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Small fiber neuropathy in coeliac disease and gluten sensitivity

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ABSTRACT

Objectives
The commonest types of peripheral neuropathy in the context of Coeliac Disease (CD) and gluten sensitivity (GS) are length dependent symmetrical sensorimotor neuropathies and sensory ganglionopathies. In patients with such neuropathy, (gluten neuropathy), peripheral neuropathic pain is prevalent suggesting involvement of small fibers. The purpose of this report was to describe the clinical characteristics of patients with CD or GS and pure small fiber neuropathy (SFN).

Methods
We reviewed the records of all patients that had been referred to the Gluten Related Neurological Disorders clinic who had clinical and neurophysiological evidence of SFN. All patients had serological evidence of gluten sensitivity (GS) prior to commencing GFD. All patients were offered a duodenum biopsy. Patients with comorbidities that could cause SFN were excluded.

Results.
We identified 13 patients (9 males) with SFN and gluten sensitivity. Of 11 patients who underwent duodenal biopsy 10 had evidence of enteropathy (CD). Mean age at onset of pain was 53.5±11.4 years (range 34-72) and mean age of CD/GS diagnosis was 50.8±10.4 years (range 34-68). In 8 patients (61.5%) pain was the presenting feature.

Neurophysiological assessment suggested a length dependent small fiber neuropathy in 11 patients, whereas in 2, a non-length dependent pattern was identifying suggesting that the predominant pathology lies in the dorsal root ganglia.

Conclusion.
SFN can be a presenting feature of CD and GS and, therefore, screening for CD and GS should be included in the diagnostic work up of patients with idiopathic SFN.
Keywords: pain; small fiber neuropathy; gluten; coeliac disease
INTRODUCTION

Small fiber neuropathy (SFN) is a neurological entity gaining increasing attention in recent years. In SFN, unmyelinated C and thinly myelinated Aδ fibers are affected \[1\]. A classical presentation of dysfunction of the somatosensory small fibers is painful feet, often reported by patients as “burning feet”.

The exact incidence and prevalence of SFN is unknown as no robust epidemiological studies exist to date \[2\]. Although some patients with SFN will eventually develop large fiber peripheral neuropathy (PN) \[3\], the general consensus of natural history studies is that in most patients SFN does not progress to affect large fibers \[4\].

Known causes SFN include diabetes mellitus (accounting for about a third of all SFN cases), vitamin B12 deficiency, amyloidosis, alcohol \[5\], toxin exposure, chemotherapy drugs \[6\] and inherited sensory and autonomic neuropathies \[7\]. Often, despite extensive testing, no cause is identified, leading to a diagnosis of idiopathic SFN. Follow-up of such patients is important, though, as a cause may be identified at a later review. For example, Devigili et al reported that more than 40% of patients have idiopathic SFN at diagnosis, but at 2-year follow-up a potential cause could be determined in 25% of them \[8\].

Coeliac disease (CD) describes a small bowel enteropathy in genetically susceptible individuals, triggered by ingestion of gluten \[9\]. Although the gastrointestinal manifestations of CD are the most well studied and popularly recognized, there are a range of debilitating neurological manifestations of CD which are increasingly established as the cause of significant disability. Such neurological conditions include cerebellar ataxia \[10\], headaches with white matter abnormalities on MR imaging \[11\], large fiber peripheral neuropathy (gluten neuropathy) \[12\] and epilepsy with occipital calcifications \[13\].
In this paper, we present a case series of patients with small fiber neuropathy related to CD and gluten sensitivity (GS) in an attempt to shed light into the possible links between the two entities.

METHODS

Procedure and Participants

This is a retrospective observational case series of patients with symptoms of small fiber neuropathy (painful burning symptoms, predominantly in the feet) that are regularly attending the Gluten Related Neurological Disorders clinic based at the Royal Hallamshire Hospital (Sheffield, UK). In this clinic we see patients with neurological manifestations that have CD or serological evidence of GS.

The South Yorkshire Research Ethics Committee has confirmed that no ethical approval is indicated given that all investigations were clinically indicated and did not form part of a research study.

Serological testing. Serological testing for GS and CD included antigliadin IgG and IgA antibodies (native), endomysium antibodies and transglutaminase 2 antibodies. Additional testing was performed, including extensive testing for other possible acquired causes of SFN or PN [1]. Patients with comorbidities that could cause SFN (i.e. diabetes, vitamin deficiencies) were excluded. Human leukocyte antigen (HLA) typing was performed by the regional blood-transfusion service.

Gluten sensitivity and coeliac disease diagnosis. All patients who had positive serological testing for GS were offered a gastroscopy and duodenal biopsies. Patients without enteropathy who were only positive for antigliadin antibodies were considered to have GS [14]. A diagnosis of CD was made when there was evidence of enteropathy (triad of villous atrophy, crypt hyperplasia, and increase in intraepithelial lymphocytes).
**Small fiber neuropathy diagnosis.** All patients underwent nerve conduction studies (NCS), which included median nerve (sensory and motor), ulnar nerve (sensory and motor), superficial radial nerve (sensory), tibial nerve (motor), peroneal nerve (motor), superficial peroneal nerve (sensory) and sural nerve (sensory). Patients with findings suggestive of large fiber peripheral neuropathy [15] or sensory ganglionopathy [16] were excluded.

All patients underwent quantitative sensory testing (QST), which was carried out using a Medoc TSA-II Neurosensory analyser, using the method of levels [17]. The test took place in a quiet room, with a temperature of 24°C. The site used for testing the lower limb was the dorsum of the foot and the site in the upper limb was the palm of the hand. Cold sensation and warm sensation threshold were determined. The patients were instructed clearly the nature of the test. A 3 cm x 3cm thermode was used. Manufacturer’s normal values, stratified for age, that are embedded in the software [18] were used to determine whether the test was normal or abnormal.

As per the proposed diagnostic criteria, patients with symptoms of small fiber neuropathy, normal conduction studies and abnormal QST findings were diagnosed with definite small fiber neuropathy [2, 19].

**Statistical analysis.** A database was developed using the statistical software package SPSS (version 25.0 for Macintosh). Descriptive statistics were examined for each variable.

**RESULTS**

**Clinical characteristics.** We identified 13 patients (69.2% males) with SFN and gluten sensitivity. Of the 11 patients who consented for a gastroscopy, 10 patients (90.9%) had evidence of enteropathy (9 had CD and 1 had increased intraepithelial
lymphocytes). Two patients refused gastroscopy and were considered to be GS. In total our population comprised of 9 patients with CD and 4 patients with GS.

Mean age at onset of pain was 53.5±11.4 years (range 34-72) and mean age of CD/GS diagnosis was 50.8±10.4 years (range 34-68).

**Pain as a first manifestation of CD.** In 8 patients (61.5%) pain was the first manifestation of CD/GS, whereas in the rest, CD was already diagnosed when patients presented with peripheral neuropathic pain. Of the 5 patients with CD who developed SFN, 3 were not on a strict gluten free diet. In 6 patients (46.2%) pain remained the only manifestation. Of interest is that only two patients (15.4%) had gastrointestinal symptoms as the first manifestation of CD.

**SFN and other neurological manifestations.** Six patients (46.2%) with SFN also had cerebellar ataxia, which is the commonest neurological manifestation of GS/CD whereas three patients with SFN (23.1%) also had dermatitis herpetiformis. One patient with SFN also had headaches and white matter abnormalities on MR brain imaging and one of the patients with SFN and ataxia also had cortical myoclonus. In six patients SFN was the only neurological manifestation.

**Neurophysiological assessment.** Five patients (38.5%) showed exclusively abnormalities in the warm sensation threshold, whereas seven patients (53.8%) showed abnormalities in both the warm and cold sensation threshold. Only in one patient the sole abnormality was in the cold sensation threshold. The majority of the patients (84.6%) showed a length dependent involvement of the small fibers, with the feet being more affected than the hands.

Two of the patients were newly diagnosed with SFN. Eleven patients, have interval NCS as are under regular follow-up in our clinic. Despite repeated NCS, these patients have not developed large fiber peripheral neuropathy for a mean of 6.9±5.3 years (range 1-17) since the manifestation of peripheral neuropathic pain.
**HLA type.** HLA typing was performed in all patients. Of them, 10 (76.9%) patients, all with enteropathy, had the DQ2 type and 3 patients (23.1%) had the DQ1 type.

Table 1 provides the clinical, neurophysiological and serological characteristics of all patients.

**DISCUSSION**

We presented a case series of patients with CD or serological evidence of GS and SFN. Our case series highlights that SFN can be the first and only manifestation of CD and GS.

To our knowledge, this is the largest case series where such an association is described. Previously, Brannagan et al. reported the characteristics of 7 patients with CD and small-fiber neuropathy, confirmed by a skin-biopsy, without any electrophysiological evidence of large fiber peripheral neuropathy [20]. Of those, 3 patients (42.9%) had decreased epidermal nerve fiber density at the proximal thigh or the distal forearm, which was more severe than at the distal leg, suggesting a non-length-dependent process. In our study, only a minority of patients had a non-length-dependent pattern (15.4%), which is more in keeping with the respective figures of non-length dependent pattern of involvement in CD patients with large-fiber neuropathy [21]. This pattern is similar to that described by Gorson et al [22] suggesting that the primary pathology might be in the dorsal root ganglia rather than the axons themselves. This probably suggests that the asymmetric small fiber neuropathy is a precursor of a sensory ganglionopathy, which eventually will affect the neurons of the large fibers too. However, in order to confirm this, a prolonged follow-up study of a cohort of patients with SFN and CD is needed.

Another novelty of our study is that we described the whole spectrum of neurological comorbidities in our patients with CD and SFN. In seven patients had SFN as their sole neurological manifestation of CD. The other six patients had a central nervous system involvement. It has already been demonstrated that cortical
excitability is affected in CD patients [23-25]. Whether there is a central involvement that plays a role in increased perception of pain is yet to be determined in future studies. We have also made the observation that the prevalence of enteropathy in this group is much higher to what we have previously observed in the context of gluten related large fiber neuropathies [21].

Some patients may be complaining of peripheral neuropathic pain for years before the diagnosis of CD or GS as often patients present with extraintestinal manifestations of CD or GS with minimal or no gastrointestinal symptoms. A striking paradigm of our case series is that one patient (case #10) had been complaining of painful symptoms for 17 years before being diagnosed with GS, when he was seen in our specialist clinic. Diagnosing CD or GS early has significant implications to clinical practice as it has been clearly demonstrated that patients with CD or GS suffering from painful gluten neuropathy do benefit from a strict gluten free diet [21], which eventually leads to better overall quality of life since pain is a major determinant of the latter [26]. Whether starting a gluten free diet also protects patients with small fiber neuropathy from developing large fiber neuropathy remains to be determined in prospective cohort studies.

Although CD is more prevalent in females with a male:female ratio of approximately 1:3 [27], in our case series the majority of patients with SFN and CD were males. Higher prevalence of other neurological manifestations of CD in males has also been demonstrated in gluten ataxia [10] and gluten neuropathy [21]. This might suggest that males are more prone to neurological manifestations, including SFN.

The majority of abnormalities seen involved the warm sensation threshold. Warm sensation is predominantly mediated by C fibers [26], which are thin unmyelinated fibers, and cold sensation is predominantly mediated by Aδ fibers [29], which are thin myelinated fibers. Only in one patient (case #5) the cold sensation threshold was abnormal with the warm sensation being normal. This suggests that C fibers are more prone to damage, however precise phenotyping of SFN with determination of
the degree of involvement of Aδ and C fibers is important in order to understand the pathophysiology of gluten related SFN.

Our findings should be interpreted with some caution given the limitations of our design. Firstly, this is a retrospective observational case series of patients regularly attending our specialist Gluten Related Neurological Disorders clinic and, therefore, we are unable to provide epidemiological data about the exact prevalence of SFN in patients with CD. Moreover, the diagnosis of SFN was based on the clinical symptoms and the abnormal QST. The tests that have the highest sensitivity for the diagnosis of SFN are considered to be skin biopsy [30] and microneurography [2], which were not routinely performed in our department until very recently. Finally, we did not make direct comparisons between the CD and GS groups because of the small number of patients in latter. From the gastroenterology point of view CD and GS are considered to be different conditions [31], however from the neurological perspective this has not been the case in other neurological manifestations. Future research should shed light to any potential differences between SFN in CD and SFN in GS.

CONCLUSION

In conclusion, SFN can be the first and only manifestation of CD and GS. Similar to other neurological manifestations of CD and GS, such as ataxia and large fiber peripheral neuropathy, where increased prevalence of TG6 antibodies occurs [32, 33], future studies should investigate whether TG6 antibodies are also a biomarker in SFN related to CD and GS.
Ethical Approval and Consent to participate
The South Yorkshire Research Ethics Committee has confirmed that no ethical approval is indicated given that all investigations were clinically indicated and did not form part of a research study.

Availability of supporting data
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References


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**Table 1.** Demographic, clinical and neurophysiological characteristics of our case series. CD, coeliac disease; GS, gluten sensitivity; SFN, small fiber neuropathy; NCS, nerve conduction studies; QST, quantitative sensory testing; DH, dermatitis herpetiformis; GRD, gluten-related disorder; GFD, gluten-free diet; HLA, human leukocyte antigen; M, male; F, female