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ORIGINAL COMMUNICATION

Gluten neuropathy: prevalence of neuropathic pain and the role of gluten-free diet

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Abstract

Background and aim Peripheral neuropathy is a common extraintestinal manifestation of gluten sensitivity (gluten neuropathy). We aimed to establish the prevalence of neuropathic pain in patients with otherwise idiopathic PN and gluten sensitivity (positive antigliadin, endomysial, and/or transglutaminase antibodies, with or without enteropathy) and to describe any contributory factors.

Methods All consecutive patients with gluten neuropathy (GN) attending a specialist gluten/neurology clinic were invited to participate. Pain was assessed via the DN4 questionnaire and the visual analog scale. Overall Neuropathy Limitations Scale was used to assess the severity of neuropathy. The Mental Health Index (MHI-5) was used to measure participants' general mental health status.

Results In total, 60 patients (76.7% males, mean age 69.9 ± 10.1 years) with GN were recruited. Neuropathic pain was present in 33 patients (55.0%). Comparison between groups of painful and not painful GN did not show significant differences regarding age, gender, neuropathy severity and neuropathy type. Patients with painless GN were more likely to be on a strict gluten-free diet (55.6 versus 21.2%, $p = 0.006$). Patients with painful GN presented with significantly worse MHI-5 score (75.9 ± 13.8 versus 87.4 ± 8.1, $p < 0.001$). Multivariate analysis showed that, after adjusting for age, gender and MHI-5, strict gluten-free diet was associated with lowering the odds of peripheral neuropathic pain by 88.7% (95% CI 47.2–97.6%, $p = 0.006$).

Conclusion Neuropathic pain is very prevalent in GN and is associated with poorer mental health status. Strict gluten-free diet might be protective as it is associated with a significant reduction of the odds of peripheral neuropathic pain associated to GN.

Keywords Gluten neuropathy · Neuropathic pain · Gluten-free diet

Introduction

Gluten neuropathy (GN) is the second commonest neurological manifestation of gluten sensitivity, after cerebellar ataxia [1]. It is defined as an otherwise idiopathic neuropathy, in the absence of an alternative etiology despite extensive investigations [2], and in the presence of serological evidence of gluten sensitivity (primarily positive antigliadin antibodies with/without endomysial and/or transglutaminase 2 antibodies) [1, 3]. This is irrespective of the presence of enteropathy (Coeliac disease) or not.

The main neurophysiological type of GN is symmetrical "length-dependent" sensorimotor axonal peripheral neuropathy occurring in about two-thirds of the patients [1]. Sensory ganglionopathy (SG), which occurs in about one-third of the patients, leads to pure sensory large-fiber axonal loss. Very rarely other forms of neuropathies such

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as mononeuritis multiplex (MMX) may occur [1, 4, 5]. Although the exact pathophysiology of GN is yet to be determined, the role of autoimmunity seems to be prominent. Peripheral nerve tissue biopsies of patients with GN showed focal inflammatory cell infiltrate [6].

Amongst patients with chronic axonal neuropathy, 25% of patients have serological evidence of gluten sensitivity, a percentage that increases to 34% when looking to patients initially thought to suffer from chronic idiopathic axonal polyneuropathy [7]. The risk of peripheral neuropathy in CD increases with age and overall is 2.5 times higher compared to the risk of peripheral neuropathy in the general population [5, 8]. Epidemiological data of the risk of peripheral neuropathy in patients with serological evidence of gluten sensitivity in the absence of enteropathy are not yet available.

Gluten neuropathy is of mild-to-moderate severity and does not lead to severe disability, but affects the patients' quality of life [9]. Gluten-free diet (GFD) has proven to stop the disease progression in patients with SG [6] and can lead to improvement of the neurophysiological parameters in patients with the sensorimotor "length-dependent" axonal type [10].

Peripheral neuropathic pain is a frequent symptom in peripheral neuropathy (PN) of any etiology, including diabetes [11], HIV related [12], cancer [13–15], and idiopathic [2, 16]. The purpose of our cross-sectional study was to estimate the prevalence of peripheral neuropathic pain in patients with GN and identify any contributory factors.

Methods

Procedure and participants

This was a cross-sectional study conducted at the Sheffield Institute of Gluten Related Diseases (SIGReD). Patients were recruited from the gluten/neurology clinic based at the Royal Hallamshire Hospital (Sheffield, UK).

To be enrolled, the patients had to meet the following inclusion criteria: (1) diagnosis of PN, as confirmed on nerve conduction studies, (2) serological evidence of gluten sensitivity (positive in one or more of antigliadin IgG and/or IgA, endomysial and transglutaminase antibodies) at diagnosis prior to commencing gluten-free diet, (3) absence of other risk factors for developing PN (i.e., diabetes, vitamin deficiencies, and exposure to neurotoxic agents) (4) age equal to or greater than 18 years, and (5) able to provide a written informed consent.

The study protocol was approved by the local ethics committee.

Measures

Demographic characteristics included age and gender. All patients went through extensive investigations for possible causes of PN [2]. Patients with a family history of neuropathy were excluded.

The type of neuropathy (sensorimotor length-dependent PN, sensory ganglionopathy [17, 18], mononeuritis multiplex) for all patients was determined based on nerve conduction studies, which were performed by the same clinician on the day of the recruitment.

All patients were referred for an endoscopy and duodenal biopsy to establish the presence of enteropathy. All biopsies were histologically assessed by an experienced pathologist for evidence of enteropathy (triad of villous atrophy, crypt hyperplasia, and increase in intraepithelial lymphocytes).

The severity of neuropathy was assessed by the overall limitations neuropathy scale (ONLS), which is a validated scale that measures limitations in the everyday activities of the upper and lower limbs [19].

Neuropathic pain was assessed via the DN4 questionnaire [20]. DN4 is a clinician administered screening tool consisting of ten yes/no items. A score of equal to or greater than 4 is considered as diagnostic of neuropathic pain [21].

Pain intensity was assessed via a visual analog scale (VAS) ranging from 0 (no pain at all) to 10 (worst pain you can imagine). Pain intensity was assessed for two time points: neuropathic pain at recruitment and maximum peripheral neuropathic pain experienced during the disease course. Only patients reporting pain intensity of equal to or greater than 4 at any point were considered to suffer from a painful neuropathy.

The Mental Health Index (MHI-5) was used to measure participants' general mental health status. MHI-5 is a five-item tool, part of the Short Form Health Survey (SF-36) [22]. A summed score for MHI-5 can linearly be transformed to a 0–100 scale, with higher scores corresponding to better mental health [23]. The instrument has been satisfactory predictive validity in screening for depressive and anxiety disorders [24].

Biagi score was used to verify adherence to a gluten-free diet [25]. We considered as a strict gluten-free diet patients with a Biagi score of equal to or above 3 and negative serology at the time of recruitment.

Statistical analyses

A database was developed using the Statistical Package for Social Science (version 23.0 for Mac; SPSS). Frequencies and descriptive statistics were examined for each variable. Comparisons between patients with painful

GN and patients with painless GN were made using Student's *t* tests for normally distributed continuous data, Mann–Whitney's *U* test for non-normally distributed, and chi-square test or Fisher's exact test for categorical data.

Where differences with a *p* value of lower than 0.10 were found, these variables were entered in a logistic regression model, with neuropathic pain being the dependent variable. All accuracy and generalization assumptions for the model were checked.

The level of statistical significance was set at the 0.05 level.

Results

Study population

Sixty-five patients with neuropathy and gluten sensitivity were recruited. Out of them, one patient was also diagnosed with hereditary neuropathy with liability to pressure palsies (HNLPP), three were also diagnosed with diabetes mellitus, and one had received chemotherapy in the past, and therefore were excluded from the study. The final study population consisted of 60 patients with gluten neuropathy (76.7% male, mean age 69.9 ± 10.1 years). Twenty-two patients (36.7%) were on a strict gluten-free diet.

Fourty-three patients (71.7%) had sensorimotor length-dependent axonal PN and 16 (26.7%) had SG. One patient (1.7%) had MMX. Mean age at neuropathic symptoms' onset was 57.6 ± 11.9 years. Overall ONLS scores ranged from 1 to 7 (mean 3.1 ± 1.8).

Not all of the patients agreed to a duodenal biopsy. Nine of 43 (20.9%) patients who did have an endoscopy and duodenal biopsy had enteropathy (8 coeliac disease, 1 increased intraepithelial lymphocytes).

Based on the DN4 questionnaire, neuropathic pain was present in 33 patients (55.0%). The characteristics of pain based on the DN4 questionnaires are summarized in Table 1. The prevalence of neuropathic pain in patients on strict gluten-free diet was 21.2% and in patients not on strict gluten-free diet was 68.4%.

In 12 patients (20.0%), neuropathic pain was the first symptom at presentation. Based on VAS, the neuropathic pain intensity on examination at recruitment, ranged from 0 to 7 (mean 2.8 ± 2.3), when the maximum neuropathic pain experienced, since the neuropathy diagnosis, ranged from 4 to 10 (mean 7.6 ± 1.7).

Table 1 Characteristics of pain in patients with painful gluten neuropathy, based on the DN4 questionnaire

DN4 item	Characteristic	Percentage of patients with painful GN ($n=33$) (%)
1	Burning	60.6
2	Painful cold	57.6
3	Electric shocks	60.6
4	Tingling	93.9
5	Pins and needles	75.8
6	Numbness	97.0
7	Itching	45.5
DN4 item	Examination	Percentage of patients with painful GN ($n=33$) (%)
8	Hypoesthesia to touch	84.8
9	Hypoesthesia to pinprick	100
10	Allodynia or hyperalgesia	27.3

Univariate analysis

Table 2 summarizes the demographic and the clinical characteristics of the patients with painful and the patients with painless gluten neuropathy. The two groups did not differ significantly regarding age, gender, type or severity of neuropathy, age at onset of neuropathic symptoms, or presence of enteropathy. Patients with painless GN were more likely to be on a strict gluten-free diet (55.6 versus 21.2%, $p=0.006$). Patients with painful GN presented with significantly worse MHI-5 score (75.9 ± 13.8 versus 87.4 ± 8.1, $p<0.001$).

Multivariate analysis

The following independent variables were entered into the multivariate logistic regression model: age, gender, MHI-5 score, and being on a strict gluten-free diet or not. The full model significantly predicted neuropathic pain ($\chi^2=25.61$, $df=4$, $p<0.001$). As shown in Table 3, after adjusting for age, gender, and mental health status, strict gluten-free diet remained as a statistically significant determinant of neuropathic pain, as being on strict gluten-free diet was associated with lowering the odds of peripheral neuropathic pain by 88.7%. (95% CI 47.2–97.6%, $p=0.006$).

Discussion

This cross-sectional study demonstrates that almost three out of five patients with GN experience peripheral neuropathic pain (prevalence 55.0%). More importantly it shows that strict gluten-free diet might have a protective effect as it is associated with a 88.7% reduction of the odds of peripheral neuropathic pain.

Abdominal pain can be seen in patients with CD and gluten sensitivity as part of other gastrointestinal symptoms such as indigestion, diarrhea and bloating [26]. The novelty

Table 2 Characteristics of patients with gluten neuropathy, with and without pain

	Total population ($n=60$)	Painful PN ($n=33$)	Painless PN ($n=27$)	p value
Demographics				
Age, in years (SD)	69.9 (10.1)	68.6 (9.8)	71.5 (10.4)	0.271
Male gender (%)	46 (76.7)	24 (72.7)	22 (81.5)	0.425
Clinical characteristics				
Normal duodenum biopsy[a]	20.9%	10.0%	30.4%	0.142
Type of neuropathy				0.537
Sensorimotor axonal PN (%)	43 (71.7)	24 (72.7)	19 (70.4)	
Sensory ganglionopathy (%)	16 (26.7)	9 (27.3)	7 (25.9)	
Mononeuritis multiplex (%)	1 (1.7)	0 (0.0)	1 (3.7)	
Age at of neuropathic symptoms	57.6 (11.9)	56.1 (11.2)	59.4 (12.6)	0.287
Neuropathy severity				
ONLS Arm score (SD)	1.3 (0.9)	1.3 (0.9)	1.2 (0.9)	0.826
ONLS Leg score (SD)	1.9 (1.2)	2.1 (1.1)	1.6 (1.3)	0.114
Total ONLS score (SD)	3.1 (1.8)	3.4 (1.7)	2.8 (1.8)	0.232
Strict gluten-free diet (%)	22 (36.7)	7 (21.2)	15 (55.6)	0.006
MHI-5 score (SD)	81.1 (12.9)	75.9 (13.8)	87.4 (8.1)	< 0.001

PN peripheral neuropathy, *ONLS* overall neuropathy limitation scale, *SD* standard deviation, *MHI* mental health index

[a]Duodenum biopsies were performed in a total of 43 patients

Table 3 Patients' characteristics investigated for their association with peripheral neuropathic pain

Variable	OR[a] (95% CI)	Wald	p
Age per year	0.956 (0.893–1.023)	1.681	0.195
Male gender	0.576 (0.100–3.310)	0.383	0.536
Strict gluten-free diet	0.113 (0.024–0.528)	7.669	0.006
MHI-5 score	0.900 (0.844–0.961)	10.059	0.002

CI confidence intervals, *MHI* mental health index

[a]Adjusted odd ratios presented

of this study is that it highlights the prevalence of peripheral neuropathic pain in gluten neuropathy, which is an underdiagnosed gluten-related extraintestinal manifestation [27].

Peripheral neuropathic pain results from small fiber dysfunction (Aδ and C fibers). In this current study, we did not focus on small fiber testing (i.e., quantitative sensory testing, microneurography, autonomic testing, and skin biopsy) and, therefore, the degree of involvement of small fibers has not been studied in depth. However, the figure that pain is prevalent in three out of five patients with GN is very consistent with the prevalence of pain in other forms of PN such as diabetic [28], paraneoplastic [14], platin-induced [29], and chronic idiopathic axonal polyneuropathy [2].

It has already been shown that strict gluten-free diet improves GN, both in patients with length-dependent sensorimotor axonal peripheral neuropathy and patients with sensory ganglionopathy [6, 10]. Gluten-free diet was effective in improving nerve conduction parameters even within 12 months of starting the diet [10]. Patients also report a subjective improvement in neuropathy symptoms after being on the diet for 12 months [10]. The effect is irrespective of the presence or absence of enteropathy [10].

The current study focused primarily on neuropathic pain—possibly the most distressing neuropathic symptom—and showed that strict gluten-free diet can be protective regardless of the type of neuropathy or the presence or not of enteropathy. This finding is analogous to the observation that gluten-free diet is effective in easing abdominal discomfort and pain in patients with CD [30, 31] or patients with gluten sensitivity without enteropathy [32].

Perception of pain varies among individuals and depends on many variables [33]. Psychological factors, situational and emotional, that exist when we experience pain, can profoundly alter the strength of such perceptions [33]. Depression and anxiety (which are common in CD) tend to influence pain perception [34]. In this study, we also looked at the overall mental health status of patients with GN showing that patients with neuropathic pain have significantly worse overall mental health status, pointing toward depression and anxiety disorders. However, even after adjusting for the overall mental health status in our logistic regression model the association of gluten-free diet and neuropathic pain remained statistically significant, regardless of the presence of depression or anxiety.

Our results should be interpreted with some caution given the limitations of our design. This is a cross-sectional observational study comparing GN patients with and without peripheral neuropathic pain and therefore the effect of gluten-free diet on neuropathic pain can only be shown indirectly. A prospective double-blind randomized placebo-controlled trial of the effect of gluten-free diet on neuropathic pain secondary to GN is the best methodological approach to directly confirm our findings. However, such a study will be difficult to perform given the nature of the intervention and the established benefits of a gluten-free diet in patients with enteropathy and those with neurological manifestations. In addition, our cohort comprised of users of one specialized service, and the results may not be generalizable to other settings. No nerve biopsies were done and, therefore, the remote possibility of additional rare causes for the neuropathy as reported in a large case series by Farhad et al. (i.e., vasculitic) [35] cannot be entirely excluded. Finally, our cohort included patients with large-fiber axonal peripheral neuropathies only. Small fiber neuropathy associated with serological evidence of gluten sensitivity is another area that merits further consideration.

In conclusion, neuropathic pain is very prevalent in GN; however, a strict gluten-free diet is associated with significant reduction in the odds for neuropathic pain and should be considered in patients with painful GN.

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Compliance with ethical standards

Conflicts of interest Panagiotis Zis, Dasappaiah Ganesh Rao, Ptolemaios Georgios Sarrigiannis, and Marios Hadjivassiliou have nothing to disclose.

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