Celiac neuropathy

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Abstract—*Background:* Celiac disease (CD) is a chronic inflammatory enteropathy resulting from sensitivity to ingested gluten. Neurologic complications are estimated to occur in 10% of affected patients, with ataxia and peripheral neuropathy being the most common problems. The incidence and clinical presentation of patients with CD-associated peripheral neuropathy have not previously been investigated. *Objective:* To determine the incidence of CD in patients with neuropathy and to characterize the clinical presentation. *Methods:* The records of 20 patients with neuropathy and biopsy-confirmed CD were reviewed. *Results:* Six of the 20 patients had neuropathic symptoms alone without gastrointestinal involvement, and neuropathic symptoms preceded other CD symptoms in another 3 patients. All patients had burning, tingling, and numbness in their hands and feet, with distal sensory loss, and nine had diffuse paresthesias involving the face, trunk, or lumbosacral region. Only two had weakness. Results of electrophysiologic studies were normal or mildly abnormal in 18 (90%) of the patients. Sural nerve biopsies, obtained from three patients, revealed mild to severe axonopathy. Using the agglutination assay, 13 (65%) of the patients were positive for ganglioside antibodies. Excluding patients who were referred with the diagnosis of celiac neuropathy, CD was seen in approximately 2.5% of all neuropathy patients and in 8% of patients with neuropathy and normal electrophysiologic studies seen at our center. *Conclusion:* CD is commonly associated with sensory neuropathy and should be considered even in the absence of gastrointestinal symptoms.

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Celiac disease (CD) is a chronic inflammatory enteropathy resulting from sensitivity to ingested gluten. It is characterized by elevated titers of antibodies to gliadin and transglutaminase, with inflammatory cell infiltration, crypt hyperplasia, and villous atrophy in the mucosa of the small intestine.[1] Approximately 10% of CD patients have an associated neurologic disease, most often peripheral neuropathy or ataxia but also seizures, dementia, or psychiatric illness.[2,3] Because CD can be subclinical, with approximately half of adult-onset patients lacking prominent gastrointestinal symptoms,[1] we screened patients with neuropathy at our center for the presence of elevated antigliadin or transglutaminase antibodies. The diagnosis of CD in patients with elevated antibody titers was confirmed by small bowel biopsy. The records of these patients and those referred to our center with the diagnosis of CD were reviewed to determine whether there is a characteristic clinical presentation.

Methods. *Patient evaluation.* The medical records of all patients with neuropathy and biopsy-confirmed CD seen at the Pe-

ripheral Neuropathy Center of the Weill Medical College of Cornell University between July 1, 2001 and June 30, 2002 were reviewed. Approximately 400 patients were seen during this period and screened for immunoglobulin (Ig) G and IgA antigliadin and IgA transglutaminase antibodies using a commercial assay (Quest Diagnostics, Teterboro, NJ). Twenty of these patients had elevated antigliadin or transglutaminase antibody levels with CD subsequently confirmed by duodenal biopsy (see table E-1 on the *Neurology* Web site). Six patients (Patients 9, 13, 14, 15, 18, and 19) sought treatment for neuropathy and were found to have CD during the course of evaluation. Five other patients (Patients 2, 3, 10, 11, and 20) were seen for peripheral neuropathy but gave a history of childhood CD. Nine of the 20 patients were diagnosed elsewhere with CD and were referred for evaluation of celiac-associated neuropathy. In all 20 patients, the diagnosis of CD was confirmed by duodenal biopsy, which showed the characteristic histologic features of villous atrophy, crypt hyperplasia, and inflammatory cell infiltrates. All duodenal biopsies were reviewed by one of the authors (P.G.). Three additional patients with sensory neuropathy had elevated IgA antigliadin or transglutaminase antibodies, which are more specific than IgG antigliadin antibodies,[1] but small bowel biopsy did not confirm the diagnosis of CD, and they were not included in the study.

All patients underwent neurologic examination, electrophysiologic studies, and blood tests for known causes of neuropathy. Three of the patients (Patients 11, 13, and 19) had sural nerve biopsies. All patients were tested on at least one occasion for antiganglioside antibodies using the ganglioside agglutination assay.[4]

Results. *Clinical presentation.* Of the 20 patients, 6 sought treatment at our center for neuropathic symptoms only and without a diagnosis of CD. Three of the 20 patients reported neuropathic symptoms as their earliest symptoms and were later

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Table 1 *Neuropathic Symptoms*

Symptom	Percentage (N)	Patients
Distal extremity (dysesthesias/paresthesias)	100% (20)	
Facial dysesthesias	35% (7)	Nos. 1, 3, 5, 8, 10, 15, 18
Diffuse multifocal body pains	30% (6)	Nos. 1, 2, 5, 8, 13, 15
Gait (unsteadiness/instability)	25% (5)	Nos. 3, 4, 9, 17, 19
Foot drop	5% (1)	No. 9

diagnosed with CD subsequent to the development of gastrointestinal symptoms or anemia. Eleven were diagnosed with CD because of symptoms of gluten intolerance, including loose stools, diarrhea, or weight loss, which preceded their neuropathic symptoms by 1 year to approximately 60 years. The patients included a mother and daughter (Patients 17 and 4), with the daughter recognizing her own neuropathic symptoms while accompanying her mother to the physician. One patient (Patient 15) had a positive family history of CD and a son with a history of childhood seizures.

All patients had distal paresthesias and dysesthesias in the arms and legs (table 1). These were described as burning, tingling, numb, heavy, and "pins and needles" sensations. Seven of the 20 patients (Patients 1, 3, 5, 8, 10, 15, and 18) also reported facial dysesthesias, including tingling, numbness, formication, hypersensitivity, and chills. Six patients (Patients 1, 2, 5, 8, 13, and 15) reported multifocal painful dysesthesias involving other regions of the body, including the torso, thighs, and buttocks. Five patients reported gait instability (Patients 3, 4, 9, 17, and 19), with one (Patient 9) additionally reporting foot drop.

On neurologic examination, all but three patients (Patients 3, 13, and 19) had mild to moderate sensory abnormalities in the feet, involving pin, light touch, or vibratory perception. Only two patients had weakness, confined to the ankles, on manual muscle testing (Patients 9 and 19). Seven patients (Patients 3, 4, 9, 13, 16, 17, and 19) had impaired balance on Romberg testing or tandem walking.

Associated conditions. Two patients had a history of thyroid disease (Patient 12, hyperthyroidism; Patient 15, hypothyroidism). Other patients had the following diagnoses: sarcoidosis (Patient 7), psoriasis (Patient 10), and gout (Patient 10). One patient (Patient 14) had a 20-year history of type I diabetes mellitus, which was well controlled with an insulin pump, and normal electrodiagnostic studies. Two patients (Patients 10 and 15) had a history of pericarditis. Patient 9 had a remote history of a right foot drop and IgM monoclonal gammopathy without identifiable antibody activity. Patient 3 had a history of eczema and dermatitis herpetiformis. Patients 15 and 16 had a history of iron deficiency anemia. Five patients (Patients 1, 7, 8, 15, and 20) were taking medications for mood disorders (anxiety, depression), and Patient 13 was taking medication for attention deficit–hyperactivity disorder.

Laboratory tests. Results of glucose tolerance testing were normal in the 16 patients who were tested. Vitamin B12 levels were normal in 18 patients and low normal (i.e., 300 to 350; reference, 211.0 to 911.0 pg/mL) in 2 patients (Patients 5 and 14), who had normal methylmalonic acid and homocysteine levels. Vitamin B1 levels were normal in the 15 patients who were tested, and vitamin B6 and E levels were normal in the 16 patients who were tested. Results of tests for other known causes of neuropathy, including thyroid dysfunction, anti–myelin-associated glycoprotein (MAG), anti-Hu, antisulfatide, and Sjögren's antibodies, were negative.

Serum was tested for the presence of antiganglioside antibodies using the ganglioside agglutination immunoassay,[4] with 14 of the patients tested more than once. Six of the 20 patients (30%) were positive on initial testing, and 13 (65%) were positive on at least one occasion (table 2).

Neuroimaging studies. MRI of the lumbosacral spine, obtained in seven patients (Patients 2, 3, 4, 5, 13, 16, and 17), was normal or revealed only mild changes without nerve root compression. MRI of the cervical spine, obtained in 10 patients (Patients 3, 4, 5, 7, 9, 10, 12, 13, 17, and 18), was normal or revealed only mild to moderate degenerative changes in 8 patients. Patient 3 had C5-6 and C6-7 central and right-sided disc herniations, and Patient 12 had an extruded C5-6 disc with mild compression; neither had signal intensity changes within the spinal cord. MRI of the brain, obtained in eight patients, was normal in six patients (Patients 1, 2, 7, 8, 13, and 18) and showed periventricular white matter disease in two patients (Patients 3 and 9). None had evidence of cerebellar atrophy.

Electrodiagnostic testing. EMG and nerve conduction studies were normal in 10 patients and minimally abnormal in 7 patients. In addition, one patient (Patient 14) had the sole finding of absent bilateral H-reflexes, which may be a normal variant. The minimally abnormal findings included mild median neuropathies at the wrist and mild motor or sensorimotor findings predominantly affecting the legs. Two of the 20 patients had severely abnormal findings, including severe sensorimotor involvement of the legs and arms in one patient (Patient 19) and severe dysfunction in the distribution of the right peroneal nerve in another patient (Patient 9). All abnormal electrophysiologic findings were consistent with an axonal process except for prolonged blink reflex R1 latencies, which were two standard deviations above normal in one patient (Patient 19) and more than three standard deviations above normal in another patient (Patient 1).

Nerve biopsy studies. Sural nerve biopsy, including analysis of semithin plastic sections, was performed in three patients (Patients 11, 13, and 19). Patient 11 had a moderately severe, chronic axonopathy with moderate to severe loss of large-diameter myelinated fibers. Regenerative clusters of myelinated nerve fibers and a few isolated thinly myelinated fibers were found. No onion bulbs were identified. Patient 19 had a severe, chronic axonal neuropathy with electron micrographs showing complete loss of myelinated axons. No onion bulbs, infiltrating lymphocytes, or macrophages were seen. Patient 13 had a mild chronic axonopathy. No immune deposits were identified by immunofluorescence stains.

Antigliadin and antitransglutaminase antibodies, and response to therapy. With the exception of 1 patient (Patient 10), all 14 patients who were known to have CD at the time of presentation reported adherence to a gluten-restricted or gluten-free diet for periods ranging from 6 months to 22 years. Initial antigliadin or transglutaminase antibody levels were not available for 3 of these 14 patients (Patients 4, 6, and 11). Of the remaining 11 patients, 5 were negative for antigliadin or antitransglutaminase antibodies when they sought treatment at our center, whereas 6 were positive (4 with elevated IgG antigliadin antibodies, 1 with severely elevated IgG and IgA antigliadin and IgA transglutaminase levels, and 1 with elevated IgA transglutaminase antibodies). Seven of the 14 patients were following a gluten-free diet at the onset of their neuropathic symptoms.

Of the six patients diagnosed with CD during the course of evaluation for neuropathy, all had elevated antigliadin or transglutaminase antibodies when they sought treatment, and all began gluten-free diets after the diagnosis was made. Follow-up serum studies were available for two of these six patients. One patient (Patient 15) had persistent elevation of IgG antigliadin antibody levels with normalization of IgA antigliadin and antitransglutaminase antibody levels, and one (Patient 19) had normalization of IgA antigliadin antibody levels. Two of the six patients (Patients 14 and 19) reported subjective improvement within 2 months of initiating a gluten-free diet, although their neurologic examinations remained unchanged. All together, 13 of the 20 patients were not following gluten-restricted diets at the onset of their neurologic symptoms.

Five patients received IV Ig therapy: four patients (Patients 9, 10, 13, and 15) had 3-month trials without improvement, and one patient (Patient 19) with multifocal sensorimotor neuropathy reported improvement in balance and lower extremity strength and sensation. Trials of plasmapheresis in one patient (Patient 9) and etanercept in another (Patient 13) were without benefit.

Discussion. This study required that the diagnosis of CD be confirmed by small bowel biopsy and

Table 2 *Patient Antibody Studies*

Patient	Known Celiac disease at presentation (Y/N)	Gluten-free diet at presentation (Y/N)	Anti-gliadin antibodies (IgG/IgA)	Anti-transglutaminase antibodies (IgA) (date of study)	Ganglioside agglutination (positive result/total no. of tests)
1. F/63	Y	Y	1/1	3	1/1
2. F/63	Y	Y	22/3	5	0/2
3. F/84	Y	Y	15/3	6	1/2
4. F/44	Y	Y	NA	NA	2/3
5. F/55	Y	Y	14/5	6	1/2
6. F/53	Y	Y	NA	NA	1/2
7. M/44	Y	Y	77/5	NA	1/2
8. F/49	Y	Y	11/6	29	0/1
9. M/79	N	N	33/35	7 (9/7/01)	0/4
10. M/72	Y	N	>200/521	87 (2/1/01)	1/4
			196/200	161 (7/26/01)	
			166/195	64 (4/6/02)	
			110/126	45 (6/27/02)	
11. F/68	Y	Y	NA	NA	1/1
12. F/68	Y	Y	33/17	9	2/2
13. M/55	N	N	14/22	35	0/1
14. M/48	N	N	30/61	256	0/1
15. F/47	N	N	62/55	107 (11/05/01)	0/2
			39/<20	<20, (4/16/02)	
16. F/77	Y	Y	2/11	16	2/4
17. F/70	Y	Y	8/3	6	1/3
18. M/31	N	N	177/33	6	0/1
19. M/54	N	N	13/22	6 (1/14/02)	1/2
			16/18	11 (4/20/02)	
20. F/53	Y	Y	25/16	20	1/2

Reference values: Anti-transglutaminase (IgA) and anti-gliadin (IgG, IgA) antibodies: <20 units, negative; 20–30 units, weak positive; >30 units, moderate to strong positive.

NA = not available.

excluded patients with elevated antigliadin or transglutaminase antibody titers and negative biopsy results. Patients meeting these criteria represented approximately 5% of all patients with neuropathy seen at our center, or 2.5% if the nine patients who were referred with the diagnosis of celiac neuropathy were excluded. This is a considerably higher number than the 0.5% prevalence of CD in the general population,[5] indicating more than a coincidental association.

A majority of the patients had sensory neuropathy and normal or mildly abnormal electrophysiologic studies. Only two had weakness, which was distal and asymmetric. Where abnormal, the electrophysiologic studies suggested an axonal process, which is consistent with previous descriptions of axonal neuropathy in such patients.[6–11] Diagnosis of neuropathy in patients with normal electrophysiologic studies was based on the clinical presentation and distal sensory loss and confirmed by sural nerve biopsy in three

patients. Although patients with neuropathy and normal electrophysiologic studies are frequently classified as having small fiber neuropathy,[12] the presence of distal vibratory loss and the findings on sural nerve biopsy make that diagnosis unlikely. It may be that in patients with CD there is fascicular or spotty fiber loss that may not always be detected with routine electrophysiologic testing, possibly because of a sufficient number of remaining normal fibers. Normal sensory nerve action potentials have been reported in some patients with demyelinating polyneuropathies.[13] In one study, 11% of patients with neuropathy and normal sensory conductions had demyelinating abnormalities detected using near nerve recordings.[14] We also found that some patients with biopsy-proven sensory chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) may have normal routine electrophysiologic studies.[15] Excluding patients who were referred for CD-associated neuropathy, the patients with celiac

neuropathy and normal electrophysiologic studies constituted approximately 8% of all patients with neuropathy and normal electrophysiologic studies seen at our center.

Our experience differs from that of Hadjivassiliou et al.,[3] who reported that 40% of their patients with idiopathic neuropathy had gluten sensitivity based on serologic testing. However, most of their patients had selective elevations of IgG antigliadin antibodies, which may occur in 12% of the normal population,[16] with only approximately one-third exhibiting villous atrophy on duodenal biopsy. Serologic studies may miss some cases of CD, and duodenal biopsy may show only lymphocytic infiltration rather than unequivocal CD changes.[17,18] Therefore, the true incidence of CD in patients with neuropathy may be higher than that seen in our study.

Approximately one-third (n = 6) of our patients with neuropathy and biopsy-proven CD sought treatment for neuropathic symptoms alone, without gastrointestinal symptoms, and the diagnosis would have been missed if they had not been screened for antigliadin or antitransglutaminase antibodies. Gastrointestinal symptomatology in patients with CD depends on the extent of small bowel involvement,[19] and the symptoms may be mild or absent in less severely affected patients. Only 50% of adults with CD seek treatment for a classic diarrhea-predominant illness[1] with the other common presentations, including iron deficiency anemia,[20] osteoporosis,[21] and incidental recognition at endoscopy for dyspeptic symptoms.[22] Other associated inflammatory conditions include type I diabetes, dermatitis herpetiformis, Sjögren's syndrome, and thyroiditis.[1,23] Two of our patients had history of pericarditis, which might also be related to CD.

Two of our patients were a mother and daughter, and one patient had relatives who were diagnosed with CD subsequent to her diagnosis. This is consistent with the known genetic predisposition for developing CD, with an increased risk of 13% in first-degree relatives vs 0.5% in the general population and concordance rates of 0.86 and 0.20 in monozygotic and dizygotic twins, respectively.[24] Therefore, the diagnosis of CD should be considered for patients with familial neuropathy or when they or family members exhibit one of the CD-associated conditions. In patients with a positive family history of CD, small bowel biopsy may be positive, even with normal levels of antigliadin or antitransglutaminase antibodies.[25,26]

The pathogenesis of celiac neuropathy is poorly understood. Three of the patients had other possible causes for neuropathy, including diabetes, sarcoid, and IgM monoclonal gammopathy, but the others did not. Nutritional causes have been suspected but rarely found,[8] and none of our patients who were tested had deficiencies in levels of folate or vitamins E, B12, B6, and B1. Patients with CD are also predisposed to developing diabetes, which may cause small fiber neuropathy,[27] but only one of our patients had type I diabetes mellitus, and none of the others had glucose intolerance. Perhaps in those with CD there is chronic activation of the immune system that predisposes patients to the development of other immune conditions, or there is an underlying genetic predisposition to developing autoimmune disease, including gluten sensitivity.[23,28–30] Oral tolerance, for example, which is mediated in part by transforming growth factor beta and involves transglutaminase, may be disrupted by the action of antitransglutaminase antibodies in the gut.[31] In affected patients, it is not uncommon for the autoimmune disease to be diagnosed before the CD.[32] Neuropathy in patients with CD may be mediated in part by antiganglioside antibodies[33] or by antibodies that target transglutaminase bound to extracellular proteins such as fibronectin.[34] However, these mechanisms have yet to be demonstrated.

Elimination of dietary gluten in patients with CD reverses the enteropathy and skin rash and results in normalization of the IgA antigliadin and antitransglutaminase antibodies. The effect of gluten elimination in patients with CD-associated neuropathy is less clear. Although some patients experienced improvement in their neuropathic symptoms and general well being while adhering to the gluten-free diet, as has been described by others,[11] there was no objective improvement in the neurologic examination, and some developed neuropathic symptoms while on the diet. However, the duration of dietary therapy was limited, and the CD-associated neuropathy might be sensitive to small amounts of gluten, which are difficult to eliminate entirely. This may explain the persistence of antigliadin or transglutaminase antibodies in some patients despite a purported gluten-free diet. Alternatively, the neuropathy may be independent of exposure to gluten, or there may be damage to peripheral nerves or dorsal root ganglion neurons that is permanent or difficult to reverse, so the diet would only prevent further progression. Further investigations are required to determine the incidence of celiac neuropathy, elucidate the disease mechanisms, and develop effective therapies.

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