

Small-Fiber Neuropathy/Neuronopathy Associated With Celiac Disease

Skin Biopsy Findings

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Background: Celiac disease (CD) is increasingly recognized in North America and is associated with a peripheral neuropathy.

Objective: To report the clinical characteristics and skin biopsy results in patients with CD and small-fiber neuropathy symptoms.

Design: Case series.

Setting: Academic peripheral neuropathy clinic.

Patients: Eight patients with CD and neuropathy symptoms.

Intervention: Three-millimeter punch biopsy using the panaxonal marker protein gene product 9.5 to assess epidermal nerve fiber (ENF) density and a gluten-free diet.

Main Outcome Measure: Clinical data and ENF density.

Results: All patients had asymmetric numbness and paresthesias. Three had more prominent involvement of hands than feet, and 3 had facial numbness. Celiac disease was diagnosed in 5 after their neuropathy be-

gan. The following serum antibody levels were elevated: tissue transglutaminase (n=6), IgA gliadin (n=4), and IgG gliadin (n=7). Results of nerve conduction studies were normal in 7 patients. One patient had mildly reduced sural amplitudes. The ENF density was at the low limit of the normal range in 3 additional patients, 2 of whom had morphologic changes in axons. Three patients had decreased ENF density at the thigh or forearm, which was more severe than at the distal leg, compatible with a non-length-dependent process. Four reported improvement with a gluten-free diet. One had no improvement after 4 months. Symptoms developed in 2 while receiving a gluten-free diet.

Conclusions: Patients with CD may have a neuropathy involving small fibers, demonstrated by results of skin biopsy. The pattern of symptoms, with frequent facial involvement and a non-length-dependent pattern on skin biopsy findings, suggests a sensory ganglionopathy or an immune-mediated neuropathy. Improvement of symptoms in some patients after initiating a gluten-free diet warrants further study.

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CELIAC DISEASE (CD) IS AN autoimmune disease of the small intestine, which results from ingestion of gluten (the storage protein of wheat) in genetically susceptible people. There is an HLA antigen association with specific *DQ2* and *DQ8* alleles. Celiac disease is a common disease and increasingly recognized in North America. The prevalence is estimated at 1 in 133 to 1 in 250.^{1,2} Celiac disease may be associated with extra-gastrointestinal tract conditions such as anemia, osteoporosis, or neurological disorders, often without the presence of gastrointestinal tract symp-

oms. Signs and symptoms of a peripheral neuropathy constitute the most common neurological manifestation of CD.³ Whether patients with idiopathic neuropathy should undergo testing for CD is controversial.^{4,5} We previously reported that more than 50% of patients with CD and symptoms of peripheral neuropathy seen in our center had normal results of nerve conduction studies, suggesting the possibility of a small-fiber neuropathy.⁶ In this study, we describe skin biopsy results to assess epidermal nerve fiber (ENF) density⁷ in patients with CD and symptoms of neuropathy, which could aid in defining these patients.

Table 1. Clinical Characteristics of 8 Patients With Symptoms of Small-Fiber Neuropathy

Patient No.	Sensory Symptoms	Results of Sensory Examination			Sural Nerve Conductions	
		Light Touch	Position/Vibration	Pin/Cold	Amplitude, μ V	CV, m/s
1	Tingling in L arm; L leg>R leg	Absent in fingers and toes	Normal/ \downarrow in hands>feet	\downarrow (Hands and feet) /NP	10.0	57
2	Burning pain, tightness, feeling as if "coming out of snow into warmth," onset in L foot, followed by R foot, followed by R hand and intermittent right-sided facial and left-sided tongue numbness	\downarrow	Normal/ \downarrow (moderately)	\downarrow/\downarrow	3.5 (Antidromic)	35
3	Stabbing, tingling, pins and needles, itchiness, with onset in R foot, months later L foot, then face and arms	\downarrow (L foot>R foot); normal in hands	Normal/ \downarrow (mild in feet)	\downarrow (Hands and feet)/NP	13.9	47
4	Numbness, tingling, burning (R foot>L foot)	Normal	Normal/ \downarrow (mild in R toes)	Normal/NP	21.8	54
5	Burning, stabbing, tingling, onset in arms and legs simultaneously, face, torso involved, felt hot and raw	Normal	Normal/ \downarrow (mild in toes)	Normal/NP	27.7	50
6	Burning and tingling in hands>feet	Normal	Normal/ \downarrow (mild in toes)	\downarrow (R hand>L hand)/NP	12.3	39
7	Numbness in hands, before legs	\downarrow (L side>R hands and R feet)	Normal/normal	\downarrow (L>R hand, R>L foot)/ \downarrow (L>R hand)	14	45
8	Severe pins-and-needles tingling in feet >hands	\downarrow (L>R hands)	Normal/normal	\downarrow (Hands and feet)/ \downarrow (L hand and foot)	10	47

Abbreviations: CV, conduction velocity; L, left; R, right; NP, not performed.

METHODS

The Institutional Review Board of the Weill Medical College of Cornell University, New York, NY, approved this study. Patients included those with CD diagnosed as having partial or total villous atrophy on results of duodenal biopsy and symptoms of neuropathy. Patients were seen at the Peripheral Neuropathy Center of Cornell University. No patients from our previous publication⁶ are included. A 3-mm punch biopsy specimen was obtained 10 cm proximal to the lateral malleolus and at the lateral proximal thigh.⁷ A biopsy specimen was obtained from the extensor side of the distal forearm in 1 patient.⁸ Cryosections were cut at a thickness of 50 μ m and stained by an immunoperoxidase method using polyclonal antibodies directed against the panaxonal marker protein gene product 9.5. Total ENFs are counted in 5 different tissues sections and expressed as the number per millimeter of length of the epidermis. We compared the mean number with published normative data.^{7,8} We excluded a ninth patient with an elevated fasting glucose level and CD.

RESULTS

Eight patients (6 women) with neuropathy symptoms that began at ages ranging from childhood to 59 years underwent evaluation (**Table 1**). All patients had asymmetric numbness or paresthesias, although in some the asymmetry was minimal and close to a length-dependent pattern. Three patients had more prominent involvement of the hands than feet, and 3 had facial numbness. Ankle reflexes were normal in 5 patients

and diminished in 3. Celiac disease was diagnosed in 5 patients after their neuropathy began. We saw 3 patients for neurological evaluation before their diagnosis of CD. An additional patient saw another neurologist before the diagnosis of CD, although we did not perform a neurological evaluation until after the diagnosis. One patient received a diagnosis as an infant, and neuropathy developed after a long period of dietary non-compliance in the middle of his sixth decade of life. In the patients with neuropathy and CD, no other cause of neuropathy was found. All patients had levels of vitamin B₁₂ and thyrotropin within reference ranges and no evidence of a monoclonal protein. Results of a 2-hour glucose tolerance test did not show diabetes mellitus or impaired glucose tolerance⁹ in the 7 patients who underwent the test.

Tissue transglutaminase antibody levels were elevated in 6 patients (68–186 U; reference range, <20 U) (**Table 2**). Levels of IgA gliadin antibodies were elevated in 4 patients (62–164 U; reference range, <20 U). Levels of IgG gliadin antibodies were elevated in 7 patients (33–138 U; reference range, <20 U). One patient had only an elevated IgG gliadin antibody level of 33 U.

Only 1 patient had diarrhea, the classic symptom of CD. Three additional patients had abdominal bloating or cramping. One patient had only constipation. The remaining 3 patients had no gastrointestinal tract symptoms.

All patients received a diagnosis of CD on the basis of duodenal biopsy results, with partial or complete

Table 2. Antibodies in Patients With Small-Fiber Neuropathy and CD

Patient No.	Antibody Level, U*		
	Transglutaminase, U	IgA Gliadin, U	IgG Gliadin, U
1	83	11	12
2	4	11	33
3	186	112	138
4	17	110	63
5	68	7	35
6†	75 (10)	164 (9)	55 (21‡)
7	60	62	87
8	65	15	121

Abbreviation: CD, celiac disease.

*Abnormal values are in boldface type. Unless otherwise indicated, the reference range for all antibody levels is less than 20 U.

†Patient 6 had elevated transglutaminase and IgG and IgA gliadin antibody levels (boldface values) at the time of CD diagnosis. Neuropathic symptoms developed after she started a gluten-free diet. The values in parentheses were obtained during the neuropathy evaluation.

‡Reference range, <24.

villous atrophy demonstrated in 3 and 5 patients, respectively.

Results of motor nerve conduction studies (median, ulnar, tibial, and peroneal) were normal in all patients. The tibial and peroneal nerve studies were performed bilaterally in 7 patients. Results of sural nerve conduction studies were normal in 7 patients, with an orthodromic sural amplitude of 10 to 27 μ V (reference range, ≥ 6 μ V). Six patients had bilateral sural studies. Patient 2 had mildly reduced evoked response amplitudes of the sural nerve. Results of ulnar sensory nerve conduction studies were normal in all patients. Results of median sensory nerve conduction studies were normal in 7 patients. One patient had a mild median neuropathy at the wrist. Five patients had blink reflex studies, with normal findings.

The ENF density was reduced in 5 patients (**Table 3, Figure**). We considered values to be abnormal if they were below the fifth percentiles of the reference range at the distal leg and proximal thigh, in subjects older than 20 years.⁷ Two patients (1 who underwent a forearm biopsy and 1 who was 16 years of age) had reduced ENF density compared with the normal published means; however, a fifth percentile cutoff has not been published for the forearm or for subjects of this age. We do not have quantitative data for patient 2, whose biopsy was performed at another institution; however, the ENF density was reported as reduced in the distal leg and distal thigh and in the low range of normal at the proximal thigh, with axonal swellings and fragmented fibers. The ENF density was in the low range of normal in 3 additional patients. In 2 of these (patients 1 and 7), the following morphologic changes in axons were seen: increased axonal swelling, horizontal orientation of nerve fibers, fragmented fibers, excessively thin fibers, and reduction of ENF density occurring with patches of increased density, likely due to regeneration. Three patients had decreased ENF density at the proximal thigh or the distal forearm, which was more severe than at the distal leg, compatible with a non-length-dependent process.

The mean ENF density in the distal leg was 6.0 ENF/mm (SD, 2.2 ENF/mm; normal mean, 13.8 ENF/mm). The mean ENF density in the proximal thigh was 9.5 ENF/mm (SD, 5.7 ENF/mm; normal mean, 21.1 ENF/mm). The ENF density in the distal forearm in 1 patient was 4.4 ENF/mm (normal mean, 17.1 ENF/mm).

Four patients reported improvement in neuropathy symptoms with a gluten-free diet (GFD). One of these (patient 8) initially did not respond to the GFD after 5 months. She responded after further dietary adjustments suggested by a dietician specializing in CD. Another patient had no improvement at a 4-month follow-up. Of these 5 patients, the response to the GFD was observed after our initial evaluation in all except for patient 8, who provided the history of improvement with a GFD at her initial evaluation. Symptoms developed in 2 patients while receiving a GFD. Both of these patients reported that they followed the GFD; however, one had persistently elevated levels of transglutaminase antibodies, which are thought to be a marker of continued gluten exposure. Symptoms developed in 1 patient after poor compliance with a GFD.

COMMENT

Patients with CD may have a neuropathy involving small fibers, which can be demonstrated by results of a skin biopsy assessing ENF density. The neuropathy may be the presenting symptom of the disorder and may occur without gastrointestinal tract symptoms. The pattern of symptoms, with frequent facial involvement, multifocal clinical involvement, and a non-length-dependent pattern on skin biopsy, suggests the possibility of an immune-mediated process or sensory ganglionopathy. Although we have no pathological confirmation of a ganglionopathy, antigliadin antibodies have been reported to bind to Purkinje cells¹⁰ and could potentially also bind to dorsal root ganglion neurons.

Improvement in symptoms in some patients after initiating a GFD warrants further study. Not all of our patients improved. The benefit of a GFD on peripheral neuropathy is unknown.¹¹ Some previous investigators have reported improvement in neuropathy with the GFD.^{3,12-14} Other investigators, however, have reported that the peripheral neuropathy does not respond to a GFD.¹⁵ Even patients following a GFD who are in clinical and histological remission may have a clinical or subclinical neuropathy.^{3,16}

The lack of response to a GFD could be due to many reasons. Patients could be noncompliant. Even minimal gluten exposure can cause a persistent immune response.¹ The lack of improvement could also be due to an insufficient follow-up period, incomplete recovery after axonal or neuronal loss, differences in the methods of assessing neuropathy improvement, or different mechanisms of neuropathy that are unresponsive to the GFD. Antiganglioside antibodies have been demonstrated in 65% of patients with celiac neuropathy,⁶ but it is unknown whether these antibodies are pathogenic or whether the levels fall once a GFD is strictly followed.

Most investigators have reported that some patients with symptoms of a small-fiber neuropathy may have nor-

Table 3. Epidermal Nerve Fiber Density

Patient No./ Age, y	ENF Density, No. of ENF/mm		
	Distal Leg*	Proximal Thigh†	Distal Forearm‡
1/61	4.7	6.9	NP
2/42	Reduced	Low normal	NP
3/50	5.5	4.8	NP
4/58	2.1	10.2	NP
5/41	6.4	21.5	NP
6/25	6.9	7.2	4.4
7/29	9	10.5	NP
8/16	7.3§	5.5§	NP

Abbreviations: ENF, epidermal nerve fiber; NP, not performed.

*The normal mean (fifth percentile of normal) is 13.8 ENF/mm (3.8 ENF/mm).

†The normal mean (fifth percentile of normal) is 21.1 ENF/mm (5.2 ENF/mm).

‡The normal mean is 17.1 ENF/mm.

§The normal values for ages 10 to 19 years at the distal leg are 20.3 ENF/mm and 31.6 ENF/mm at the proximal thigh.

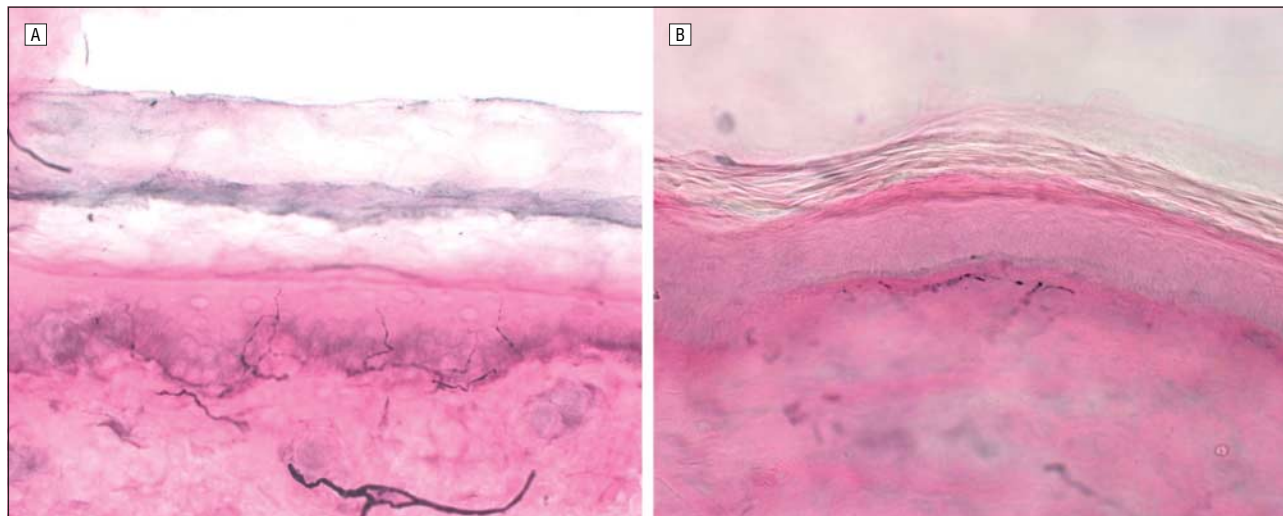


Figure. Fixed cryosections of skin biopsy specimens from the distal part of the leg of a healthy subject (A) and patient 4 (B), who has an abnormally low epidermal nerve fiber density (immunoperoxidase stain of protein gene product 9.5 [a panaxonal marker], original magnification $\times 400$).

mal ENF density. Some of these patients have morphologic changes that may be predegenerative, preceding loss of nerve fibers.¹⁷⁻²⁰ In 3 of our patients, the ENF density was in the low range of normal, but in 2 there were morphologic changes, including abnormal axonal swelling, excessive branching, and a horizontal orientation of nerve fibers.

Celiac neuropathy may occur in patients with silent CD (those without prominent gastrointestinal tract symptoms).¹ The diagnosis is aided by the presence of antibodies associated with CD; however, most of our patients had only some of the antibodies present, and could have been missed if only single antibody levels such as transglutaminase were measured, emphasizing the role of performing a celiac antibody panel.¹

Several recent prospective studies have noted a high prevalence of neuropathy in patients with CD. A prospective study of 176 patients from a gastrointestinal unit found that 52% had signs of neuropathy and 49% had symptoms of neuropathy.³ Fifty-two percent had hyporeflexia; 18% had decreased vibration; 49% had cramps;

44% had paresthesias; and 31% had weakness. Another study of patients with CD who consumed a GFD for at least 2 years found that 35% complained of numbness and paresthesias, and 23% had electromyographic evidence of a chronic neuropathy.¹⁶

In our previous series, some patients had a large-fiber neuropathy, confirmed by abnormal results of nerve conduction studies.⁶ Some of the patients described in this series had mild vibratory sense loss, despite normal results of nerve conduction studies, which suggests a mild involvement of large nerve fibers. There is likely a spectrum of fiber involvement with CD as occurs with diabetes mellitus.⁹ In our previous study, we noted that 8% of the patients in our center with symptoms of neuropathy and normal results of sensory nerve conduction studies that suggested small-fiber neuropathy had CD.⁶ Peripheral neuropathy, even after extensive evaluation, is idiopathic in approximately 20% of patients.^{21,22} Among patients with small-fiber neuropathy, it has been estimated that the disease is idiopathic in 90%,²³ although results of a glucose tolerance test can identify additional

patients with impaired glucose tolerance or diabetes mellitus.⁹ Celiac disease may be another identifiable cause of peripheral neuropathy and particularly of small-fiber neuropathy. Results of a skin biopsy could help identify these patients in prospective trials to identify the frequency of CD as a cause of idiopathic neuropathy.

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