Peripheral Neuropathy and Celiac Disease

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Opinion statement

Peripheral neuropathy (PN) is one of the most frequently reported neurologic manifestations associated with celiac disease (CD), a multigenetic, T-cell–mediated autoimmune disorder that results from a loss of tolerance to gluten. Sensory axonal and small fiber sensory polyneuropathies are the most frequently reported PN subtypes. Multifocal motor or sensorimotor neuropathies and a more fulminant neuropathy, associated with ataxia and other neurologic manifestations, also have been reported. The effect of a gluten-free diet on CD-associated PN has not been studied systematically or prospectively; nevertheless, a gluten-free diet currently is the cornerstone of therapy. Although idiopathic ataxia associated with anti-gliadin antibodies and other neurologic complications have been reported to respond to this diet; there is data that indicate that neurologic manifestations may develop or persist, independent of gluten exposure. There is evidence to suggest that inflammatory processes may be involved. Immunomodulatory agents (such as intravenous immunoglobulin or infliximab), described to be beneficial in the treatment of refractory CD or CD-associated ataxia, may have a role in the management of CD-associated PN

Introduction

Celiac disease (CD) is a multigenetic, T-cell–mediated, autoimmune disorder that results from a loss of tolerance to gluten (the storage protein found in wheat) and similar proteins in barley and rye. This results in an immune reaction in the small intestinal epithelium and lamina propria, which typically regresses with gluten withdrawal [1••]. CD is linked closely to the human leukocyte antigen alleles DQ2 and DQ8, and is estimated to occur in 0.5% to 1% of the population, with an incidence of up to 5% in at-risk groups [2••, Class I]. Extra-intestinal signs and symptoms (such as iron-deficiency anemia, osteoporosis, infertility, and neurologic manifestations) are increasingly recognized to be the common clinical presentations of CD in adults in the fourth to sixth decades. Other autoimmune disorders, such as diabetes mellitus, thyroid disease, cardiomyopathy, or IgA deficiency, occur more frequently in patients with CD than in the general population [3••].

Celiac disease is diagnosed by characteristic changes in a duodenal biopsy or the finding of improved clinical symptoms or histologic tests after adherence to a gluten-free diet (GFD). Serologic tests, including antibodies directed against gliadin (IgG and IgA), endomysium (IgA), or transglutaminase (IgA), the auto-antigen for the endomysial antibodies, are useful for screening and monitoring. However, their diagnostic value is limited by the lack of sensitivity in patients with mild disease or IgA deficiency and the lack of specificity of the IgG gliadin antibodies [1••].

Celiac disease implies a disease characterized by an abnormal duodenal biopsy with either clinical or histologic improvement while following a GFD, whereas the term “gluten sensitivity” has been used to describe patients with CD-associated antibodies or clinical improvement on a GFD, who may not have had a confirmatory duodenal biopsy.

Table 1. Neurologic manifestations reportedly associated with celiac disease or gluten sensitivity

Peripheral neuropathy
Ataxia
Epilepsy
Epilepsy and cerebral calcifications
Anxiety/depression
Schizophreniform disorder
Dementia
Headache with white matter abnormalities
Cerebral vasculitis
Brainstem encephalitis
Progressive multifocal leukoencephalopathy
Huntington's disease
Myoclonus
Chorea
Neuromyotonia
Stiff-person syndrome
Inclusion body myositis
Polymyositis

NEUROLOGIC MANIFESTATIONS ASSOCIATED WITH CELIAC DISEASE

Neurologic manifestations are estimated to occur in 6% to 10% of patients with CD, with higher percentages reported in patients with gluten sensitivity [4••]. Numerous neurologic manifestations have been described, particularly during the last decade (Table 1). Peripheral neuropathy and ataxia are the two most frequently reported manifestations [5••].

Peripheral neuropathy and celiac disease The exact incidence of peripheral neuropathy in CD or gluten sensitivity is unknown. Luostarinen *et al*. [6••, Class II] found that six (23%) of 26 patients with CD that was well-controlled by diet had peripheral neuropathy versus a 4% occurrence rate in the control group. Patients with CD also were observed to have higher heat pain and tactile thresholds. At our tertiary care referral center, 2.5% of the patients evaluated for neuropathy had CD [7••, Class III].

CLINICAL PRESENTATIONS

The timing of PN symptoms in relation to enteropathic symptoms or adherence to a GFD is variable. PN may develop before or after the onset of enteropathic symptoms, or in isolation [4••]. Several types of PN have been described.

A predominantly small fiber sensory neuropathy is a common presentation. We described 20 patients with CD and sensory neuropathic symptoms and signs, who had normal or minimally abnormal electrodiagnostic studies. All patients reported painful limb paresthesias and 30% reported facial or oral paresthesias. Five patients (25%) reported mild gait instability. On examination, a sensory neuropathy with variable involvement of small and large fibers was found. Impaired imbalance was detected in seven (35%) of the patients, and distal weakness was detected in two patients. We found that 5% of patients with neuropathic symptoms and signs and normal electrodiagnostic studies seen during a 1-year period had CD [7••, Class III].

Symmetric predominantly sensory neuropathy with mild lower limb weakness has been described in patients with CD [8–10, Class III] or gluten sensitivity [5••]. Other findings include absent ankle jerks, variable gait imbalance, and predominantly axonal electrodiagnostic features.

Neuropathy associated with other features such as ataxia (limb or gait), extrapyramidal or autonomic features, dysarthria, or myoclonus. The first detailed pathologic data on patients with CD and PN was obtained from 16 patients, most of whom had severe, fulminant peripheral neuropathies associated with cerebellar dysfunction, spinal cord dysfunction (particularly of the dorsal or lateral columns), or myopathy [11••, Class III]. Four additional patients with similar clinical pictures were described 30 years later [12, Class III]. The global neurologic manifestations in these patients developed within months to years of the CD diagnosis and persisted despite strict adherence to a GFD.

Patients with gluten sensitivity [13••, Class II] or CD [14, Class III] also may present with ataxia (possibly of central or peripheral origin) as the predominant feature and may have minimal or subclinical findings of peripheral neuropathy. Such patients have been reported to respond to respond to a GFD [13••, Class II; 14, Class III] or immunomodulatory treatment [15,16•, Class III].

Mononeuritis multiplex or multifocal motor or sensorimotor polyneuropathy also have been found. Kelkar *et al*. [17, Class III] first reported a case of mononeuropathy multiplex (MM) associated with CD in 1996. They described a patient who presented with acute left wrist drop and right hand symptoms. Muscle biopsy revealed perivascular and perineural lymphocytic infiltrates that were highly suspicious for vasculitis. Hadjivassiliou *et al*. [5••] also have mentioned MM as a neurologic presentation in 15 patients with gluten sensitivity.

Other reported neuromuscular manifestations associated with CD include motor neuropathy, inclusion body myositis, neuromyotonia, or a combination of polymyositis and neuropathy [18•, Class III].

Electrodiagnostic features Chronic, axonal changes or normal or minimally abnormal electrodiagnostic findings have been the most frequently reported electrodiagnostic abnormalities in CD-associated PN [7••,8–10, Class III]. Demyelinating features rarely have been reported [19,20, Class III].

Pathologic studies Necropsy of patients with severe, progressive neuropathy and gait or limb ataxia has shown cerebellar findings (neuronal loss in the cerebellum, Purkinje cell loss), spinal cord pathology (degeneration of the dorsal columns), and inflammatory cell infiltrates (lymphocytes and macrophages) in the spinal nerve roots [11••,12, Class III]. Neuronal loss in the cerebral cortex and deep gray matter structures also may occur. Cooke and Smith [11••, Class III] found the internal structure of an axon's terminal expansion to be disorganized and detected phagocytosis of degenerating axoplasm by Schwann cells. Intramuscular nerve trunks showed collateral branching and diffuse swelling of terminal axons, as seen in distal axonopathy.

Sural nerve biopsies from three patients with CD and PN revealed axonopathic findings, with a wide range of severity. No onion bulbs, infiltrating lymphocytes, macrophages, or immune deposits were seen [7••, Class III]. Demyelinating features have been detected in a patient with a rapidly progressive neuromyopathy [12, Class III].

Quantitation of the epidermal nerve fiber density in skin biopsies obtained from the distal leg, proximal thigh, or distal forearm is a useful method for confirming the diagnosis of small fiber neuropathy. In a series of eight patients with CD, PN and normal or minimally abnormal electrodiagnostic studies, the epidermal nerve fiber density was below the fifth percentile in five patients. The remaining three patients had morphologic changes and the epidermal nerve fiber density was in the low normal range [21•, Class III].

DISEASE MECHANISMS

The mechanisms by which gluten ingestion leads to damage to the neuraxis remain obscure. Deficiencies of vitamin E, folate, calcium, and magnesium have been reported as reversible causes of neurologic manifestations [8,20,22, Class III] but rarely are found. Several lines of evidence suggest that an immune-mediated mechanism is a more plausible explanation and inflammatory processes may persist, independent of gluten-exposure.

Immunologic factors that contribute to the development of the disease may include molecular mimicry, with the presence of common epitopes shared by gliadin and nerve components. Ganglioside molecules of peripheral nerves are well-known targets of immune-mediated neuropathies and as many as 65% of studied patients with celiac neuropathy were found to have raised antibody titers against one or more gangliosides [7••,23•, Class III]. Additionally, glycosylated gluten species may contain epitopes that mimic ganglioside carbohydrates, with the potential to generate antibody cross-reactivity [24].

Gliadin proteins and cerebellar Purkinje cells also may share common epitopes. Sera from patients with gluten ataxia were found to stain human cerebellar and rat CNS tissue at high dilutions. Sera from these patients also were adsorbed with crude gliadin to remove anti-gliadin antibodies. However, staining of the cerebellar tissue by the post-adsorption sera persisted, suggesting that additional antibodies (other than anti-gliadin antibodies) may play a pathogenic role. The target antigen has yet to be characterized [25•, Class II].

Tissue transglutaminase (tTG), the autoantigen recognized by anti-endomysial antibodies, is an enzyme with protein cross-linking capabilities, primarily found in the cytoplasm of epithelial cells. It also is found in neurons and has been implicated in neurodegenerative diseases, such as Alzheimer's disease, supranuclear palsy, Huntington's disease, and Parkinson's disease [26]. Conceivably, antibodies could develop against tTG cross-linked to other proteins of the neuraxis, resulting in various manifestations, such as ataxia or seizures.

Treatment

Diet and lifestyle

- Currently, strict adherence to a GFD is the only available treatment for patients with CD or CD-associated PN. This requires the complete avoidance of wheat, barley, and rye. Oats, which may be contaminated by gluten during processing, generally are avoided, at least initially [3••]. Careful scrutiny of the contents of medications and processed food products is necessary. Consultation with an experienced gastroenterologist and dietician and participation in support groups is advised. Clinicians should be alert for osteoporosis, anemia, or any deficiencies of iron, folate, or vitamins D and E.
- Although improvement or normalization of intestinal histopathologic findings or serologic abnormalities typically results from adherence to a GFD, the response of CD-associated PN to this diet has not been studied in a systematic, prospective fashion. Patients with intractable intestinal symptoms and fulminant neurologic presentations generally did not respond to

a GFD and patients have been reported to develop neurologic symptoms, or show no beneficial response, while strictly adhering to a GFD [6••, Class II; 7••, Class III].

- However, there are case reports of patients who, after dietary indiscretion, developed clinical deterioration and axonal [9,12, Class III] or demyelinating [19, Class III] neuropathies that improved with resumption of the GFD. One patient with ataxia and subclinical CD was reported to have a beneficial response to a GFD [14, Class III]. Similarly, a cohort of 26 patients with gluten ataxia was found to have improvement of ataxic symptoms at 1 year, in comparison with the control group of 14 patients [13••, Class II]. There also are case reports of other associated neurologic or psychiatric conditions (such as seizures, headaches, or mood disorders) responding to a GFD [4••].
- The apparent lack of benefit of a GFD in some patients with PN could be attributable to several factors such as dietary noncompliance, irreversible injury to peripheral nerves or dorsal root ganglia, or the presence of an inflammatory process independent of gluten exposure.

Pharmacologic treatment

- Intravenous immunoglobulin has not been studied in patients with CD and PN. However, it has been reported to be beneficial in one patient with ataxia and CD [16•, Class III] and in four patients with gluten ataxia [15, Class III].
- Although immunosuppressive treatments, such as steroids, azathioprine, or infliximab [27–29, Class III] have been reported to benefit CD patients with refractory gastrointestinal symptoms, their effect on neurologic manifestations of CD has not been studied.

Symptomatic treatments

- Standard treatments for neuropathic pain (such as anticonvulsants [gabapentin, lamotrigine, oxcarbazepine, and topiramate], tricyclic antidepressants, tramadol, transdermal lidocaine or fentanyl, or methadone) may be tried if necessary. Methods of use of these agents have been reviewed elsewhere [30•].
- A spinal cord stimulator reduced the pain level in one patient with CD and a painful, chronic, presumably small fiber peripheral neuropathy that was refractory to a GFD [31, Class III].

Emerging therapies

- A deeper understanding of the mechanisms behind loss of tolerance to gluten will have therapeutic implications for the prevention and management of the neurologic manifestations of CD. The development of genetically modified wheat lacking key peptides or the development of agents which block intestinal tTG or the human leukocyte antigen molecules, which present the key peptides to anti-gluten T cells, may hold therapeutic promise [1••].

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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