PAPER

Should coeliac disease be considered in the work up of patients with chronic peripheral neuropathy?

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J Neurol Neurosurg Psychiatry 2005;76:1415–1419. doi: 10.1136/jnnp.2004.048413

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Received 24 June 2004
In revised form
27 December 2004
Accepted 11 January 2005

Objective: To investigate whether there is an association between chronic peripheral neuropathy and coeliac disease.

Methods: The cause of chronic peripheral neuropathy was first investigated in a group of 478 patients. Published reports were then examined systematically for an association between chronic peripheral neuropathy and coeliac disease. Cases were divided into two groups: group A, polyneuropathy preceding duodenal biopsy and controls undergoing duodenal biopsies; group B, coeliac disease preceding polyneuropathy. Patients with cerebellar ataxia, small fibre neuropathy, or a cause for their neuropathy were excluded.

Results: In 425 of the 478 patients, a cause other than coeliac disease was established. In the patients with no determined cause for neuropathy, one had abnormally increased IgA antigliadin antibodies but duodenal biopsy was normal. Ten previous studies of patients with chronic peripheral neuropathies were reviewed. The incidence of biopsy proven coeliac disease in patients with polyneuropathy did not differ from the controls (group A). In patients with a proven coeliac disease (group B), polyneuropathy could not be diagnosed more often than in the general population.

Conclusions: The results of both the clinical study and the literature review suggest that it is unlikely that chronic peripheral neuropathy without other neurological signs is associated with coeliac disease.

The annual incidence of peripheral neuropathies is estimated to be 40 per 100 000.¹

Over the years a cause for chronic peripheral neuropathy has been found in increasingly large numbers of patients, but there is still a group—approximately 10%—in whom no cause can be detected even after extensive evaluation.² The diagnostic label given to this group is “chronic idiopathic axonal polyneuropathy” (CIAP).^{3–4}

Coeliac disease is associated with neurological diseases. The spectrum of neurological disorders includes cerebellar ataxia, myoclonus, dementia, encephalitis, myopathy, and peripheral neuropathy.^{5–17} The pathogenesis of neurological disorders in coeliac disease is poorly understood. There are several possible mechanisms—for example, malabsorption of vitamins, metabolic complications of osteomalacia, and autoimmune reactions.^{6–13–18–19} The neurological manifestations may follow or precede the symptoms and diagnosis of coeliac disease.⁹ There is little doubt about the association between coeliac disease and cerebellar ataxia, but the association with peripheral neuropathies is less clear.²⁰

As there is still a group of patients with chronic peripheral neuropathy in whom no cause for the neuropathy can be demonstrated, the question arises as to whether coeliac disease is the cause of the neuropathy in some of these patients. To answer this question we first investigated the cause of the neuropathy in a large group of patients with chronic peripheral neuropathy. Second, we investigated whether coeliac disease was the cause of the neuropathy in patients in whom no explanation for the neuropathy was found. None of these appeared to have coeliac disease. Therefore we finally investigated whether a systematic review of published reports reveals such an association.

METHODS

Case series

We selected patients from the department of neurology of the Academic Medical Centre of Amsterdam who had a diagnosis of chronic peripheral neuropathy.

Included in the study were outpatients who had presented between 1993 and 2000 with symptoms or signs of a polyneuropathy. All patients had been evaluated at the general neurology outpatient department to which they were referred by their general practitioners, using the same guideline for assessing chronic polyneuropathy. This department is not a unit specialising in neuromuscular diseases. When the clinical diagnosis of polyneuropathy had been confirmed by electrophysiological tests, a set of laboratory tests (table 1) and chest radiography were carried out. In the history, emphasis was placed on family history, drugs used, and alcohol consumption.

Standard techniques for electrophysiological examination were used. Skin temperature was maintained at between 32°C and 35°C. The electrophysiological studies included motor and sensory conduction velocities in at least two arm nerves and one leg nerve, F responses of the ulnar nerve and peroneal nerve, H reflex of the soleus muscle, and electromyography (EMG) of distal arm and leg muscles.

Patients in whom no cause for the neuropathy was found were re-evaluated at least three years later. In the re-evaluation, we recorded the clinical course (mild or severe progression/no progression/recovery) over the years. We checked whether all the laboratory tests had been done (table 1), and if not the missing tests were carried out. All patients were asked again whether family members were known to have had polyneuropathy or had the same

Abbreviations: CIAP, chronic idiopathic axonal polyneuropathy

Table 1 Laboratory tests in patients with chronic polyneuropathy

ESR	Folate
Haemoglobin	Vitamin B-1, B-12
Mean cell volume	Glucose
White cell count	TSH
Platelets	Serum protein electrophoresis
Sodium	ANF
Potassium	ANCA
Creatinine	Nuclear antigen antibodies
Alkaline phosphatase	Serum ACE
Blood urea nitrogen	Urine: glucose, proteins
γ -Glutamyltransferase	

Lyme and HIV tests, anti-Hu: if indicated

ACE, angiotensin converting enzyme; ANCA, antineutrophil cytoplasmic antigen antibodies; ANF, antinuclear factor; ESR, erythrocyte sedimentation rate; TSH, thyroid stimulating hormone.

symptoms, and in all cases a neurological examination was repeated. After recording all these data, we made a decision about whether or not the polyneuropathy was idiopathic.

In the patients with no determined cause for the neuropathy blood was drawn for enzyme linked immunosorbent assays (ELISA) to detect IgA/G antigliadin antibodies, IgA anti-tissue transglutaminase antibodies, and IgA endomysium antibodies. Values for IgA/G antigliadin antibodies (arbitrary units (AE) per ml) were: normal, <10 AE/ml; borderline, 10–24 AE/ml; abnormal, >24 AE/ml. Values for IgA anti-tissue transglutaminase antibodies (U/ml) were: normal, <5 U/ml; borderline, 5–7 U/ml; abnormal, >7 U/ml. IgA endomysium antibodies were recorded as present or absent.²¹

If antibodies were present or had abnormally high values, duodenal biopsy was considered. A biopsy of four specimens was taken from the distal part of the duodenum. The following histological features were scored as absent or present: crypt hyperplasia, villous atrophy, increase in intraepithelial lymphocytes, and other pathology.

Systematic review

We undertook a literature search for studies of patients with coeliac disease and neurological complications, especially peripheral neuropathies, and their controls. To identify such studies we carried out a MEDLINE search (1960 to 2003) using the keywords “c(o)eliac disease”, “peripheral neuropathies”, and “(peripheral) nervous system diseases”. We also searched the references listed in those published studies and in reviews and textbooks.

Study selection and data extraction

Eligibility was determined by reading the methods section of the papers. Papers that met the following criteria were considered eligible:

- original data, prospective or retrospective in design;
- sufficient number of patients (that is, no case reports);
- patients and/or controls evaluated for coeliac disease by screening antigliadin and/or transglutaminase and/or endomysium antibodies and/or duodenal biopsies;
- patients were evaluated for the presence of neurological complications, at least polyneuropathy;
- controls were neither suffering from polyneuropathy nor had signs or symptoms suggestive of coeliac disease before screening;
- antibody quantification described;
- biopsy described;
- human studies only;

- English language publication;
- only adult subjects.

As a first step, we included the data on all patients, as presented in the studies. We then excluded patients for the following reasons: the neurological symptoms were not consistent with polyneuropathy, in particular cerebellar ataxia without polyneuropathy; a cause for the neuropathy was established; or the electrophysiological results were normal but the sensory symptoms suggested small fibre neuropathy.

Data were collected on all patients and controls who were screened for coeliac disease by investigating antibodies or by duodenal biopsy, or both. These patients and controls were divided in five groups: patients in whom polyneuropathy of unknown cause preceded the antibody screening tests; patients in whom polyneuropathy of unknown cause preceded the biopsy to confirm or reject the diagnoses coeliac disease; controls who were screened for antibodies; controls who underwent biopsy to confirm or reject the diagnoses coeliac disease; patients known to have coeliac disease who were investigated for the presence of polyneuropathy.

In patients with positive antibodies, the diagnosis of coeliac disease could not be confirmed by biopsy in all cases. Because biopsy is the gold standard for the diagnosis of coeliac disease, we restricted our results to two groups in which the subjects underwent a biopsy to confirm or reject the diagnosis of coeliac disease. *Group A* consisted of patients in whom polyneuropathy of unknown cause preceded a biopsy to confirm or reject the diagnosis coeliac disease; the occurrence of coeliac disease was compared with the occurrence in controls without polyneuropathy. *Group B* consisted of patients known to have coeliac disease, proven by biopsy, who were investigated for the presence of polyneuropathy and were compared with the general prevalence of polyneuropathy in the population.

Statistical analyses

In the general population the prevalence of coeliac disease is approximately 1/280 to 1/330.^{22–23} If there is an association between peripheral neuropathy and coeliac disease we would expect at least one or two patients with coeliac disease in the study group of 478 patients with peripheral neuropathy we investigated in our department.

In the systematic review, data on homogeneous groups were pooled, and weighted frequencies with 95% confidence interval (CI) were calculated using the study size as weights.

RESULTS

Case series

We selected the patients for this study out of a group of 478 patients with peripheral neuropathy. In 425 of these a cause for the neuropathy was determined. As in these patients a cause was already detected, it was not considered necessary to investigate them for the prevalence of coeliac disease. In the remaining 53 patients no cause could be found for the neuropathy.

After re-evaluation of these 53 patients at least three years after the diagnosis idiopathic neuropathy, only 16 still had no determined cause for their neuropathy. Twelve patients had died, three were lost at follow up, and in 22 cases a cause for the neuropathy could be established (table 2).

Of the 16 patients with no determined cause for their neuropathy, one had IgA antigliadin antibodies in the high range. Duodenal biopsy in this patient was normal.

Systematic review

We identified 36 papers with our search strategy. Of these studies we rejected 25 for one of the following reasons:

Table 2 Final diagnosis in patients who initially had a diagnosis of chronic idiopathic axonal polyneuropathy

Drug induced neuropathy
Diabetes mellitus
Renal failure
Carcinoma; paraneoplastic syndrome
Rheumatoid arthritis
Hypothyroidism
Sjögren's syndrome
Vitamin B-12 deficiency (n = 2)
Hereditary sensory neuropathy
Too young (CMT-2?)
Multiple system atrophy
Carpal tunnel syndrome; both sides
CMT-2 (n = 4)
Sensory neuropathy, no CIAP
Cervical spondylitic myelopathy
Painful legs and moving toes syndrome
No CIAP (recovery after losing weight)
No CIAP (recovery after prednisone)

CIAP, chronic idiopathic axonal polyneuropathy; CMT, Charcot-Marie-Tooth disease.

- only description of patients and/or median group values and/or methods and techniques provided^{7 24-32};
- case reports without relevant control groups^{5 33-40};
- coeliac disease in children⁴¹⁻⁴³;
- results presented in an editorial without details^{44 45};
- one study showed polyneuropathy in 16 patients with coeliac disease, but all these patients had cerebellar ataxia; this study was therefore not included.⁶

The remaining 10 studies fulfilled the eligibility criteria and were used for further analysis.^{20 46-54} The study design was described in all studies.

Data extraction

First we divided data from the 10 eligible studies and our case series into five groups (table 3). Thereafter we restricted our analysis to the studies in which patients underwent a biopsy to reject or confirm the diagnosis of coeliac disease.

Patients in whom polyneuropathy preceded duodenal biopsy (group A)

We found three papers eligible for our review and included our own study results in this group.

The first paper (Hadjivassiliou *et al*²⁰), presenting patients with a positive biopsy, confirmed the diagnosis of coeliac disease in 20 patients with polyneuropathy of unknown cause. Of these, four had cerebellar ataxia. Neither in this paper nor in correspondence with the author were any comments made about the presence of cerebellar ataxia in the patients with proven coeliac disease.

In the second study (Luostarinen *et al*⁴⁶), three of 204 patients with polyneuropathy of unknown origin had coeliac disease. One of these patients also had ataxia. Another patient died from a lymphoma, which might have been related to progressive neuropathy. These two patients were excluded from our review. A third patient had normal electrophysiological tests, which is not consistent with chronic polyneuropathy, and therefore this patient was also excluded from the review.

The third paper (Chin *et al*⁴⁷) described a group of 400 patients with polyneuropathy (of various causes) who were tested for the presence of antibodies. Of these 400 patients, 75 had signs and symptoms consistent with peripheral neuropathy, but with normal electrodiagnostic studies and unremarkable laboratory tests. These patients do not fulfil the criteria for polyneuropathy and were excluded. Twenty of the 400 patients appeared to have biopsy proven coeliac disease. Five of these were known to have had coeliac disease in childhood; nine had the diagnosis of coeliac disease before they had neurological symptoms and were excluded from the review. Six patients had a diagnosis of polyneuropathy before coeliac disease was established. Of these, three had a cause for neuropathy (diabetes mellitus, hypothyroidism, paraproteinaemia). One patient appeared to have multifocal neuropathy, which is not compatible with a polyneuropathy of unknown cause, and was also excluded. The remaining two patients had normal or minimally abnormal electrophysiological results and therefore did not fulfil the criteria for chronic polyneuropathy; these patients were excluded. Of the 325 patients with abnormal electrophysiological results, there

Table 3 Summary of reports examined

	n/N; % (95% CI)				
Reference	Group 1	Group 2	Group 3	Group 4	Group 5
Hadjivassiliou <i>et al</i> , 1996 ²⁰	7/20; 35 (15.4 to 59.2)	1/20; 5 (0.1 to 24.9)	6/50†; 12 (4.5 to 24.3)	0/50; 0 (0.0 to 7.1)	
Rosenberg <i>et al</i> (current study)	1/16; 6 (0.2 to 30.2)	0/16; 0 (0.0 to 20.6)			
Luostarinen <i>et al</i> , 1999 ⁴⁶		0/20; 0 (0.0 to 16.8)			
Chin <i>et al</i> , 2003 ⁴⁷		0/323; 0 (0.0 to 1.1)			
Hadjivassiliou <i>et al</i> , 2003 ⁴⁸			149/1200†; 12 (10.6 to 14.3)		
Fasano <i>et al</i> , 2003 ⁴⁹			27/2845; 0.9 (0.6 to 1.4)		
Grodzinsky <i>et al</i> , 1992 ⁵⁰			124/1866; 7 (5.6 to 7.9)	7/1866; 0.4 (0.2 to 0.8)	
Luostarinen <i>et al</i> , 2003 ⁵¹					4/24; 17 (4.7 to 37.4)
Pengiran <i>et al</i> , 2002 ⁵²					3/620*; 0.5 (0.1 to 1.4)
Holmes <i>et al</i> , 1997 ⁵³					2/388*; 0.5 (0.1 to 1.8)
Volta <i>et al</i> , 2002 ⁵⁴					1/159; 0.6 (0.0 to 3.4)

†† and **, probably the same study groups.

Group 1, patients in whom the polyneuropathy of unknown cause preceded the antibodies screening tests: number of patients with polyneuropathy (N) and antibodies (n); group 2, patients in whom the polyneuropathy of unknown cause preceded biopsy to confirm or reject the diagnoses coeliac disease: number of patients with polyneuropathy (N) and proven coeliac disease by biopsy (n); group 3, controls who were screened for antibodies: number of controls (N) and antibodies (n); group 4, controls who underwent biopsy to confirm or reject the diagnosis coeliac disease: number of controls (N) and proven coeliac disease by biopsy (n); group 5, patients known with coeliac disease who were screened for polyneuropathy: number of patients with coeliac disease (N) and polyneuropathy (n).

CI, confidence interval.

were only two with proven coeliac disease, but one had a paraproteinaemia and the other had multifocal neuropathy; both were excluded. No data are known on the final diagnoses in the remaining 323 patients. The referral pattern to the centre and the focus of the paper suggested that most subjects were referred with autoimmune or inflammatory diseases, a different population from that found in neurological practice. The high incidence (75/400) of coeliac disease in patients with clinical features of polyneuropathy and normal or minimally abnormal electrodiagnostic studies is remarkable. These patients may, according to the author, fall into the category of idiopathic small fibre neuropathy.

Patients with coeliac disease investigated for polyneuropathy (group B)

One study was included which showed polyneuropathy in six of 26 patients with coeliac disease.⁵¹ In two of these patients the polyneuropathy was probably related to alcoholism or Graves disease, so both patients were excluded.

In two other studies from the same group, three patients of 620 (0.5%) and two of 388 (0.5%) with coeliac disease had evidence of polyneuropathy. Details of the polyneuropathy were not given.^{52 53}

In another study included in this review,⁵⁴ 160 patients with biopsy proven coeliac disease had been investigated for the presence of neurological symptoms. Two of these (1%) had symptoms of polyneuropathy. One patient complained of muscle pain and leg paraesthesiae but had normal electrophysiological tests. This patient had a diagnosis of small fibre neuropathy and was excluded. The other patient was diagnosed as having distal axonopathy. This patient had no response to treatment. In both patients the neurological symptoms preceded the diagnosis of coeliac disease.

Statistical analyses

Group A

In the overall group of 560 patients with polyneuropathy of unknown cause, who all underwent a biopsy, the diagnosis of coeliac disease was confirmed in one patient (0.2%; 95% CI, 0.0 to 1.0).

In the control group, seven of 1916 subjects who underwent a biopsy appeared to have coeliac disease (0.4%; 95% CI, 0.2 to 0.8), which is consistent with the prevalence of 0.3% found in other studies.^{22 23 55}

Group B

In the overall group of 1191 patients with biopsy proven coeliac disease who were screened for polyneuropathy, 11 were found to have polyneuropathy (0.9%; 95% CI, 0.4 to 1.6). The overall prevalence of polyneuropathy is estimated to be between 0.3% and 3%.⁵⁶⁻⁵⁸

DISCUSSION

In this study of patients with chronic peripheral neuropathy, an explanation other than coeliac disease was found in 95% of the cases. In the remaining patients coeliac disease could have been the cause of the neuropathy. We estimated that there would be one or two cases of coeliac disease in a group of 478 patients with peripheral neuropathy if there is an association between these two conditions. We expected to find these one to two patients in the group without known cause for polyneuropathy. However, we found IgA antigliadin antibodies in only one patient, and a biopsy in that patient showed no signs of coeliac disease. We therefore concluded that an association of coeliac disease and chronic peripheral neuropathy is unlikely.

Another reason for believing that an association between chronic peripheral neuropathy and coeliac disease is unlikely is that we have not seen any patients with this disease

combination in the years during which we have been increasingly aware of coeliac disease. On the other hand we had not tested for the presence of coeliac disease in cases where a cause for the neuropathy had already been demonstrated. We cannot exclude the possibility that some of the patients did in fact have coeliac disease as a cause for their neuropathy. We therefore decided to carry out this systematic review of published reports in this area, to investigate the probability of coeliac disease being associated with isolated chronic peripheral neuropathy. Ten studies were eligible for our systematic review.

Patients were initially divided into five groups, but we finally restricted our analysis to two groups of patients, who all underwent a biopsy to confirm or reject the diagnosis of coeliac disease. Patients were excluded if a cause was found for their peripheral neuropathy or if cerebellar ataxia was present. It is not easy to distinguish ataxia caused by sensory neuropathy from a cerebellar syndrome. If there was doubt about the origin of the ataxia, these patients were not excluded from the analysis.

There were studies on patients who had normal electrophysiological test results and whose final diagnosis was small fibre neuropathy. These patients were excluded from our review. The distinction between polyneuropathy, confirmed by electrophysiological tests, and small fibre neuropathy is probably of clinical significance, as patients with small fibre neuropathy may respond to a gluten-free diet.

We found a wide variation in the frequency of occurrence of polyneuropathy in cases of established coeliac disease. A probable explanation for this is that not all the studies used the same definition of polyneuropathy. Electrophysiological tests were not always required to confirm the diagnosis, and it is not clear whether other causes for peripheral neuropathies were excluded in all studies; neither do we know the frequency of ataxia in combination with polyneuropathy, nor the frequency of all small fibre neuropathies. Another explanation for the variation in results could be differences in the centres where the patients were seen; several of these were tertiary referral centres.

In patients with polyneuropathy of unknown cause, biopsy proven coeliac disease was found less often than in the control group, although a small difference has not been excluded. In patients with proven coeliac disease, polyneuropathy was not diagnosed more often than in the general population. The results overall make an association between peripheral neuropathy and proven coeliac disease unlikely. We therefore decided not to embark on a large scale study to investigate the association more definitively. In addition, we decided that coeliac disease should not be considered in the work up of patients with chronic peripheral neuropathy.

It has been suggested that in patients with small fibre neuropathy and gastrointestinal symptoms the diagnosis of coeliac disease ought to be considered. This group of patients was not included in our study. Thus our results cannot be extrapolated to patients with small fibre neuropathy.

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Competing interests: none declared

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