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Copper Levels in Patients With Celiac Neuropathy

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Abstract

Objective:
Neurological complications of celiac disease (CD) include neuropathy, myeloneuropathy, and cerebellar degeneration. The cause of neuropathy in patients with CD is not known. Prior publications describe copper deficiency in CD patients with myeloneuropathy and neuropathy and posit that hypocupremia is the cause of these neurological conditions. However, based on our clinical experience, we hypothesized that CD patients with polyneuropathy are not deficient in copper.

Methods:
Patients who met diagnostic criteria for CD and peripheral neuropathy were included. We reviewed the patient's records, including assessment of serum copper level and other clinical parameters.

Results:
Eighteen patients met inclusion criteria. Sixteen patients (89%) had normal copper levels, 2 had mild hypercupremia, and none had low copper levels. Of the 18 patients, 4 (22%) had large fiber neuropathy and 14 (78%) had a small fiber neuropathy.

Conclusions:
No patient in this study showed hypocupremia. We are unable to demonstrate a relationship between our CD patients with Peripheral Neuropathy and copper deficiency.

Key Words: peripheral neuropathy, small fiber neuropathy, copper, skin biopsy, celiac disease

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INTRODUCTION

Celiac disease (CD) is a chronic inflammatory enteropathy mediated by an autoimmune reaction to ingested gluten. Immunological and pathological characteristics of CD include elevated titers of antibodies to gliadin and transglutaminase, as well as small intestinal villous atrophy and mucosal inflammatory cell infiltration.[1] Micronutrient malabsorption in CD can lead to deficiencies of iron; vitamins B1, B2, B3, B6, B12, D, and E; copper and calcium, and these deficiencies may lead to systemic complications.[2–5] The cause of neuropathy in CD is uncertain, and although proposed etiologies include an association with copper deficiency,[2,5,6] we do not believe that this link is valid. This is supported by the observation that no improvement in celiac neuropathy was noted following vitamin therapy.[7]

Copper plays a key role in hematopoiesis and in the development and maintenance of the nervous system, and possible symptoms of copper deficiency include anemia, neutropenia, and myeloneuropathy.[8–11] Neuropathy has been reported in the context of hypocupremia because of malabsorption after gastrectomy and as a result of treatment with zinc and chelators in a patient with Wilson disease.[12,13] Polyneuropathy and ataxia are the most common neurological manifestations of CD, but the pathophysiologic mechanisms are still in question. Just as it is important to know what factors might be relevant to the etiology of neuropathy in CD, we believe it is also important to establish which are not. More information about copper levels in CD patients with peripheral neuropathy was needed not only to guide further research into the pathophysiology of this condition but also to inform patient

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care, particularly regarding recommendations on micronutrient supplementation. Here, we provide a description and analysis of 18 patients with CD and neuropathy, none of whom are deficient in copper.

METHODS

Patient Evaluation

We reviewed the medical records of all patients with neuropathy and biopsy-confirmed CD seen at the Peripheral Neuropathy Center of Columbia University between 2008 and 2010. Thirty patients suspected of having both neuropathy and CD were identified, and assessment for diagnostic criteria was conducted. The diagnosis of neuropathy required the presence of neuropathy symptoms and/or signs on examination, as well as evidence of neuropathy on nerve conduction studies (NCS), reduced epidermal nerve fiber density (ENFD) on skin biopsy, and/or abnormal quantitative sydomotor axon reflex test (QSART). Diagnosis of CD required pathologic findings on small intestinal biopsy. In addition, the clinical mode of presentation of CD for each patient is noted in Table 1. Although most (13/18) patients reported gastrointestinal symptoms, commensurate with the "classical" presentation of CD, others presented with so-called "atypical" manifestations, such as osteoporosis and anemia.[14,15]

In addition to serum copper, laboratory evidence for diabetes, including 2-hour oral glucose tolerance testing or fasting glucose level, was reviewed for each patient. The presence of diabetes mellitus was assessed to exclude other common causes of neuropathy, and also because patients with CD can be predisposed to type 1 diabetes, which can cause neuropathy.[16] The presence of clinical or radiographic evidence for myelopathy or cerebellar dysfunction was noted, as these have been identified as neurological manifestations associated with CD; however, central nervous system imaging was not routinely ordered for patients.[2,5] Serum white blood cell (WBC) count were recorded in light of the connection between copper deficiency and abnormal hematopoiesis.[9] Vitamin B12 levels, serum protein electrophoresis and serum immunofixation were recorded for patients to account for other potential common causes of neuropathy.

Of the 30 patients, 12 were eliminated because of nondiagnostic or inadequate diagnostic information. The remaining 18 patients were included in our analysis. This study was approved by Columbia University's Institutional Review Board.

RESULTS

Clinical Presentation—Symptoms

All patients had symptoms of neuropathy, including numbness, sensory ataxia, paresthesias, and/or pain (Table 1). Six of the 18 patients described burning sensations in their extremities and 5 described other painful paresthesias or allodynia. Most of the patients (17) said that their symptoms were predominantly distal. Six patients described numbness. Two patients reported incoordination and imbalance. On review of each patient's mode of presentation of CD, 13 patients reported a history of gastrointestinal symptoms (Table 1).

Clinical Presentation—Examination

The most common abnormality on physical examination was reduction in pinprick or cold sensation over the distal extremities (17 of 18 patients). Reduced toe vibration sensation and/or joint position sensation was seen in 5 patients. Diminished or absent ankle deep tendon reflexes were observed in 5 patients. Weakness of the extensor hallucis longus muscle was found in 5 patients. Two patients had pathological cerebellar signs. Patient number 6 was wheelchair-bound and had pseudoathetosis of his legs, and patient number 8 had dysmetria and disdiadochokinesia of one arm. Finally, patient number 10 had additional examination findings suggestive of myelopathy, including right leg weakness and bilateral leg hyperreflexia.

TABLE 1. Study Subject Characteristics

Subject	Gender/ Age, Yrs	Neuropathy Signs on Examination	Neuropathy Symptoms	Diagnostic NCS/ Skin Biopsy	Low Copper (Value, μg/dL)	Low WBC (Value)	Presenting Signs of CD*	Other
1	F/58	Y	Distal burning paresthesias	Y/—	N (94)	N (9.9)	GI	
2	M/47	Y	Distal burning paresthesias	N/—	N (83)	N (6.3)	Neuropathy	Positive QSART
3	F/36	Y	Distal burning paresthesias	N/Y	N (167)	N (8.6)	GI	
4	M/60	Y	Allodynia both legs	Y/—	N (125)	N (9.4)	GI	
5	F/21	Y	Distal numbness	N/Y	N (159)	Y (2.8)	GI and anemia	Mildly elevated copper
6	M/58	Y	Numb feet, finger paresthesias	Y/—	N (137)	N (8.5)	GI	Ataxia
7	F/38	Y	Burning paresthesias involving feet and face	N/Y	N (86)	N (9.0)	GI	
8	F/55	Y	Lower extremity paresthesias	N/Y	N (103)	N (4.0)	GI	Right arm ataxia on examination
9	F/46	Y	Lower extremity allodynia	N/Y	N (94)	N (5.2)	GI	
10	M/63	Y	Lower extremity numbness	Y/—	N (94)	N (4.6)	Neuropathy	Myelopathic findings on examination
11	F/16	Y	Distal painful paresthesias	N/Y	N (125)	N (7.3)	Neuropathy	
12	F/36	N	Paresthesias	N/Y	N (136)	N (5.7)	GI	
13	F/61	Y	Distal burning paresthesias	N/Y	N (77)	N (5.7)	Anemia and fatigue	
14	F/48	Y	Distal numbness and paresthesias	N/Y	N (118)	N (6.9)	GI	
15	F/58	Y	Paresthesias	N/Y	N (132)	N (8.0)	GI	
16	M/53	N	Distal numbness and paresthesias	N/Y	N (110)	N (8.8)	GI	
17	F/39	N	Paresthesias	—/Y	N (110)	N (6.6)	Osteoporosis	Mildly elevated B6
18	F/36	Y	Numbness and burning paresthesias	N/Y	N (86)	Y (3.5)	GI	

F, female; M, male; N, no; Y, yes; —, data not applicable for subject.

*GI, Gastrointestinal; symptoms include diarrhea, stomach cramps, bloating, nausea, abdominal pain, and indigestion. All GI symptoms were not present in each patient. The most common GI symptom (reported in 8/13 patients with GI symptoms) was diarrhea.

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The Presence of Diabetes Mellitus

Diabetes is a common disease, and 3 of the 18 patients had a history of type 2 (non–insulin-dependent) diabetes mellitus. However, for 2 of these patients neurological presentations were distinct from the typical diabetic sensorimotor polyneuropathy.[17] Patient number 1 (Tables 1 and 2) had a prior diagnosis of diabetes, with a Hgb A1c of 8%. Patient number 6 (Tables 1 and 2) also had a history of diabetes (no related laboratory data are available); a distinguishing feature of this patient's presentation was the additional presence of clinical cerebellar (paravermian) signs on examination (Table 1), which has been previously described as a neurological manifestation of CD.[2] Patient 10 (Tables 1 and 2), whose Hgb A1c was 7.4%, also had neurological involvement considered atypical for diabetes, including mononeuritis multiplex neuropathy pattern on NCS (Table 2) and myelopathic findings on clinical examination (described below in the Neuroimaging Studies Section and in Table 1). For the remaining 15 patients, 11 had normal 2-hour oral glucose tolerance tests and 4 had normal fasting glucose levels.

Serum Copper and Other Laboratory Tests

Copper deficiency was found in none of the patients in this study (Table 1). The normal serum copper range was between 70 and 155 μg/dL. Sixteen of 18 patients (89%) had normal serum copper levels (ranging between 74 and 137 μg/dL), and in 2 patients, serum copper was mildly elevated (159 and 167 μg/dL). Two patients had a mildly reduced peripheral WBC count of 2.8 and 3.5, with the normal range between 3.54 and 9.06 $\times$ 10^9/L (Table 1). Fourteen patients had normal WBC, ranging between 4.0 and 9.0. Two patients had mildly elevated WBCs of 9.4 and 9.9. All patients had normal serum vitamin B12 levels. No patients demonstrated paraproteinemia, per serum protein electrophoresis and serum immunofixation tests.

TABLE 2. Electrodiagnostic Findings in Patients With Large Fiber Neuropathy*

Subject†	Peroneal Motor NCS (DML, Amp.‡, CV‡)	Peroneal Sensory NCS (Amp., CV)	Tibial Motor NCS (DML, Amp., CV)	Sural Sensory NCS (Amp., CV)	Ulnar Motor NCS (DML, Amp., CV)	Ulnar Sensory NCS (Amp., CV)
1	4.35 ms, 4.1 mV, 39 m/s	NA	4.3 ms, 7.8 mV, 35 m/s	1.1 μV, 36 m/s	2.9 ms, 10.3 mV, 50 m/s	6.0 μV, 48 m/s
4	6.5 ms, 4.3 mV, 38 m/s	3 μV, 40 m/s	4.6 ms, 7.8 mV, 34 m/s	7 μV, 43 m/s	3 ms, 11.9 mV, 64 m/s	7 μV, 53 m/s
6	5.65 ms, 0.6 mV, 44 m/s	NA	Left: 4.45 ms, 3.9 mV, 39 m/s Right: 4.0 ms, 1.8 mV, 44 m/s	Right: Absent response	2.65 ms, 9.4 mV, 56 m/s	3.3 μV, 50 m/s
10	Left: 5.9 ms, 2.8 mV, 42 m/s Right: Absent response	Left: 4 μV, 38 m/s Right: 4 μV, 53 m/s	3.6 ms, 5.7 mV, 42 m/s	9 μV, 50 m/s	3.2 ms, 9.5 mV, 54 m/s	3 μV, 51 m/s

Amp., amplitude; CV, conduction velocity; DML, distal motor latency; NA, not available.
*Normal NCS values for the EMG laboratory at Columbia University: peroneal motor (recording at extensor digitorum brevis), DML <6.5 ms, amp. >2.2 mV, CV ≥40 m/s; antidromic peroneal sensory amp. >5 μV, CV ≥40 m/s; tibial motor (recording at abductor hallucis), DML <5.5 ms, amp. >4.0 mV, CV ≥40 m/s; antidromic sural amp. >4 μV, CV ≥42 m/s); ulnar motor (recording at abductor digiti minimi), DML <3.5 ms, amp. >6 mV, CV ≥48 m/s; orthodromic ulnar sensory amp. >5 μV, CV ≥45 m/s.
†Subject numbers correlate with those from Table 1.
‡For motor NCS, distal amplitudes and distal segment conduction velocities are reported.

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Neuroimaging Studies

Despite clinical examination findings in several patients suggestive of cerebellar pathology or myelopathy, we did not identify corresponding specific neuroaxis magnetic resonance imaging (MRI) findings. The brain MRI of patient number 5 (Table 1) showed several "nonspecific subcortical white matter lesions" in the context of a history of viral meningitis; we do not believe these findings were directly relevant to our present study. Patient number 8 had right-arm ataxia on clinical examination; a brain MRI with and without contrast showed only nonspecific, nonenhancing, scattered foci of subcortical white matter T2 hyperintensity. Patient number 6 (Table 1) had ataxia on examination and was also evaluated by a Movement Disorders specialist who agreed that the clinical findings were suggestive of paravermian involvement. However, no cerebellar atrophy was seen on brain MRI. Patient number 10 had potentially myelopathic examination findings, including leg weakness and hyperreflexia; however, no abnormal spine MR signal was found. As previously noted, central nervous system imaging was not routinely conducted on all patients.

Electrodiagnostic Testing

Seventeen of 18 patients underwent electrodiagnostic testing, including NCS. Of the 17, 4 patients (24%) had abnormalities on NCS, all showing axonal sensorimotor neuropathy (Table 1). The NCS values are presented in Table 2.

Skin Biopsy (ENFD) and QSART

One of the 18 patients was diagnosed with small fiber neuropathy via abnormalities on QSART testing (patient 2). Thirteen patients underwent skin biopsy of the distal leg and proximal thigh for detection of small fiber neuropathy through quantification of ENFD, and all 13 patients had reduced ENFD consistent with small fiber neuropathy (Table 1). Accepted abnormal values for distal leg ENFD fall below the fifth percentile, or less than 5 ENFs per millimeter; the abnormal threshold for the proximal thigh is below 8 ENF per millimeter. Ten patients showed reduced ENFD in the distal leg only, or at both sites. Three patients showed reduced proximal thigh ENFD and normal distal leg ENFD, consistent with a non–length-dependent small fiber neuropathy.

DISCUSSION

We have described 18 patients with CD and peripheral neuropathy. Out of the 18 patients, none had copper deficiency. Overall this description of patients with celiac neuropathy is consistent with previous publications of the topic.[18,19]

Copper is essential to normal neuronal function; it is required at the catalytic site for many cellular enzymes involved in free radical scavenging, neurotransmitter synthesis, and posttranslational modification of numerous neurohormones and neuropeptides.[11] Low levels of copper have been shown to result in a diverse array of neuronal dysfunction. In humans, neurodegeneration was first linked with copper deficiency in Menke disease,[20] neuropathy has been attributed to hypocupremia in some clinical reports,[12,13] and a recent murine model of copper deficiency revealed a pattern of neuronal damage on histopathological analysis, which could link copper metabolism to pathophysiology of Alzheimer disease, prion diseases, and amyotrophic lateral sclerosis.[21] Although secondary copper deficiency has previously been described in CD patients, it is also recognized as rare in this population, overall.[5,22] That said, previous clinical descriptions have linked myeloneuropathy, cerebellar degeneration, and myelopathy in CD patients with low copper levels.[2,5] However, based on our observations of 18 patients with CD and PN with normal serum copper, we are unable to demonstrate a relationship between hypocupremia and the neurological manifestation of neuropathy in CD patients.

It remains that the pathogenesis of celiac neuropathy is poorly understood, and although micronutrient deficiencies have

been suspected, they are rarely found.[7] Patients with CD have a predisposition to the development of type 1 (insulin-dependent) diabetes, which may cause small fiber neuropathy[16]; however, in our study only one patient had type 2 (non–insulin-dependent) diabetes and was characterized as having a large fiber axonal neuropathy. There is some evidence that neuropathy in CD is an extra-intestinal manifestation of CD, associated with antinerve antibodies.[19] Although indeed more research on the cause of celiac neuropathy is needed, we found no evidence in this study for the association of copper deficiency and neuropathy in CD.

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