ORIGINAL COMMUNICATION

Gluten neuropathy: electrophysiological progression and HLA associations

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Abstract

Objective Gluten neuropathy (GN) is the term used to describe peripheral neuropathy that occurs in patients with gluten sensitivity (GS) or coeliac disease (CD) in the absence of other risk factors. We aimed to describe the neurophysiological progression rate of GN across time and look into the potential role of genetic susceptibility in its development.

Methods This is a cohort study of 45 patients with GN with a mean follow-up period of 8 ± 5 years. The assessments included clinical and neurophysiological data and HLA-DQ genotyping.

Results The mean age at diagnosis was 60 ± 12 years. The majority of patients had a length-dependent neuropathy (75.6%), whereas the rest were diagnosed with sensory ganglionopathy (SG).

DQA1*02-positive patients were more likely to suffer with SG compared to the DQA1*02 negative patients (60% versus 13.8%, $p = 0.009$). There was also a trend for statistical significance regarding the DQB1*06 allele and the DQA1*01/DQB1*06 haplotype were found more frequently in patients with GN than in healthy controls ($p = 0.026$ and $p = 0.047$, respectively). A linear effect of time on the neurophysiological findings was found in radial sensory nerve action potential (1.9% mean annual decrement, $p = 0.036$), sural sensory nerve action potential (3.3% mean annual decrement, $p = 0.013$) and tibial nerve motor compound action potential (6.5% mean annual decrement, $p < 0.001$) amplitudes, independently from age or gender.

Conclusions GN is a late manifestation of GS and CD. The majority of patients have the length-dependent neuropathy with a linear deterioration over time. HLA genotyping of GS and CD patients who suffer from neuropathic symptoms is recommended as it can help identifying patients at risk for developing SG.

Keywords Peripheral neuropathy · Gluten sensitivity · Coeliac disease · Progression · HLA genotyping

Introduction

Coeliac disease (CD) is an autoimmune disorder triggered by the ingestion of gluten in genetically susceptible individuals. The association of CD and the development of peripheral neuropathy (PN) has been first described more than a century ago [1]; whereas, more recently, the development of PN has been also associated with serological evidence of gluten sensitivity (GS) without enteropathy [2]. The term gluten neuropathy (GN) is used to describe patients with GS or CD with peripheral neuropathy when other causes of neuropathy have been excluded.

GN is the second commonest neurological manifestation of CD and GS after gluten ataxia (GA) [2, 3]. GN can lead to poor quality of life, mainly because of the pain and the disability that it causes [4]. As it happens with other forms of PN, it is difficult to predict the progression rate and advise patients on the prognosis of the disease accordingly.

Moreover, it remains unclear as to why some patients with CD or GS present only with gastrointestinal symptoms such as bloating, abdominal pain, diarrhea, weight loss,

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when others primarily or exclusively suffer from neurological manifestations [5].

The aim of this study was twofold: to describe the neurophysiological progression rate of GN across time and look into the potential role of genetic susceptibility in its development.

Methods

Type and length of study

This is a cohort study conducted at the Sheffield Institute of Gluten Related Diseases (SIGReD). Since their diagnosis, all patients were under regular follow-up assessments every 6 to 12 months, by the same clinicians.

The study protocol has been approved by the local ethics committee (STH19011).

Inclusion and exclusion criteria

To be enrolled, the patients had to meet the following inclusion criteria: (1) diagnosis of PN, as confirmed on nerve conduction studies as described below; (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 (GFD); (3) absence of other risk factors for developing PN (i.e., diabetes, vitamin deficiencies, exposure to neurotoxic agents); (4) age equal to or greater than 18 years, (5) able to provide a written informed consent.

Demographic characteristics and clinical assessment

Demographic characteristics included age and gender. All patients went through extensive investigations for possible causes of PN [6]. We considered that patients were on a strict GFD if serological testing showed normalization of the level of circulating antigliadin IgG and/or IgA, endomysial and/or transgultaminase antibodies.

Neurophysiological evaluation

As part of the standardized operating procedures followed in our department, for all nerve conduction studies (NCS), the temperature was above 32 ◦C for the upper extremity and above 31C° for the lower extremity, measured before and after each study on the dorsum of the hand and foot. Frequency filters were 2 Hz (low) and 2 kHz (high) for the

sensory studies, and 3 Hz (low) and 10 kHz (high) for the motor studies. The following recorded NCS were used, as we have already shown that they are the best determinants of the severity of neuropathy [7]:

1. Superficial radial sensory nerve action potential (SNAP): the active recording electrode was placed over the anatomical "snuff box" formed by the extensor pollicis brevis and abductor pollicis longus tendons laterally and the extensor pollicis longus tendon medially. The reference recording electrode was placed 3 cm distal to the active electrode. Stimulation was 10 cm proximal to the active recording electrode, over the dorsolateral edge of the radius bone.
2. Sural SNAP: the active recording electrode was placed between the lateral malleolus and the Achilles tendon. The reference recording electrode was placed 3 cm distal to the active electrode. Stimulation was 10 cm proximal to the active recording electrode, over the distal posterolateral leg.
3. Tibial CMAP: the active electrode was placed over the belly of the abductor hallucis (AH) muscle, one fingerbreadth from the navicular bone of the foot towards the plantar surface and one fingerbreadth towards the great toe. The reference electrode was placed in the medial aspect of the big toe. Stimulation was posterior to the medial malleolus.

SNAP amplitudes were measured as peak-to-peak, whereas CMAP amplitudes were measured as onset-to-peak. In our department we use the following published normal values: sural SNAP (≥ 14 µV for ages ≤ 39 years, ≥ 6.9 µV for ages 40–59, ≥ 3.2 µV for ages ≥ 60); radial SNAP (≥ 25.5 µV for ages ≤ 39 years, ≥ 17.4 µV for ages 40–59, ≥ 12.1 µV for ages ≥ 60); tibial CMAP (> 3.5 mV) [8, 9].

To be diagnosed with a length-dependent PN, patients had to exhibit symptoms and signs of peripheral neuropathy in a length-dependent manner (reduced or absent tendon reflexes, reduced vibration sensation, etc.) as well as to have bilaterally reduced sural SNAPs.

To be diagnosed with a sensory ganglionopathy, patients needed to fulfill the published criteria [10], which in summary include presence of a degree of sensory ataxia, asymmetrical sensory symptoms, no motor involvement and asymmetrical SNAP recordings between the left and the right side [11].

All patients had at least two neurophysiology assessments; one of which took place during their enrollment to the study and one at least 1 year later. As the majority of patients were under regular follow-up for many years before their enrollment to the study, we also collected and

utilized any previous neurophysiological data obtained at the same department.

Endoscopy

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).

HLA genotyping

The HLA-DQ typing was performed using the polymerase chain reaction utilizing sequence-specific primers.

Statistical analyses

A database was developed using the Statistical Package for Social Science version 21.0 (Armonk, NY: IBM Corp). Frequencies and descriptive statistics were examined for each variable.

Comparisons between groups were made using Fisher's exact test for categorical and Mann–Whitney U test for continuous variables. The level of significance for these comparisons was set at 0.05.

The Hardy–Weinberg proportions (HWP) for HLA-DQ were ascertained by using PyPoP software [12]. HLA-DQ allele and haplotype frequencies in patients were compared with that reported for 177 healthy subjects in the general English population [13] by using Chi-square test; Yates correction or Fisher's exact tests were applied when appropriate. Odds ratios and 95% confidence intervals were reported. For the above analysis a p value correction took place according to the Benjamini–Yekutieli method (or B–Y) based on the following formula: p (B–Y) $= a/(\Sigma 1/i)$, where i denotes the number of comparisons and $a = 0.05$ [14, 15].

Longitudinal changes in NCS studies for tibial CMAP, radial SNAP and sural SNAP were analyzed by using linear mixed-effects models. Random intercepts were used to account for the role of each participant in the model. Also, the fixed effect of time was explored for linear, quadric and cubic trends, along with age and/or gender. The fitting of all possible models was assessed after using first-order autoregressive structure with heterogenous variance by comparing the Akaike's information criterion values. The final formula was constructed according to the best fitted model. In the final models, the role of neuropathy type and HLA groups (i.e., by allele and haplotype positivity) was explored by introducing an HLA group and HLA group×time effect.

Data availability statement

All datasets that were obtained and were analyzed during the current study are available from the corresponding author on reasonable request.

Results

Our study population consisted of 45 consecutive GN patients (73.3% males). The mean age of symptom onset was 56 ± 12 years (ranging from 34 to 80 years). The mean age at diagnosis was 60 ± 12 years (ranging from 37 to 86 years). The mean age at last clinical follow-up was 69 ± 10 years (ranging from 44 to 88 years).

The most common first manifestation of GN was numbness (36%) followed by tingling sensation (18%). Pain was the first manifestation in 13% of the patients. Only 9% of the patients had motor symptoms (weakness and/or fasciculation) at their disease onset.

At the last follow-up the mean ONLS scores where 1.2 ± 0.8 for the arms, 1.7 ± 1.2 for the legs and 2.9 ± 1.7 for the total, which indicates that the severity of GN is mild. The majority of our patients (78%) could walk independently, whereas 7 patients (16%) needed unilateral support (ONLS leg score of 3) and 3 patients (9%) needed bilateral support (ONLS leg score of 4 or 5). None of our patients was restricted to wheel chair or bed (ONLS leg score of 6 or 7).

The majority of patients had a length-dependent neuropathy (75.6%), whereas the rest were diagnosed with sensory ganglionopathy. Thirty-six patients underwent duodenal biopsy. Of them 6 (16.7%) had coeliac disease.

The clinical data of our cohort are provided as a Supplementary Table.

HLA-DQ frequencies and associations

HLA-DQ genotyping was available for DQA1 in 39 patients and for DQB1 in 43 patients.

Five distinct DQA1 and DQB1 alleles were identified (78 total alleles). There were 14/39 (35.9%) homozygotes for DQA1 and 15/43 (34.9%) homozygotes patients for DQB1. No deviations from the HWP [$F(1) = 0.36$, $p = 0.549$ for DQA1 and $F(1) = 0.22$, $p = 0.639$ for DQB1] were recorded. The most common DQA1 allele was DQA1*01 (38.5%) and DQB1*03 (32.6%) for DQB1, while the most frequent haplotype was DQA1*01/DQB1*06 with a frequency of 29.5%, followed by DQ2 (19.2%), DQA1*03/DQB1*03 (19.2%) and DQ8 (11.5%) among patients. As shown in Table 1, there was a trend for statistical significance regarding the DQB1*06 allele and the DQA1*01/DQB1*06 haplotype, as they were found more frequently in patients than in healthy controls ($p = 0.026$ and $p = 0.047$, respectively).

Table 1 HLA-DQ allele and haplotypic frequencies among GN patients ($N = 78$ alleles) and the general English population ($N = 354$ alleles)

	GN patients, N (%)	General population, %	OR (95% CI)	Sig.[1]
DQA1				
*01	30 (38.5)	33.4	1.25 (0.75–2.08)	0.464
*02	11 (14.1)	12.8	1.13 (0.55–2.29)	0.885
*03	15 (19.2)	22.4	0.82 (0.44–1.51)	0.618
*04	1 (1.3)	1.7	0.75 (0.09–6.35)	1.000
*05	21 (26.9)	18.1	1.67 (0.95–2.95)	0.105
DQB1				
*02	25 (29.1)	23.2	1.36 (0.80–2.30)	0.315
*03	28 (32.6)	30.1	1.11 (0.67–1.85)	0.772
*04	0 (0)	1.7	-	0.602
*05	7 (8.1)	14.8	0.52 (0.23–1.18)	0.155
*06	26 (30.2)	18.6	1.89 (1.11–3.22)	**0.026***
DQA1/DQB1				
01/06	29.5%	18.6	1.83 (1.05–3.18)	**0.047***
05/02 (DQ2)	19.2%	12.7	1.64 (0.86–3.11)	0.185
03/03:02 (DQ8)	11.5%	15.3	0.73 (0.34–1.54)	0.506
03/03	19.2%	22.4	0.82 (0.44–1.51)	0.618
02/02	10.3%	10.5	0.98 (0.44–2.19)	1.000
05/03	7.7%	5.4	1.47 (0.57–3.81)	0.424
01/05	7.7%	14.8	0.48 (0.20–1.17)	0.145
02/03	3.9%	2.3	1.73 (0.45–6.68)	0.426
01/02	1.3%	0	–	0.181
04/02	1.3%	0	–	0.181

*$p \leq 0.05$, not reaching $pc \leq 0.022$ (5 comparisons for DQB1) and $pc \leq 0.018$ (9 comparisons for DQA1–DQB1 haplotypes) according to the Benjamini–Yekutieli method

[1] Chi-square tests (Yates correction or Fisher's exact tests)

DQA1*02-positive patients were more likely to suffer from a sensory ganglionopathy compared to the DQA1*02 negative patients (60% versus 13.8%, $p = 0.009$). No other significant HLA-DQ-related association with the patients' clinical characteristics was found.

Nerve conduction studies

Linear mixed models were applied in all 34 GN patients with length-dependent neuropathy to ascertain the trajectory of NCS-derived nerve amplitudes across time. The mean follow-up time was 8 ± 5 years since diagnosis (ranging from 1 to 21 years). On average each patient was electrophysiologically evaluated 3.4 ± 1.2 times (median 3, range 2–6).

Among GN patients with length-dependent neuropathy 41.2% had normal radial SNAP based on their last NCV examination. The time of follow-up since diagnosis was not different between patients with normal and abnormal radial SNAPS ($p = 0.862$). In the patients with abnormal radial SNAP, a significant mean decrement of radial SNAP amplitude of 1.9% per year, independently from age or gender, was found ($p = 0.036$).

Among GN patients with length-dependent neuropathy 20.6% had normal CMAP tibial based on their last NCV examination. The time of follow-up since diagnosis was not different between patients with normal and abnormal tibial CMAP ($p = 0.824$). In the patients with abnormal tibial NCS, a significant mean decrement of tibial CMAP amplitude of 6.5% per year, independently from age or gender, was found ($p < 0.001$).

Finally, all GN patients with length-dependent neuropathy had abnormal sural SNAP. The amplitude of sural SNAP was found to significantly decrease with time by a

Table 2 Significant predictors of nerve conduction study parameters across time in patients with length dependent gluten neuropathy

	Formula
Radial SNAP amplitude (in µV)	11.1 – (0.21 × years since diagnosis)
Tibial CMAP amplitude (in mV)	2 – (0.13 × years since diagnosis)
Sural SNAP amplitude (in µV)	3 – (0.1 × years since diagnosis)

mean of 3.3% each year, independently from age or gender ($p = 0.013$).

No significant associations between demographic characteristics, being on a gluten-free diet or the HLA-DQ type and the progression rates were found.

Table 2 presents the formulas that can be used to predict the radial SNAP, the sural SNAP and the tibial CMAP across time. Figures 1, 2 and 3 depict the linear effect of time since diagnosis on nerve conduction parameters in patients with gluten neuropathy.

Discussion

In our study, we recruited a large consecutive cohort of patients with GN. In this cohort, we showed that three out of four patients with gluten neuropathy have the so-called length-dependent PN, whereas in the remaining sensory ganglionopathy was detected. Only one in six patients with GN suffer from CD, which is in contrast to other neurological manifestations of GS. For example, the percentage of patients with gluten ataxia (cerebellar ataxia with positive antigliadin antibodies) that have CD is 40% [16]. This is even higher in patients with gluten ataxia and cortical myoclonus, as all of them have CD (100%) [17]. The mean age at diagnosis of PN in our population was 60 years. This is significantly older than the mean age at diagnosis of CD in patients who present with gastrointestinal symptoms (42 years) and the mean age at diagnosis of CD/GS for patients who present with GA, which is 53 years [16]. This
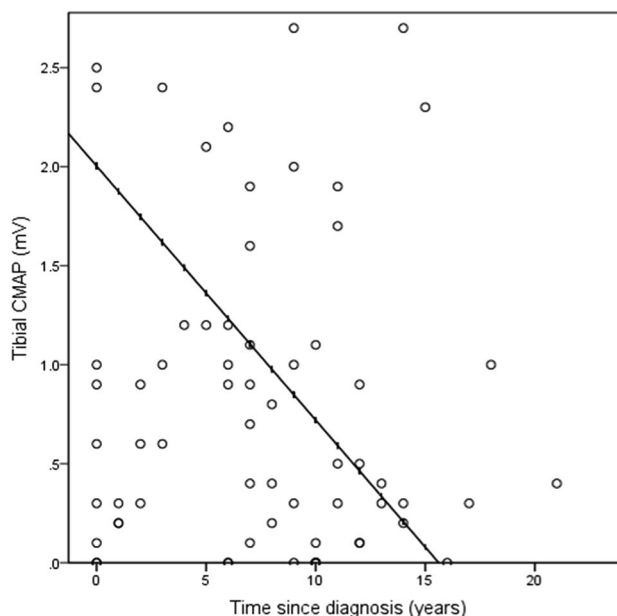

Fig. 2 Line graphs showing the linear effect of time since diagnosis on tibial compound muscle action potential (CMAP)

suggests that GN is a late manifestation of gluten sensitivity. The reason for this remains unclear. We can speculate that for the neuropathy to develop there is a need for more years of exposure to gluten in patients who have GS or CD, something that has also been observed in other extraintestinal manifestations such as dermatitis herpetiformis. Along the same lines we are not aware of any reports of GN in children,
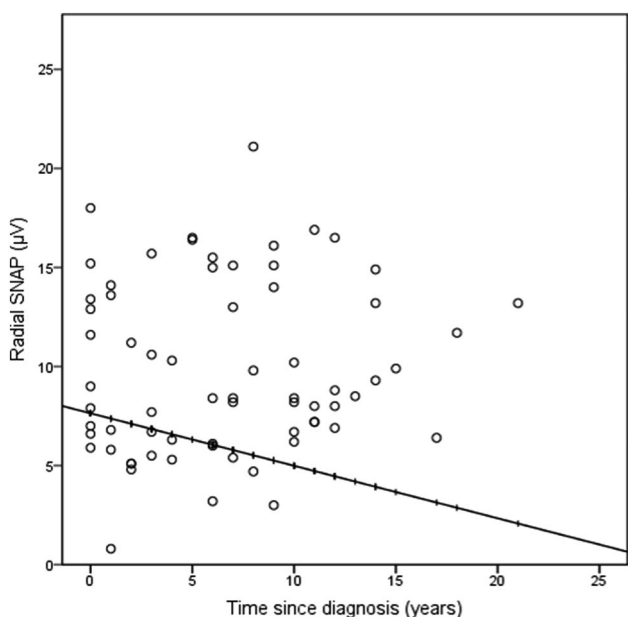

Fig. 1 Line graphs showing the linear effect of time since diagnosis on radial sensory nerve action potential (SNAP)
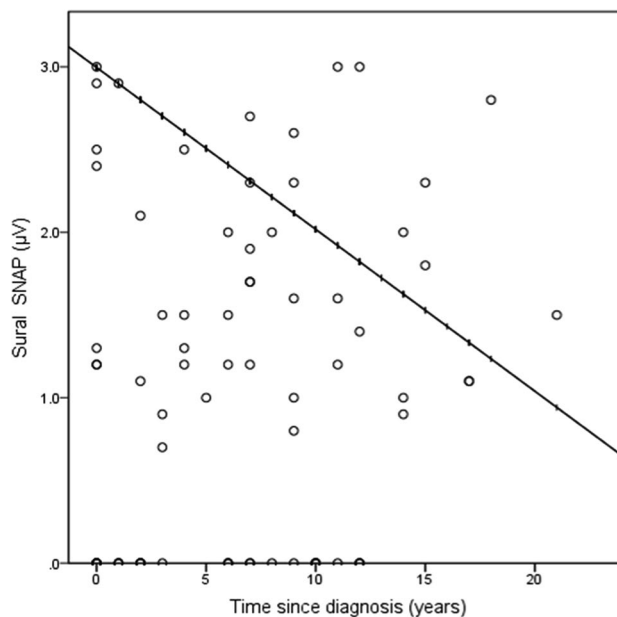

Fig. 3 Line graphs showing the linear effect of time since diagnosis on sural sensory nerve action potential (SNAP)

whereas there are reports for other neurological manifestations such as GA in children [18].

Another novel aspect of this study is the description of the neurophysiological progression rate of GN across time. The fixed effect of time was explored for linear, quadric and cubic trends, and we found that there is a linear effect of time on the neurophysiological findings, in all the electrophysiological determinants of the clinical severity of PN [7], independently from age and gender. We have quantified this in percentages, which could prove useful in the monitoring of such patients. Using the expected and comparing them with the actual neurophysiological parameters, clinicians can identify patients with higher progression rates and alter their management accordingly.

Our study, did not demonstrate any influence of the GFD on the progression of the disease. This finding, however, should be interpreted with caution as our study was not designed to evaluate the role of GFD, and patients were at variable stages of treatment with the GFD at the time of recruitment. Furthermore, one of the most important aspects of treatment in GN is the strictness of the GFD. Presence of antigliadin antibodies despite being on the diet for several years implies suboptimal adherence to the diet, which perpetuates the peripheral nerve damage. Our recommendation for patients with GN remains, that they should embark on a strict GFD as previous research specifically looking at the effect of GFD has shown that GFD is associated with improvement of the neuropathy [19] and a significant reduction of the odds of peripheral neuropathic pain [20]. Neuropathology findings suggest that in GN, there is inflammation affecting the peripheral nerves [21], and hence by removing gluten from the diet, there is reduction of the peripheral nerve inflammation and the subsequent symptoms resulting from peripheral nerve damage. Regular monitoring using antigliadin antibodies and regular dietetic input is very important in the treatment of these patients.

Our study also provides novel data on the role of genetic susceptibility in the pathogenesis of GN. There was a trend for statistical significance regarding the DQB1*06 allele and the DQA1*01/DQB1*06 haplotype, as they were found more frequently in patients than in healthy controls. DQA1*02-positive patients were more likely to develop sensory ganglionopathy, which is probably the most disabling form of neuropathy. Whether this is the main predisposing factor or one of the many remains to be studied in the future. For example, immune-mediated mechanisms seem also to play a role as there is some evidence that presence of transglutaminase 6 antibodies is linked to a length-dependent neuropathy rather than a sensory ganglionopathy [22].

The DQ2 (DQA1*05/ DQB1*02) and the DQ8 (DQA1*03/ DQB1*03:02) haplotypes are known to be more frequent in patients with CD [23]. However, in our study neither DQ2 nor DQ8 were found to be more frequent in GN patients compared to controls. A possible explanation for this is that only a small percentage of patients had CD, whereas the majority had GS. Indeed, in our cohort 5 out of 6 (83.3%) GN patients with CD had the DQ2 ($n = 3$) or the DQ8 ($n = 2$) haplotype. However, our study population is small to allow meaningful comparisons between GN patients with and without enteropathy.

In conclusion, GN is a late manifestation of GS and CD. The majority of patients have the length-dependent type, which shows a linear progression over time. HLA genotyping of GS and CD patients who suffer from neuropathic symptoms is recommended as it can help identifying patients at risk for developing sensory ganglionopathy.

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Ethical standards The study protocol has been approved by the local ethics committee.

Disclosures Panagiotis Zis, Ptolemaios Georgios Sarrigiannis, Artemios Artemiadis, David Sanders and Marios Hadjivassiliou have nothing to disclose.

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