ileal receptors uptake and motility function of the small bowel. Another possible reason for vitamin B12 deficiency is the presence of autoimmune gastritis with pernicious anemia accompanied by celiac disease.⁴⁷ Vitamin E deficiency can lead to ataxia and sensory neuropathy in patients with celiac disease.⁴⁸ Niacin deficiency may present by dementia, ataxia, and seizure but this problem is rare.⁴⁹

Diagnosis

Heightened suspicion and increased awareness about celiac disease result in a substantially increased rate of diagnosis. In patients with any neurological manifestations and a positive familial history of celiac disease, other autoimmune diseases, or malabsorption manifestations, celiac disease should be considered as a differential diagnosis. Further evaluations will thus be necessary.⁵⁰

A small bowel biopsy is the cornerstone of diagnosis in celiac disease. A good biopsy should be performed from D2 portion and distal part of duodenum. D1 biopsies are not diagnostic for celiac disease since their normal appearance resembles celiac changes in pathology. In other words, absent or shorter intestinal villi can be normally seen in mucosal biopsies from D1 portion. A small intestine biopsy should be performed in persons with malabsorption syndrome or complications related to malabsorption such as nutrient deficiency with a positive endomysial antibody test.¹ In addition, it is more prudent to perform a biopsy than to obtain another test of intestinal absorption which can never completely exclude or establish this diagnosis.¹

Many changes in pathology are suggestive of celiac disease. Among these changes are cuboidal appearance, increased lymphocyte and plasma cell infiltration in lamina propria, absence of villi or reduced villous height resulting in flat appearance, and increased crypt cell proliferation. Such changes are characteristic but

not diagnostic in celiac disease because the same appearances can be seen in many conditions such as Crohn's disease, gastrinoma, lymphoma, eosinophilic gastroenteritis, tropical sprue, bacterial overgrowth, and milk protein intolerance in children. Therefore, definite diagnosis of celiac disease is based on histological appearance and clinical and histological response to a gluten-free diet.^{1,51} All tests should be performed while patients are on gluten-rich diet.⁹

In summarized approach to diagnosis of celiac disease, suspected persons would be categorized to two groups with low or high probability of celiac disease. Patients with diabetes type 1, anemia, steatorrhea, unexplained iron deficiency, failure to thrive (in children) or positive family history of celiac disease will be considered as the high risk group.⁹ The first group will receive IgA anti-endomysial antibody (IgA-EMA) or tTG antibodies and the diagnosis will be excluded if serology is negative. In case of positive serology, small intestine biopsy should be performed. The second group will require both small bowel biopsy and IgA-EMA/tTG antibody. If both histology and serology are negative, the diagnosis of celiac disease will be excluded. In cases with negative serology and positive histology, further management will depend on total serum IgA level and HLA-DQ2/HLA-DQ8. In cases with positive serology and negative histology, IgA-EMA/tTG serology should be repeated and biopsy should be reviewed again by an expert pathologist.⁹ In both groups, if serology and biopsy are positive, treatment should be started.⁹ Positive serum IgA-EMA or tTG antibodies should disappear after a gluten-free diet. Readministration of gluten as a diagnostic plan with or without an additional biopsy is not necessary.¹ Diagnostic approach for celiac disease is summarized in figure 1.

Treatment

A gluten-free diet, through the removal of all substances containing wheat, barley and rye, is the cornerstone of treatment in celiac disease. Mucosal injury may occur after consumption of small amounts of dietary gluten. Therefore, reviewing patients' food list and eliminating all substances containing gluten is necessary. Although improvements of symptoms after initiation of gluten-free diet have been seen during the first and second weeks, histopathologic changes may take one to two months.^{1,51}

A gluten-free diet typically improves gastrointestinal symptoms, normalizes antibodies, and enhances small bowel mucosal histopathologic changes. Although mucosal injuries can be improved by a gluten-free diet, normalization of histopathology is not completely achieved. Consultation with a nutritionist for education is necessary.⁵²

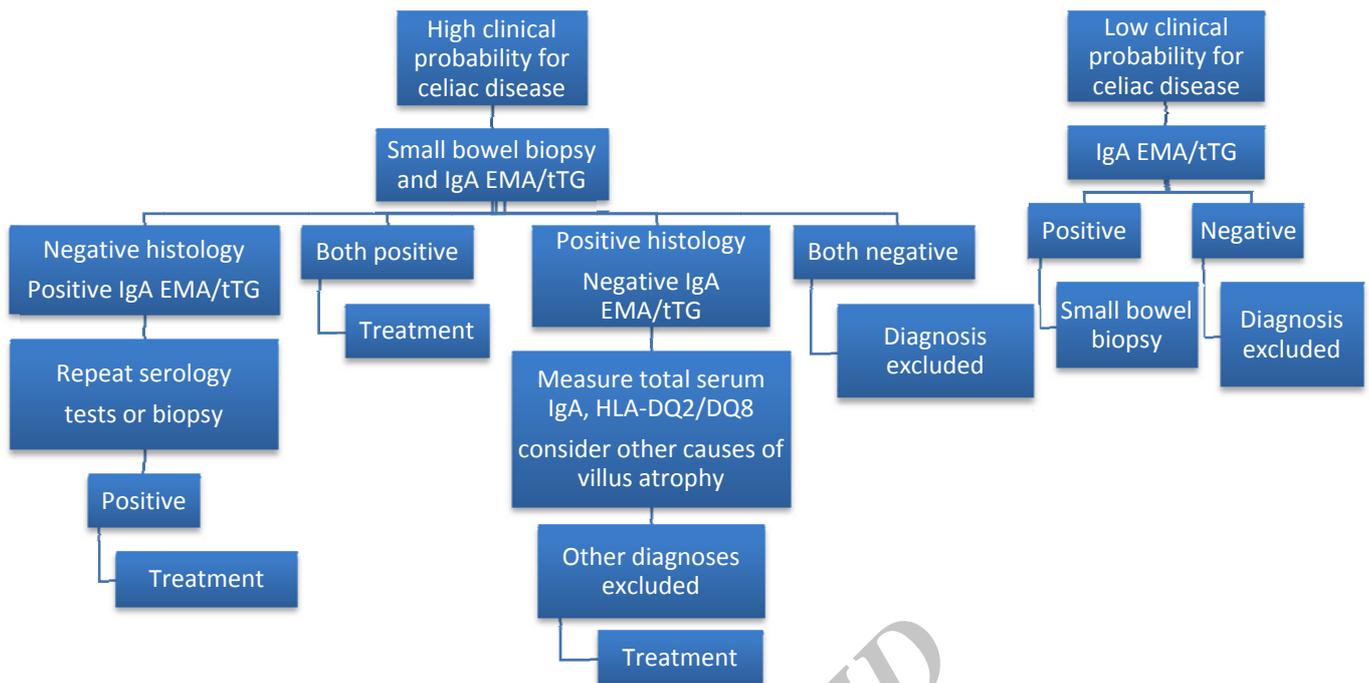


Figure 1. Diagnostic approach for celiac disease (tTG: Transglutaminase antibody; IgA EMA: Immunoglobulin A endomysial antibody; HLA: Human leukocyte antigen).

Overall, neurological manifestations will also be improved by a gluten-free diet alone. In some patients with celiac associated ataxia, supplementation with vitamin E has apparently been useful.⁵³ Recent investigations have shown intravenous immunoglobulin therapy to be the treatment of celiac associated ataxia.⁵⁴ Likewise, intravenous immunoglobulin may be beneficial in treatment of multifocal axonal polyneuropathy in patients with celiac disease.⁵⁵ A gluten-free diet, especially one initiated soon after the onset of epilepsy, is useful in controlling seizure.⁵⁶ In some cases with myoclonus syndrome among whom anticonvulsant or benzodiazepine therapy is not completely effective, improvement occurs after using a gluten-free diet.⁵⁷

More than 90% of patients improve with gluten-free strategy. The most common cause of failure of gluten-free diets is continuing gluten intake. The remaining 10% is called patients with refractory celiac disease or refractory sprue. This group includes individuals who respond to restriction of other dietary

protein, e.g. soy, respond to glucocorticoids, develop gradual improvement after months or years, and fail to respond to all sorts of interventions. The last group have poor prognosis and develop complications of celiac disease such as intestinal T cell lymphoma.¹

Conclusion

Although some authors reported that celiac disease may be initially defined after presentation with a neurological disorder, convincing documents of a causal association between celiac disease and specific neurologic conditions have not been definitely established. Accordingly, routine screening for celiac disease in patients with unknown or idiopathic neurological syndromes cannot be recommended.² Further studies are needed to determine the role of gluten-free diets in treatment of neurological manifestations in the absence of overt intestinal disease.⁸ Nutritional deficiencies, which are rarely the sole cause of neurological manifestations, are easily correctable.

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