Journal of
CLINICAL
NEUROMUSCULAR
DISEASE

Volume 13, Number 3
March 2012

Peripheral Neuropathic Symptoms in Celiac Disease and Inflammatory Bowel Disease

Ting-Chin David Shen, MD Benjamin Lebwohl, MD, MS,*† Himanshu Verma, MD,‡ Nikhil Kumta, MD,‡ Christina Tennyson, MD,*† Suzanne Lewis, MD,*† Ellen Scherl, MD,‡§ Arun Swaminath, MD,* Kristina M. Capiak,* Dan DiGiacomo,† Brian P. Bosworth, MD,‡§ Thomas H. Brannagan III, MD,‖ and Peter H. R. Green, MD*†*

Abstract

Objectives:
An association between celiac disease (CD) and peripheral neuropathy (PN) has been reported.

Methods:
Patients with CD and/or inflammatory bowel disease (IBD) were recruited from the gastroenterology clinics at a medical center and local support groups. Control subjects without CD or IBD were recruited from the staff of the medical center as well as relatives and attendees at support groups. Each participant completed a survey that used two validated PN instruments to define and characterize PN.

Results:
In the CD group, 38.9% met criteria for PN compared with 38.7% in the IBD group ($P = 0.97$) and 20.5% in the control group ($P < 0.001$). On multiple logistic regression, the odds of PN after adjusting for age, gender, diabetes, vitamin B12 deficiency, and cancer history were increased for CD (odds ratio, 2.51; 95% confidence interval, 1.82–3.47) and IBD (odds ratio, 2.78; 95% confidence interval, 1.85–4.18).

Conclusions:
PN is more often found in patients with CD and/or IBD than in the general population.

Key Words: celiac disease, peripheral neuropathy, inflammatory bowel disease

(*J Clin Neuromusc Dis* 2012;13:137–145)

INTRODUCTION

Celiac disease (CD) is a small intestinal inflammatory condition with autoimmune features that occurs in genetically susceptible individuals secondary to the ingestion of gluten, a protein commonly found in rye, wheat, and barley. This process triggers an immune-mediated response in the small intestinal mucosa that leads to both gastrointestinal and systemic manifestations.[1,2] Therapy is dietary with a strict adherence to a gluten-free diet (GFD).

In recent decades, the medical literature has reported an association between CD and neurologic complications such as ataxia and peripheral neuropathy (PN).[3–11] There have been a number of studies that demonstrated an increased likelihood of having PN in patients with established CD as well as an increased likelihood of elevations in antigliadin antibodies and antitissue transglutaminase antibodies, serum markers for gluten sensitivity, in patients with PN in comparison with control subjects.[12–16] These studies were limited by small sample sizes, inadequate definitions of CD/gluten sensitivity, or referral bias that resulted in a narrow spectrum of study subjects. Other studies have found no association between CD/gluten sensitivity and neurologic complications including PN.[17,18] As such, it remains unclear whether an association truly exists between these two entities.[19,20]

As a result of the lack of knowledge of the prevalence of PN in patients with CD in the US population, we undertook a cross-sectional case–control study to investigate the prevalence of PN in patients with CD in

From the *Department of Medicine, Division of Digestive and Liver Diseases, Columbia University Medical Center, New York, NY; †Celiac Disease Center at Columbia University, New York, NY; ‡Department of Medicine, Weill Cornell Medical College, New York, NY; §Jill Roberts Center for Inflammatory Bowel Disease at Weill Cornell Medical College, New York, NY; and ‖Department of Neurology, Columbia University Medical Center, New York, NY.

The authors declare no conflict of interest.

Reprints: Peter H. R. Green, MD, Celiac Disease Center, Columbia University College of Physicians and Surgeons, Harkness Pavilion, Suite 936, 180 Fort Washington Avenue, New York, NY 10032 (e-mail: pg11@columbia.edu).

comparison to a sample of nonceliac control subjects. To have a disease control group in this study, we enrolled patients with inflammatory bowel disease (IBD). IBD is an umbrella term for patients with ulcerative colitis and Crohn's disease, immune-mediated inflammatory conditions that affect the colon and/or the small intestine.

MATERIALS AND METHODS

Participants

The study recruited three groups of participants. The first group consisted of patients with CD recruited from both the Celiac Disease Center at Columbia University as well as attendees at support groups in New York (Westchester County, Suffolk County, and Albany) and California (Los Angeles). The second group consisted of patients with IBD from either Columbia University Medical Center or the Jill Roberts Center for Inflammatory Bowel Disease at Weill Cornell Medical College. The patients with IBD were initially recruited to serve as disease control subjects for the CD patient group. The non-CD or -IBD healthy control subjects consisted of the spouses or adult family members of patients with CD who attended the support groups as well as staff members at the medical center. All subjects were older than 18 years of age and provided voluntary consent to participate in the study. The study was approved by the Institutional Review Board of both institutions.

Study Design

Each participant was given a questionnaire that consisted of three separate sections. The first section elicited demographic information such as age and gender as well as factors that potentially contributed to the presence of PN, including major medical diagnoses, medication use, dietary supplements/restrictions, and excessive alcohol use (defined as greater than 100 mL of ethyl alcohol daily, equivalent to 3 L of beer or 300 mL of spirits). The second section addressed pertinent CD and/or IBD history, if applicable, including the date and method of diagnosis as well as duration on a GFD. The third section combined two validated PN instruments: the first identified the presence of PN based on a seven-question screening survey of symptoms experienced within past one week[21]; the second assessed the characteristics and severity of PN, if present, based on a modified neurological symptom score (NSS)[22] (Appendix).

Outcome Measures

If a participant responded "yes" to two or more questions on the seven-question screening survey based on symptoms in the week before answering the questionnaire that are unexplained by causes other than neuropathy, he or she is considered to have met criteria for PN (sensitivity 78% and specificity 82% based on previous validation[21]). If a participant screened positive for PN, the number of positive responses to the NSS questions was tallied to calculate the NSS, which correlates with the severity of PN.[22]

Statistical Analysis

For continuous variables, the means and standard deviations were reported for each group; one-way analysis of variance was used to compare groups. For binary variables, proportions and frequencies were reported for each group; the chi-square test was used to compare groups. A logistic regression model was fit to compare the proportions with PN in each group after adjusting for the following covariates: age, gender, diabetes, vitamin B12 deficiency, and cancer history. Statistical analyses were conducted using SPSS 18.0 (SPSS Inc, Chicago, IL). Assistance with statistics was provided by the Columbia University Department of Biostatistics (National Institutes of Health Grant UL1 RR 024156).

RESULTS

Patients and Enrollment

Between October 2009 and October 2010, 1800 questionnaires were distributed. A total of 1270 questionnaires were returned

Journal of CLINICAL NEUROMUSCULAR DISEASE
Volume 13, Number 3
March 2012

(71%), of which 132 questionnaires were excluded from statistical analyses as a result of incompletion or uncertainty of diagnoses. Of the remaining 1138 questionnaires, 504 participants identified themselves as patients with CD, 173 participants identified themselves as patients with IBD, eight participants identified themselves as having both CD and IBD (and underwent separate analysis from the group analyses), and 453 participants identified themselves as not having either CD or IBD and were used as healthy control subjects (referred to as control group). Analysis of the CD group was limited to those patients who were biopsy-proven (n = 401). The IBD group consisted of 59% patients with Crohn's disease and 41% patients with ulcerative colitis.

Baseline Characteristics

The demographic details of the subjects are shown in Table 1. The mean age of the control group, 49 years, was greater than that of the CD and IBD groups (46 and 45 years, respectively; $P < 0.01$). The CD group had the highest proportion of female participants (72%) compared with 60% in the control group and 58% in the IBD group ($P < 0.01$). The proportions of participants with vitamin B12 were 9% in the CD group, 10% in the IBD group, and 1% in the control group ($P < 0.01$). Seventy-one percent of the CD group, 51% of the IBD group, and 56% of the control group reported multivitamin use ($P < 0.01$). There were no statistically significant differences found in the proportions of participants with diabetes, cancer history, excessive alcohol, B vitamin, or neurotoxic medication use among the three groups.

Group Outcomes

Based on the responses to the seven-question screening survey, 38.9% of the CD group met criteria for PN as compared with 38.7% in the IBD group ($P = 0.97$) and 20.5% in the control group ($P < 0.001$). Compared with the control group, the unadjusted odds ratio (OR) for PN was 2.47 in the CD group (95% confidence interval [CI], 1.82–3.34) and 2.45 in the IBD group (95% CI, 1.67–3.58; $P < 0.001$). There was, however, no difference in the likelihood of having PN between the CD and IBD groups (unadjusted OR, 0.99; 95% CI, 0.69–1.43).

After adjustment for age, gender, diabetes, vitamin B12 deficiency, and history of cancer, the OR for PN in the CD group versus the control group remained significant (2.51; 95% CI, 1.82–3.47; $P < 0.001$) as did the OR for PN in the IBD group versus the control group (2.78; 95% CI, 1.85–4.18; $P < 0.001$). The risk of PN increased with age overall; the OR for having PN with every 10-year increase in age was 1.13 (95% CI, 1.04–1.23; $P = 0.006$). Female gender also conferred an increased likelihood of having PN (OR, 1.71; 95% CI, 1.25–2.33; $P = 0.001$) as did diabetes (OR, 1.89; 95% CI, 1.04–3.42; $P = 0.037$). Vitamin

TABLE 1. Baseline Characteristics

	CD (n = 401)	IBD* (n = 173)	Control (n = 453)	*P*
Age (years) (mean ± standard deviation)	46.0 ± 16.6	44.8 ± 19.1	49.3 ± 16.1	<0.01
Female	297 (72.1%)	101 (58.4%)	273 (60.3%)	<0.01
Diabetes	20 (4.9%)	12 (6.9%)	23 (5.1%)	0.58
Vitamin B12 deficiency	36 (9.0%)	16 (10.0%)	5 (1.1%)	<0.01
Cancer history	26 (6.4%)	5 (2.9%)	22 (4.9%)	0.21
Alcohol excess	11 (2.7%)	2 (1.2%)	15 (3.3%)	0.33
Multivitamin use	283 (70.6%)	89 (51.4)	255 (56.3%)	<0.01
B vitamin use	83 (20.3%)	37 (21.4%)	69 (15.2%)	0.08
Toxic medication use	6 (1.5%)	4 (2.3%)	2 (0.4%)	0.11
Peripheral neuropathy	156 (38.9%)	67 (38.7%)	93 (20.5)	<0.01

*In the IBD group, 13 cases are missing vitamin B12 deficiency information.
CD, celiac disease; IBD, inflammatory bowel disease.

B12 deficiency and history of cancer did not have significant associations with the presence of PN (Table 2).

The proportion of patients with PN in the CD group did not change significantly with increasing duration on GFD and duration of CD diagnosis (P = 0.36) (Fig. 1). The proportion of patients with PN in the control group trended toward statistical significance with increasing age (P = 0.054) (Fig. 2).

Severity of Peripheral Neuropathy

The severity of the neuropathic symptoms was assessed by the NSS. The average NSS for the CD group was 2.83 ± 2.24, which is significantly different from the average NSS for the control group (1.53 ± 1.815, $P < 0.01$) but not from that of the IBD group (2.84 ± 2.22, P = 0.99). In the CD group, there appeared to be no correlation between duration on GFD and the NSS (r = 0.024) (Fig. 3).

Patients With Celiac Disease and Inflammatory Bowel Disease

The eight patients with both CD and IBD were all women with a mean age of 49.8 ± 13.4 years. None had diabetes, a history of cancer, excess alcohol use, or neurotoxic medication use. One reported vitamin B12 deficiency. Three met criteria for PN (37.5%), which is not statistically different from the proportion of participants with PN in either the CD or IBD group (P = 0.99).

TABLE 2. Odds Ratio for PN in the CD Group and IBD Group Versus Control Adjusted for Covariates of Interest

			95% Confidence Interval for Odds Ratio	
	P	Odds Ratio	Lower	Upper
CD	<0.001	2.51	1.82	3.47
IBD	<0.001	2.78	1.85	4.18
Age (10 years)	0.006	1.13	1.04	1.23
Female	0.001	1.71	1.25	2.33
Diabetes	0.037	1.89	1.04	3.42
Vitamin B12 deficiency	0.420	1.27	0.71	2.28
Cancer history	0.729	1.12	0.60	2.07

CD, celiac disease; IBD, inflammatory bowel disease.

Use of Vitamins

As Table 1 illustrates, 56.3% of the control group, 51.4% of the IBD group, and 70.6% of the CD group reported multivitamin use ($P < 0.01$). In the CD group, 40.6% of those who reported multivitamin use met criteria for PN as compared with 34.7% of those who did not report multivitamin use (P = 0.32). Within the IBD group, 38.2% of those who reported multivitamin use met criteria for PN as compared with 39.3% of those who did not report multivitamin use (P = 0.99). In the control group, 21.2% of those who reported multivitamin use and 19.7% of those who did not report multivitamin use met criteria for PN (P = 0.79).

Because excess pyridoxine (vitamin B6) can cause PN symptoms, we performed additional analyses based on B vitamin use. A total of 20.3% of the CD group, 21.4% of the IBD group, and 15.2% of the control group reported B vitamin use (P = 0.08). After excluding these subjects, we found that 35.5% of the CD group, 33.1% of the IBD group, and 19.9% of the control group met criteria for PN ($P < 0.001$).

Restless Legs

One question in the seven-question screening questionnaire asked specifically of the presence of restless legs. Although there was no further opportunity for the participants to elaborate on their symptom of restless legs or a diagnosis of restless legs syndrome (RLS), we found that among participants who met criteria for PN, 41.7% in the CD group, 40.3% in the IBD group, and 40.9% in the control group reported symptoms of restless legs (P = 0.98). Of all the participants, 19.5% in the CD group, 16.8% in the IBD group, and 13% in the control group reported symptoms of restless legs (P = 0.038).

DISCUSSION

Our results demonstrate that patients with CD and/or IBD are more likely to

Journal of
CLINICAL
NEUROMUSCULAR
DISEASE

Volume 13, Number 3
March 2012

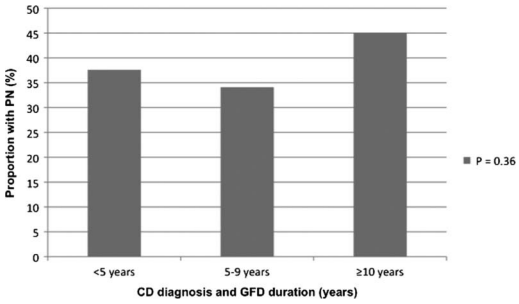

FIGURE 1. Celiac disease (CD) diagnosis and gluten-free diet (GFD) duration versus proportion of peripheral neuropathy in patients with celiac disease.

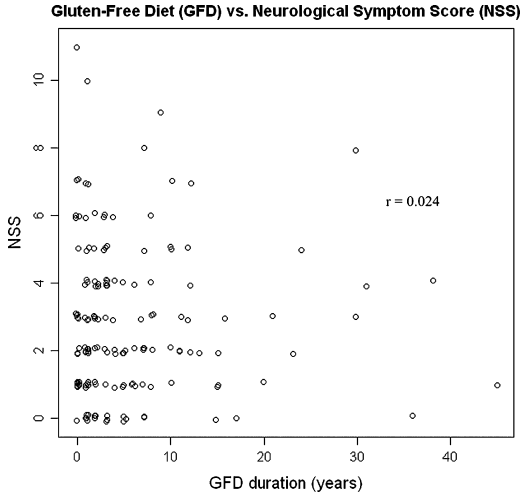

FIGURE 3. Duration of gluten-free diet (GFD) versus neurological symptom score (NSS). Jittering added to demonstrate overlap of data points.

experience symptoms of PN in comparison with the general population. However, we did not detect a difference between the patients with CD and those with IBD in the prevalence of PN. The medical literature has reported an association between CD and PN, with prior studies finding prevalence of PN in patients with CD ranging from 4.2% to 50%.[3,4,15] These results, however, were limited by small sample sizes. Our study found that 38.9% of the 401 patients with CD diagnosed by biopsy met criteria for PN, which is toward the upper level of the range of prior findings. The association between PN and IBD has also been examined with prevalence found between 0.9% and 13.4% in patients with IBD after excluding cases with known risk factors for PN.[23–26] In our study, we found that 38.7% of the patients with IBD met criteria for PN, not excluding cases with alternative potential etiologies for PN. One explanation for this difference may be that conducting a questionnaire-based study for PN, without actual assessment by neurologic examination or electrophysiological testing, elevates the proportion of patients meeting criteria for PN. The prevalence of PN in the general population has been found to range from 0.3% to 7%.[22,27,28] This is different from what we found in our healthy control group, in which 20.5% met criteria for PN. The high proportion of PN in our control group may again be explained by the use of a questionnaire to identify PN without actual neurologic assessment. There has, however, been no previous study aimed at determining the prevalence of neuropathic symptoms in a healthy (non-patient) population within the United States.

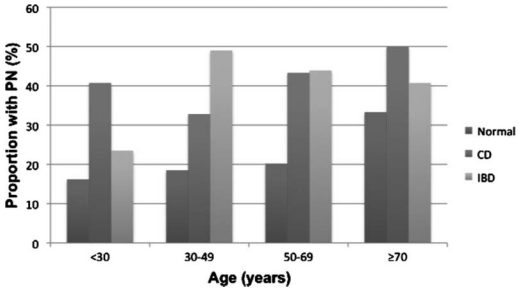

FIGURE 2. Age versus proportions of peripheral neuropathy (PN) in normal subjects, patients with celiac disease (CD), and patients with inflammatory bowel disease (IBD).

Having established the differences in the proportions of patients with PN symptoms in the patients with CD and those with IBD in comparison with healthy control subjects without CD or IBD, we examined the possible etiologies of PN that accounted for these differences. We adjusted for age, gender, and common etiologies of PN, including diabetes, vitamin B12 deficiency, and history of cancer. After these adjustments, we found that the association between PN and patients with CD and those with IBD remained significantly higher than that of control subjects. This suggests that the association between PN and these two disease entities may be intrinsic to

the disease processes themselves. Studies have suggested that there may be an immune-mediated mechanism behind the neurologic manifestations of CD. The finding that the duration of disease and presumably duration on GFD does not reduce the incidence of neuropathic symptoms in CD argues against an autoimmune pathogenic mechanisms associated with active disease (for example, circulating tissue transglutaminase antibodies) and suggests that the neuropathy is an associated autoimmune disorder that is independent of the activity of CD.

Sural nerve biopsy samples of patients with symptoms of PN and elevated serologic markers for CD have shown sparse lymphocytic infiltrates with perivascular cuffing.[14] The medical literature has further suggested that there may be antibody cross-reactivity between antigenic epitopes on nerve cells and gluten proteins. For example, antibodies against tissue-transglutaminase 6 have been detected both in the central nervous system and sera of patients found with ataxia and elevation in other serologic markers for CD.[29,30] The mechanisms of PN in IBD have also been examined in our study and others. After excluding potential factors contributing to PN in association with IBD such as vitamin B12 deficiency and metronidazole use, studies have suggested that PN in IBD may similarly have an immune-mediated etiology, because response to immunotherapy occurred not only as expected in patients with demyelinating PN (indicative of chronic inflammatory demyelinating polyneuropathy), but also in patients with nerve conduction studies and neuropathologic findings characteristic of axonal neuropathy.[26,31]

Among the various covariates adjusted for, age appeared to have a weak but statistically significant association with PN. We also found that the female gender and diabetes appeared to have moderate associations with PN in our study subjects. A history of vitamin B12 deficiency did not appear to be significantly associated with the presence of PN; however, these patients had more than likely been treated for their B12 deficiency. A history of cancer with possible use of chemotherapy or radiation in the past was also not associated with the presence of PN. We did not adjust for excess alcohol or neurotoxic medication use as a result of the small numbers. We also did not adjust for hypothyroidism, a known cause of PN,[32] because all patients who reported a history of hypothyroidism also reported receiving thyroid hormone replacement therapy.

Given the significant association between CD and PN, we hoped to glean the possible treatment options from these results. GFD remains the mainstay of treatment in CD and alleviates many of the manifestations associated with CD.[1,2] However, it remains unclear whether it significantly improves PN symptoms. Some studies, largely case reports, have reported improvements in PN symptoms with GFD.[33–36] Other studies failed to show a benefit.[13,37] In our study, we found no significant change in the proportion of patients with CD meeting criteria for PN with increasing duration on GFD, suggesting that the symptoms of PN do not resolve with GFD. We also did not find a correlation between the NSS and duration on GFD. Small case series have found intravenous immunoglobulin to be effective in treating some patients with cerebellar ataxia and small fiber neuropathy symptoms associated with CD, which may support an immune pathogenesis to the neurologic manifestations of CD.[38]

Neuropathic symptoms may be associated with vitamin deficiencies. Among the study participants, approximately 20% reported use of B vitamins, and 60% reported multivitamin use. Our analyses suggest that neither vitamin deficiency nor excess use of B vitamins was causative of PN in our study participants.

In recent years, the literature has reported an association between RLS and CD, suggesting that it may be an additional extraintestinal manifestation of CD.[9–11,39] The underlying pathogenesis is thought possibly related to iron deficiency secondary to CD or another immune-mediated mechanism. Studies have found the prevalence of RLS to range from 25% to 31% in patients with CD

Journal of CLINICAL NEUROMUSCULAR DISEASE
Volume 13, Number 3
March 2012

compared with 3% to 10% in the general population.[1,9–11,39] Our study was not designed to assess the association between RLS and CD, but one of the seven screening questions for PN inquired specifically of the symptom of restless legs. We found that 19.5% of the CD group, 16.8% of the IBD group, and 13% of the normal control group reported symptom of restless legs, the difference being statistically significant only between the CD and healthy control groups. Among those who met criteria for PN, however, there was no significant difference between any group.

Our study has a number of limitations. One limitation is that there were differences in the mean ages and proportions of females across the three groups. These differences may be inherent to the design of a study using a convenience sample for each arm, because we were unable to randomize the participants to different groups. Because CD more often affects women than men, the CD group had the highest proportion of females. There is no gender specificity in IBD, and the proportions of females in our IBD and control groups were similar.

Another limitation of our study is that the results are based on the participants' self-responses on a questionnaire. As mentioned previously, we did not conduct a neurologic examination or electrophysiological study to confirm the presence and severity of PN but based them on the results of two validated PN instruments.

A third limitation of our study relates to the selection of normal control subjects. We recruited the spouses, family members, and friends of the patients with CD and IBD who accompanied the patients to their medical appointments and support group meetings. We also recruited staff members of the medical center. It is unclear how representative this may be of the general population. However, these people did not have CD or IBD, and we did exclude participants with obvious causes of neuropathic symptoms as reported in the questionnaire. We also note that there has been no other study of the prevalence of neuropathic symptoms in a general US population. At the same time, because the questionnaires were distributed at tertiary care institutions, patients with CD and IBD may or may not be representative of such patients in the general population of the United States. Although the prevalences of CD and IBD in the general population are sufficiently low, given the hereditary susceptibilities of both CD and IBD, it is uncertain whether any cross-contamination of undiagnosed patients with CD and/or IBD into the normal control groups could have affected our results. However, it would likely only further increase the OR of our findings if we were to account for these undiagnosed patients with CD and/or IBD in the control group, because such misclassification would bias toward a null result.

Our study has a number of strengths. The relatively large sample sizes in the CD and normal control groups increased the power of our study. We did not enroll additional patients with IBD because based on our preliminary data analyses, no difference could be detected in the likelihood of having PN between the CD and IBD groups even with additional recruitment. We also included only patients with biopsy-proven CD as part of the CD group analyses. This circumvents the issue of defining gluten sensitivity versus CD, which was previously differentiated primarily by levels of serum antibodies to various CD antigen markers and biopsy results (approximately 20% of the patients with CD in our study have never had biopsies and were excluded from the study analyses). We also strictly defined criteria for meeting PN based on a validated screening survey.

In conclusion, we found that PN is significantly more likely to occur in association with CD and IBD in comparison with the general population, even after adjusting for alternative etiologies of PN. Therefore, despite the fact that our study is a questionnaire-based cross-sectional case–control study not designed to establish causality between CD and PN or IBD and PN, it is likely PN has intrinsic associations with these two gastrointestinal disease processes.

REFERENCES

1. Green PH, Cellier C. Celiac disease. *N Engl J Med*. 2007;357:1731–1743.
2. Green PH, Jabri B. Coeliac disease. *Lancet*. 2003; 362:383–391.
3. Cicarelli G, Della Rocca G, Amboni M, et al. Clinical and neurological abnormalities in adult celiac disease. *Neurol Sci*. 2003;24:311–317.
4. Briani C, Zara G, Alaedini A, et al. Neurological complications of celiac disease and autoimmune mechanisms: a prospective study. *J Neuroimmunol*. 2008;195:171–175.
5. Green PH, Alaedini A, Sander HW, et al. Mechanisms underlying celiac disease and its neurologic manifestations. *Cell Mol Life Sci*. 2005;62:791–799.
6. Bushara KO. Neurologic presentation of celiac disease. *Gastroenterology*. 2005;128(suppl 1):S92–S97.
7. Freeman HJ. Neurological disorders in adult celiac disease. *Can J Gastroenterol*. 2008;22:909–911.
8. Brown KJ, Jewells V, Herfarth H, et al. White matter lesions suggestive of amyotrophic lateral sclerosis attributed to celiac disease. *AJNR Am J Neuroradiol*. 2010;31:880–881.
9. Haddad FG, Maalouly GD, Fahed JI, et al. Restless leg syndrome in a patient with celiac disease: a coincidence or an association? *Ann Saudi Med*. 2009; 29:238–239.
10. Weinstock LB, Walter AS, Mullin GE, et al. Celiac disease is associated with restless legs syndrome. *Dig Dis Sci*. 2010;55:1667–1673.
11. Moccia M, Pellecchia MT, Erro R, et al. Restless legs syndrome is a common feature of adult celiac disease. *Mov Disord*. 2010;25:877–881.
12. Hadjivassiliou M, Grunewald R, Sharrack B, et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain*. 2003;126:685–691.
13. Chin RL, Sander HW, Brannagan TH, et al. Celiac neuropathy. *Neurology*. 2003;60:1581–1585.
14. Hadjivassiliou M, Grunewald RA, Kandler RH. Neuropathy associated with gluten sensitivity. *J Neurol Neurosurg Psychiatry*. 2006;77:1262–1266.
15. Luostarinen L, Himanen SL, Luostarinen M, et al. Neuromuscular and sensory disturbances in patients with well treated coeliac disease. *J Neurol Neurosurg Psychiatry*. 2003;74:490–494.
16. Ludvigsson JF, Olsson T, Ekbom A, et al. A population based study of celiac disease, neurodegenerative and neuroinflammatory diseases. *Aliment Pharmacol Ther*. 2007;25:1317–1327.
17. Abele M, Schols L, Schwartz S, et al. Prevalence of antigliadin antibodies in ataxia patients. *Neurology*. 2003;60:1674–1675.
18. Rosenberg NR, Vermeulen M. Should celiac disease be considered in the work up of patients with chronic peripheral neuropathy? *J Neurol Neurosurg Psychiatry*. 2005;76:1415–1419.
19. Grossman G. Neurological complications of celiac disease: what is the evidence? *Practical Neurology*. 2008;8:77–89.
20. Cross AH, Golumbek PT. Neurologic manifestations of celiac disease: proven, or just a gut feeling? *Neurology*. 2003;60:1566–1568.
21. The Italian General Practitioner Study Group.- Chronic symmetric symptomatic polyneuropathy in the elderly: a field screening investigation in two Italian regions. *Neurology*. 1995;45:1832–1836.
22. Dyck PJ, Sherman WR, Hallcher LM, et al. Human Diabetic endoneurial sorbitol, fructose, and myoinositol related to sural nerve morphometry. *Ann Neurol*. 1980;8:590–596.
23. Ben Sassi SB, Kallel L, Ben Romdhane S, et al. Peripheral neuropathy in inflammatory bowel disease patients: a prospective cohort study. *Scand J Gastroenterol*. 2009;44:1268–1269.
24. Lossos A, River Y, Eliakim A, et al. Neurologic aspects of inflammatory bowel disease. *Neurology*. 1995;45: 416–421.
25. Elsehety A, Bertorini TE. Neurologic and neuropsychiatric complications of Crohn's disease. *South Med J*. 1997;90:606–610.
26. Oliveira GR, Teles BC, Brasil EF, et al. Peripheral neuropathy and neurological disorders in an unselected Brazilian population-based cohort of IBD patients. *Inflamm Bowel Dis*. 2008;14:389–395.
27. Bharucha NE, Bharucha AE, Bharucha EP. Prevalence of peripheral neuropathy in the Parsi community of Bombay. *Neurology*. 1991;41:1315–1317.
28. Savettieri G, Rocca WA, Salemi G, et al. Prevalence of diabetic neuropathy with somatic symptoms: a door-to-door survey in two Sicilian municipalities. *Neurology*. 1993;43:1115–1120.
29. Hadjivassiliou M, Sanders DS, Grünewald RA, et al. Gluten sensitivity: from gut to brain. *Lancet Neurol*. 2010;9:318–330.
30. Hadjivassiliou M, Aeschlimann P, Strigun A, et al. Autoantibodies in gluten ataxia recognise a novel neuronal transglutaminase. *Ann Neurol*. 2008;64:332–343.
31. Gondim FA, Brannagan TH 3rd, Sander HW, et al. Peripheral neuropathy in patients with inflammatory bowel disease. *Brain*. 2005;128:867–879.
32. Nebuchennykh M, Løseth S, Mellgren SI. Aspects of peripheral nerve involvement in patients with treated hypothyroidism. *Eur J Neurol*. 2010;17:67–72.
33. Hadjivassiliou M, Kandler RH, Chattopadhyay AK, et al. Dietary treatment of gluten neuropathy. *Muscle Nerve*. 2006;34:762–766.
34. Rigamonti A, Magi S, Venturini E, et al. Celiac disease presenting with motor neuropathy: effect of gluten free-diet. *Muscle Nerve*. 2007;35:675–677.
35. Kaplan JG, Pack D, Horoupian D, et al. Distal axonopathy associated with chronic gluten enteropathy: a treatable disorder. *Neurology*. 1988;38:642–645.
36. Hadjivassiliou M, Rao DG, Wharton SB, et al. Sensory ganglionopathy due to gluten sensitivity. *Neurology*. 2010;75:1003–1008.
37. Tursi A, Giorgetti GM, Iani C, et al. Peripheral neurological disturbances, autonomic dysfunction, and antineuronal antibodies in adult celiac disease before and after a gluten free diet. *Dig Dis Sci*. 2006; 51:1869–1874.
38. Souayah N, Chin RL, Brannagan TH, et al. Effect of IVIG on cerebellar ataxia and neuropathic pain associated with celiac disease. *Eur J Neurol*. 2008;15:1300–1303.
39. Manchanda S, Davies CR, Picchietti D. Celiac disease as a possible cause for low serum ferritin in patients with restless legs syndrome. *Sleep Med*. 2009;10:763–765.

Journal of
CLINICAL
NEUROMUSCULAR
DISEASE

Volume 13, Number 3
March 2012

APPENDIX

Seven-Question Screening Survey for Peripheral Neuropathy and Neurological Symptom Score

INSTRUCTIONS: Please answer YES or NO for each question. If there is a symptom explained by something other than neuropathy, please answer NO for the symptom.

Have you had the following symptoms Within the past one week:

Muscle cramps anywhere on your body	Yes	No
Restless legs	Yes	No
Do you have burning feet?	Yes	No
Do you have muscle pain?	Yes	No
Do you have difficulty handling objects?	Yes	No
Do you have difficulty standing or walking?	Yes	No
Do you have numbness or pins and needles involving your feet or hands in a stocking and glove pattern?	Yes	No
Do you have double vision?	Yes	No
Do you have difficulty with movements of your face, such as when whistling or smiling?	Yes	No
Do you have difficulty with speaking or swallowing?	Yes	No
Do you have trouble with moving your shoulders and upper arm, such as when raising your arms above your head?	Yes	No
Do you have trouble using your hand, such as when writing or buttoning buttons?	Yes	No
Do you have difficulty getting out of the car or a chair or walking up steps?	Yes	No
Do you have difficulty standing on your toes or heels?	Yes	No
Do you have difficulty identifying objects in your mouth?	Yes	No
Do you have difficulty recognizing objects by feel with your hand?	Yes	No
Are you excessively unsteady (stumble) when walking?	Yes	No
Do you have "numbness," or "prickling" anywhere on your body? Do not include "prickling asleep-numbness" that develops from sitting too long or from lying on a limb too long producing numbness for a few minutes only.	Yes	No
Do you feel pain, such as burning, deep aching,or tenderness anywhere on your body?	Yes	No
Have you fainted more than once during the last year?	Yes	No
If you are male, do you experience impotence?	Yes	No
Do you experience loss of urinary control?	Yes	No
Do you experience diarrhea at night?	Yes	No

The first seven items represent the screening survey, and the remaining 16 items represent the neurological symptom score.