Movement Disorders
Vol. 24, No. 16, 2009, pp. 2358–2362

Neurological Symptoms in Patients with Biopsy Proven Celiac Disease

Katrin Bürk, MD,[1,2]* Marie-Louise Farecki,[1] Georg Lamprecht, MD,[3] Guenter Roth, PhD,[4] Patrice Decker, PhD,[2] Michael Weller, MD,[5] Hans-Georg Rammensee, PhD,[2] and Wolfang Oertel, MD[1]

[1]*Department of Neurology, University of Marburg, Marburg, Germany*
[2]*Department of Immunology, University of Tübingen, Tübingen, Germany*
[3]*Department of Internal Medicine, University of Tübingen, Tübingen, Germany*
[4]*Department of Microsystems Engineering, University of Freiburg, Freiburg, Germany*
[5]*Department of Neurology, University of Zürich, Zürich, Switzerland*

Abstract: In celiac disease (CD), the gut is the typical manifestation site but atypical neurological presentations are thought to occur in 6 to 10% with cerebellar ataxia being the most frequent symptom. Most studies in this field are focused on patients under primary neurological care. To exclude such an observation bias, patients with biopsy proven celiac disease were screened for neurological disease. A total of 72 patients with biopsy proven celiac disease (CD) (mean age 51 ± 15 years, mean disease duration 8 ± 11 years) were recruited through advertisements. All participants adhered to a gluten-free diet. Patients were interviewed following a standard questionnaire and examined clinically for neurological symptoms. Medical history revealed neurological disorders such as migraine (28%), carpal tunnel syndrome (20%), vestibular dysfunction (8%), seizures (6%), and myelitis (3%). Interestingly, 35% of patients with CD reported of a history of psychiatric disease including depression, personality changes, or even psychosis. Physical examination yielded stance and gait problems in about one third of patients that could be attributed to afferent ataxia in 26%, vestibular dysfunction in 6%, and cerebellar ataxia in 6%. Other motor features such as basal ganglia symptoms, pyramidal tract signs, tics, and myoclonus were infrequent. 35% of patients with CD showed deep sensory loss and reduced ankle reflexes in 14%. Gait disturbances in CD do not only result from cerebellar ataxia but also from proprioceptive or vestibular impairment. Neurological problems may even develop despite strict adherence to a gluten-free diet. © 2009 Movement Disorder Society

Key words: celiac disease; ataxia; migraine; gluten sensitivity

Celiac disease (CD) is associated with intolerance to dietary gluten, a component of cereals such as wheat, barley, and rye. The syndrome is an immune-mediated disease associated with the HLA class II DQ2 and DQ8 molecules. The pathogenesis is not completely understood but involves the infiltration of the lamina propria and the epithelial layer of the small bowel with T lymphocytes eventually leading to villous blunting and atrophy as well as crypt hyperplasia. These changes cause diarrhea with maldigestion and malabsorption. Numerous extraintestinal symptoms can occur, only some of which are related to malabsorption. Diagnosis is established by the demonstration of the characteristic histological changes in the duodenum.[1] The term gluten sensitivity (GS) refers to patients with circulating antibodies to gliadin with no or only mild histological abnormalities.

During the last years, there have been numerous reports on neurological complications affecting upto 6 to 8% of patients with CD,[2] with cerebellar ataxia being the most frequent symptom.[3] Several hypotheses have been postulated to explain neurological disease in CD including the existence of antineuronal antibodies, e.g., directed against cerebellar Purkinje cells,[4] inva-

*Correspondence to: Dr. Katrin Bürk, Department of Neurology, University of Marburg, Rudolf-Bultmann-str. 8, Marburg 35039, Germany. E-mail: buerk@ngi.de

Potential conflict of interest: Nothing to report.

Received 12 January 2009; Revised 28 July 2009; Accepted 6 September 2009

Published online 20 October 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22821

sion of CD8 positive T cells into the nervous system,[5] and deficiencies of neuroprotective substances due to malabsorption. Nevertheless, the link between CD and neurological symptoms not being elucidated to date, the issue is still a matter of debate.[6] In most studies, patients with otherwise unexplained neurological symptoms were tested for the presence of circulating antibodies to gliadin (corresponding to the term "gluten sensitivity") and/or intestinal abnormalities.[7,8] Only few studies have applied the inverse approach by primarily including patients with established CD. Regarding the high prevalence of CD in the general population (1 to 200 inhabitants),[9] a random coincidence of CD and neurological disease cannot be ruled out. We, therefore, interviewed and examined unselected patients with CD under primary medical/gastroenterological follow-up for neurological problems.

PATIENTS AND METHODS

CD Patients

Seventy-two patients were recruited through advertisements in the official journal of the German Celiac Society (*Deutsche Zöliakie Gesellschaft DZG e.V.*, Stuttgart, Germany) or personal contact (GL) (male: N = 10, female: N = 62, mean age: 51 ± 15 years). Diagnosis of CD corresponded to Marsh Stage III before the introduction of a gluten-free diet with subtotal or total villous atrophy of the small intestine. Mean disease duration (time from CD diagnosis and introduction of a gluten-free diet to the neurological assessment) was 8 ± 11 years. Another 10 self-referring patients did not meet the diagnostic criteria of biopsy proven CD and had to be excluded from the study. At the time of the study, all patients followed a gluten-free diet and were considered to be in remission. All patients gave informed consent to participate in the study, which was approved by the ethics committees of the participating institutions.

Clinical Assessment

Patients were asked about their neurological and general medical history by means of a standard questionnaire. All participants underwent a clinical neurological examination procedure.

RESULTS

Medical History

General Medical History

15% of the patients had a positive family history of CD. 9% suffered from IgA deficiency. 35% of the patients with CD reported of psychiatric problems in the past including depression and personality changes. One patient had a history of psychosis. 8% of the individuals experienced attentional deficits causing problems in daily life.

Neurological History

About one third of patients with CD reported a history of migraine (for details see Table 1). In many cases, there was a decrease of the frequency and intensity of migraine attacks after the introduction of a gluten-free diet. 20% suffered from a carpal tunnel syndrome. 8% had experienced vestibular disturbances with episodes of dizziness without concomitant hearing loss. Surprisingly, epilepsy was less common than expected: only 4 individuals presented with a history of generalized and/or focal seizures.

Neurological Features

Problems of stance and gait became obvious in almost one third of patients with CD (for details see Table 2). When analyzing these problems in more detail, afferent ataxia was obvious in 26%, cerebellar and vestibular ataxia in 6% each. Three patients presented with deficits of more than one functional system: one patient with cerebellar, vestibular, and afferent, one with cerebellar and vestibular, one with vestibular and afferent problems. Proprioception was diminished in 35%, exteroception in 6% of patients. Reduced deep tendon reflexes (DTR) were present in 14%, whereas amyotrophy was rare.

Only a minority of patients presented with basal ganglia features such as dystonia, akinesia, or cog wheel rigidity. Two patients fulfilled the diagnostic cri-

TABLE 1. *Neurological history of CD patients*

	CD patients N = 72	
Neurological disorder	N	%
Migraine	20	28
Carpal tunnel syndrome	14	20
Vestibular disturbances with dizziness	6	8
Seizures	4	6
Myelitis	2	3
Hashimoto's encephalopathy	1	1

TABLE 2. *Neurological symptoms in CD patients*

	CD patients N = 72	
	N	%
Oculomotor features		
Impaired smooth pursuit	15	21
Vestibular deficits (impaired vestibulo-ocular reflex (VOR))	9	13
Gaze evoked nystagmus	4	6
Double vision	3	4
Slow saccades	2	3
Gaze palsy	2	3
Spontaneous nystagmus	1	1
Peripheral motor system		
Reduced deep tendon reflexes	10	14
Amyotrophy	1	1
Somatosensory system		
Impaired proprioception	25	35
Impaired exteroception	4	6
Movement disorders		
Impaired stance	21	29
Impaired gait	18	25
Cog wheel rigidity	9	13
Dysarthria	4	6
Dystonia	3	4
Akinesia	2	3
Pyramidal tract signs	3	4
Spasticity	3	4
Tics	2	3
Intention tremor	2	3
Myoclonus	1	1
Autonomic dysfunction		
Urinary incontinence	10	14

teria for Parkinson's disease. Pyramidal tract signs and spasticity were restricted to 4% and single patients suffered from myoclonus or tics. On the contrary, 14% of patients complained of bladder dysfunction.

Oculomotor features included impaired smooth pursuit, impaired VOR (as tested by Halmagy's manoeuvre), gaze evoked and spontaneous nystagmus, double vision, and slow saccades.

DISCUSSION

Neurological complications have first been reported to occur in ~6% of adult patients with CD by Cooke and Smith in 1966.[2] Meanwhile, symptoms such as epilepsy, peripheral neuropathy, chronic progressive leukencephalopathy, brain stem encephalitis, myositis, neuromyotonia, myasthenic syndromes, myelopathy, multiple sclerosis, and dementia with brain atrophy have been reported in association with GS/CD.[10–17] Neuropsychiatric features include depression, attentional deficits, autism, and schizophrenia.[18–21] Systematic approaches in larger patient samples are limited so far. In a UK study, AGA were positive in 57% of 53 patients with unexplained neurological symptoms when compared with 5% of patients with defined neurological syndromes. Interestingly, highly positive rates in the control population (12%) were not further addressed by the authors.[3] Lock et al. found positive AGA (IgA and/or IgG) in 40% of idiopathic ataxia, 34% of neuropathy, 43% of hereditary ataxia, and 17% of healthy blood donors.[22] Similarly, 12.5% of 24 Italian patients with otherwise unexplained cerebellar ataxia suffered from CD with full-blown villous atrophy.[23]

Certain discrepancies between different studies suggest a certain observation bias when exclusively focusing on primary neurological patients. Indeed, the association of neurological disease and CD appears less prominent in studies of primary CD cohorts: In a retrospective analysis, 189 among 620 patients attending a British celiac clinic presented with 263 distinct neurological and/or psychiatric conditions. The most common were depression (11.5%), epilepsy (4.0%), migraine (3.2%), and carpal tunnel syndrome (CTS) (2.4%).[24] So, the present findings are in accordance to these published data. Nevertheless, the prevalence in our CD sample was much higher than in the British cohort. A possible explanation could be the recruitment properties of our study: patients with CD with a history of neurological problems would have a greater interest to participate in such a study than patients without any neurological complaint.

In this study, gait disturbances were obvious in about one third of patients with CD. Nevertheless, only a minority presented with cerebellar ataxia. 8% of patients reported on episodes with dizziness and vestibular problems, whereas VOR impairment was obvious in 13%. Thus, vestibular dysfunction is likely to contribute to the unsteadiness at least in some of the patients. The 1-year prevalence of vestibular dysfunction and dizziness is upto 4.9% in the general population.[25] So, the high rate of vestibular problems in CD patients is striking.

Problems of stance and gait might also be related to proprioceptive deficits that are common among patients with CD. Indeed, degeneration of the dorsal columns has been observed in postmortem material of patients with CD.[8] Alternatively, the combination of reduced deep tendon reflexes and sensory deficits in patients with CD is compatible with peripheral neuropathy. Actually, peripheral neuropathy of the axonal or demyelinating type has often been reported in patients with CD.[26–28] In a French study, the mean incidence rate of CTS per 1000 person-years did not exceed 1.7 in working women and 0.6 in men.[29] Actually, the high prevalence of CTS among patients with CD

(19.4%) may reflect pathogenic similarities between CTS and peripheral neuropathy.

Another feature in patients with CD is epilepsy that was rather rare in our cohort. In the contrary, almost one third of patients stated a history of migraine. In the general population, only 18% of women and 6% of men are affected by recurrent migraine attacks. Interestingly, many patients reported a significant decrease of the amplitude and frequency of migraine attacks after the introduction of a gluten-free diet. Inflammation is an important component of most migraine models and anti-inflammatory drugs are very effective in treating migraine attacks. Modifications of the immune system including the expression of certain cytokine profiles have been claimed to act as risk factors for migraine. In these models, cytokines act as powerful pain mediators in neurovascular inflammation.[30]

In CD, the mechanisms leading to neurological disease are not yet understood. Deficiencies of folic acid, vitamin E, and biopterin have formerly been implicated in the pathogenesis of neurological disease in CD. However, replacement therapy does not resolve clinical symptoms in the majority of cases. Furthermore, hypovitaminosis rarely causes overt abnormalities in patients with CD and most neurological patients with CD do not show evidence for any nutritional deficiencies.[7] Besides, all our patients followed a gluten-free diet and did not have signs of malabsorption. Neuropathological studies of CD brains point to immune-mediated mechanisms with infiltrating lymphocytes in the central and peripheral nervous system.[8] CSF analysis revealed abnormalities in about one third of the patients receiving a lumbar tap. Two of them reported a single episode of myelitis accompanied by inflammatory CSF changes without any relapse to date. In another female suffering from personality changes, complex and generalized seizures with insufficient response to anticonvulsive therapy, gait disturbances, and cognitive impairment thyroperoxidase antibody levels were 50-fold, whereas all other thyroid parameters were within the normal range. MRI showed discrete white matter lesions on T2 weighted images. Under oral steroids, her clinical condition has ameliorated considerably and Hashimoto's encephalopathy was diagnosed. These findings give support to the immune hypothesis of neurological involvement in CD.

Taken together, we found a high frequency of proprioceptive and vestibular deficits leading to problems of stance and gait. The prevalence of neurological manifestations in CD is striking and must be considered more than accidental. It is true that pathogenic mechanisms linking CD to the nervous system have not yet been identified. Obviously, the patients' gluten-free diet had resolved intestinal symptoms, but had not prevented the development of neurological deficits. Regarding the considerable clinical variability, not a single, but many different pathogenic mechanisms are likely to contribute to neurological dysfunction in CD. It is to note that neurological problems were even found in patients with CD strictly adhering to a gluten-free diet.

Acknowledgments: This study could not have been performed without the help of all patients who participated in this study. We also thank Dr. Baas, German Coeliac Society (Deutsche Zöliakie Gesellschaft DZG, *e.V.*), for referring patients.

Author Roles: Bürk—conception of research project. Bürk, Farecki, Lamprecht, Roth, Weller, Rammensee, Oertel—organization of research project. Bürk, Farecki, Lamprecht—execution of research project. Bürk—design of statistical analysis. Bürk—execution of statistical analysis. Lamprecht, Oertel—review and critique of statistical analysis. Bürk—writing of the first draft of manuscript. Farecki, Lamprecht, Roth, Decker, Weller, Rammensee, Oertel—review and critique of manuscript. Decker—preparation of revision of manuscript.

Financial Disclosures: K. Bürk: Received salaries from the Universities of Tübingen, Marburg an Göttingen. She served as an expert for the FP7 of the European Community. M. Farecki: none. H.G. Lamprecht: Received salaries from the University of Tübingen. He is further supported by the Deutsche Forschungsgemeinschaft (DFG La1066/3-2). G. Roth: Holds several IP rights and grants that are not related to the topic of this study. He also received salaries from the University of Freiburg. P. Decker: Received salaries from the University of Tübingen. His research projects are supported by the Deutsche Forschungsgemeinschaft (DFG, DE 879/1-2) and the Interdisciplinary Center for Clinical Research of the University of Tübingen (IZKF-Nachwuchsgruppe 1604-0-1). M. Weller: Member of the advisory board of IBA, Roche, Schering, and Plough. He received lecture honoraria from Merck Serono, Roche, Schering, and Plough. H.G. Rammensee: Received salaries from the University of Tübingen. He holds numerous grants and IP rights that are not related to the subject of this study. W.H. Oertel: Received salaries from the University of Marburg.

REFERENCES

1. Marsh MN. Clinical and pathological spectrum of coeliac disease. Gut 1993;34:1740.
2. Cooke WT, Smith WT. Neurological disorders associated with adult coeliac disease. Brain 1966;89:683–722.
3. Hadjivassiliou M, Gibson A, Davies-Jones GA, Lobo AJ, Stephenson TJ, Milford-Ward A. Does cryptic gluten sensitivity play a part in neurological illness? Lancet 1996;347:369–371.

4. Hadjivassiliou M, Maki M, Sanders DS, et al. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. Neurology 2006;66:373–377.
5. Finelli PF, Mcentee WJ, Ambler M, Kestenbaum D. Adult celiac disease presenting as cerebellar syndrome. Neurology 1980;30: 245–249.
6. Abele M, Schols L, Schwartz S, Klockgether T. Prevalence of antigliadin antibodies in ataxia patients. Neurology 2003;60: 1674–1675.
7. Burk K, Bosch S, Muller CA, et al. Sporadic cerebellar ataxia associated with gluten sensitivity. Brain 2001;124:1013–1019.
8. Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, et al. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet 1998;352:1582–1585.
9. Stepniak D, Koning F. Celiac disease--sandwiched between innate and adaptive immunity. Hum Immunol 2006;67:460–468.
10. Beyenburg S, Scheid B, Deckert-Schluter M, Lagreze HL. Chronic progressive leukoencephalopathy in adult celiac disease. Neurology 1998;50:820–822.
11. Brucke T, Kollegger H, Schmidbauer M, Muller C, Podreka I, Deecke L. Adult coeliac disease and brainstem encephalitis. J Neurol Neurosurg Psychiatry 1988;51:456–467.
12. Crosato F, Senter S. Cerebral occipital calcifications in celiac disease. Neuropediatrics 1992;23:214–217.
13. Gobbi G, Bouquet F, Greco L, et al. Coeliac disease, epilepsy, and cerebral calcifications. The Italian Working Group on Coeliac Disease and Epilepsy. Lancet 1992;340:439–443.
14. Gordon N. Cerebellar ataxia and gluten sensitivity: a rare but possible cause of ataxia, even in childhood. Dev Med Child Neurol 2000;42:283–286.
15. Holmes GK. Non-malignant complications of coeliac disease. Acta Paediatr Suppl 1996;412:68–75.
16. Ventura A, Bouquet F, Sartorelli C, Barbi E, Torre G, Tommasini G. Coeliac disease, folic acid deficiency and epilepsy with cerebral calcifications. Acta Paediatr Scand 1991;80:559–562.
17. Wills A, Hovell CJ. Neurological complications of enteric disease. Gut 1996;39:501–504.
18. Dohan FC. Cereals and schizophrenia data and hypothesis. Acta Psychiatr Scand 1966;42:125–152.
19. Goldberg D. A psychiatric study of patients with diseases of the small intestine. Gut 1970;11:459–465.
20. Hallert C, Derefeldt T. Psychic disturbances in adult coeliac disease. I. Clinical observations. Scand J Gastroenterol 1982;17:17–19.
21. Rudin DO. The choroid plexus and system disease in mental illness. III. The exogenous peptide hypothesis of mental illness. Biol Psychiatry 1981;16:489–512.
22. Lock RJ, Tengah DP, Williams AJ, et al. Cerebellar ataxia, peripheral neuropathy, "gluten sensitivity" and anti-neuronal autoantibodies. Clin Lab 2006;52:589–592.
23. Pellecchia MT, Scala R, Filla A, De Michele G, Ciacci C, Barone P. Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features. J Neurol Neurosurg Psychiatry 1999;66:32–35.
24. Pengiran Tengah DS, Wills AJ, Holmes GK. Neurological complications of coeliac disease. Postgrad Med J 2002;78:393–398.
25. Neuhauser HK. Epidemiology of vertigo. Curr Opin Neurol 2007; 20:40–46.
26. Kaplan JG, Pack D, Horoupian D, Desouza T, Brin M, Schaumburg H. Distal axonopathy associated with chronic gluten enteropathy: a treatable disorder. Neurology 1988;38:642–645.
27. Simonati A, Battistella PA, Guariso G, Clementi M, Rizzuto N. Coeliac disease associated with peripheral neuropathy in a child: a case report. Neuropediatrics 1998;29:155–158.
28. Polizzi A, Finocchiaro M, Parano E, Pavone P, Musumeci S, Polizzi A. Recurrent peripheral neuropathy in a girl with celiac disease. J Neurol Neurosurg Psychiatry 2000;68:104–105.
29. Roquelaure Y, Ha C, Pelier-Cady MC, et al. Work increases the incidence of carpal tunnel syndrome in the general population. Muscle Nerve 2008;37:477–482.
30. Bruno PP, Carpino F, Carpino G, Zicari A. An overview on immune system and migraine. Eur Rev Med Pharmacol Sci 2007; 11:245–248.