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Title: Quality of life in patients with gluten neuropathy; case-controlled study

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Abstract (238 words)

Background: Gluten neuropathy (GN) is defined as an otherwise idiopathic peripheral neuropathy in the presence of serological evidence of gluten sensitivity (positive antigliadin and/or transglutaminase or endomysium antibodies). We aimed to compare the quality of life (QoL) of GN patients with control subjects and to investigate the effect of a gluten free diet (GFD) on the QoL.

Methods: All consecutive patients with GN attending a specialist neuropathy clinic were invited to participate. Overall Neuropathy Limitations Scale (ONLS) was used to assess the severity of neuropathy. The SF-36 questionnaire was used to measure participants' QoL. A strict GFD was defined as effectively been able to eliminate all circulating gluten sensitivity-related antibodies whilst on the diet.

Results: Fifty-three patients with GN and 53 age and gender matched controls were recruited. Compared to controls, GN showed significantly worse scores in physical functioning, role limitations due to physical health, energy/fatigue and general health subdomains of SF-36.

After having adjusted for age, gender and disease severity, being on a strict GFD correlated with better SF-36 scores on the pain domain of the SF-36 (beta 0.317, p=0.019) and the overall health change domain of the SF-36 (beta 0.306, p=0.017).

Conclusion: In GN physical dysfunctioning is the major determinant of poor QoL compared to controls. Routine checking for elimination of gluten sensitivity-related antibodies that results from a strict GFD should be encouraged as such elimination ameliorates the overall pain and health scores, indicating better QoL.

1. Introduction

Gluten neuropathy (GN) is one of commonest neurological manifestations of gluten sensitivity [1] and it is defined as an otherwise idiopathic peripheral neuropathy [2] in the presence of serological evidence of gluten sensitivity (positive antigliadin, and/or transglutaminase or endomysium antibodies) [1, 3]. Some patients with GN have evidence of enteropathy on duodenal biopsy and are diagnosed with coeliac disease, whereas the majority of patients with GN do not have enteropathy.

The main type of gluten neuropathy is symmetrical sensorimotor axonal peripheral neuropathy [1], however sensory ganglionopathy (SG) and rarely mononeuritis multiplex (MMX) may also occur [1, 4, 5]. Gluten-free diet (GFD) has been shown to be effective in treating GN [6].

As in all chronic diseases, patients with GN are expected to have impaired quality of life (QoL) for reasons that are either directly or indirectly related to the disease. It has been shown that patients with advanced peripheral neuropathy, for example, show worse scores in questionnaires measuring QoL when compared to less impaired patients [7]. Such impairment, not only refers to motor symptoms (i.e. weakness) but also sensory and in particular pain [8 – 13]. Indirectly, however, GN might cause an additional burden of having to adhere to a strict GFD. It has been shown that the degree of difficulty in adhering to a GFD is associated with reductions in patient wellbeing and psychological distress that the dietician is critically placed to address [14].

The purpose of this study was twofold. We wanted to compare the QoL of GN patients with controls (subjects without peripheral neuropathy or gluten sensitivity) but also to investigate the effect of being on a GFD on the QoL in these patients.

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2. Methods

2.1. 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). Individuals without a diagnosis of peripheral neuropathy participated in the study as controls.

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 for antigliadin IgG and/or IgA with or without positivity for endomysial and transgultaminase antibodies) at diagnosis prior to commencing gluten-free diet, (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.

The study protocol was approved by the local ethics committee.

2.2. 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 [15, 16], 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).

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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 [17].

Biagi score was used to document adherence to a gluten-free diet [18]. Patients with a Biagi score of equal to or above 3 were considered as being on a gluten-free diet. Furthermore, patients with negative serology at the time of recruitment were considered to be on a strict gluten free diet.

The 36-Item Short Form Survey (SF-36), a self-reported measure of health status and quality of life [19], was used to determine patient health-related quality of life. SF-36 covers nine health and QoL domains. These domains include physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health and health change. Each item is measured using a Likert-type scale. Scores were converted and analysed according to the marking guidelines for the SF-36, such that higher scores (out of a total of 100 for each domain) constitute better health-related quality of life in this domain.

2.3. 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 on a gluten free diet and patients not on a gluten free diet 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 Fischer's exact test for categorical data.

Where differences with a p value of lower than 0.10 were found, these variables were entered into linear regression models, with the QoL domain score 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.

3. Results

3.1. Study population

Fifty-three patients with GN were recruited (73.6% male, mean age 68.2±9.3 years) and were age and gender matched with 53 control subjects without a history of peripheral neuropathy or gluten sensitivity. Thirty-six patients (67.9%) had a symmetrical length-dependent sensorimotor axonal PN, sixteen (30.2%) had a sensory ganglionopathy and one patient had mononeuritis multiplex (1.9%). Mean disease duration was 12.6±9.5 years (ranging from 0 to 37 years). Overall ONLS scores ranged from 1 to 7 (mean 3.1±1.8).

Not all of the patients agreed to a duodenal biopsy. Of 32 patients who underwent duodenal biopsy 9 (28.1%) had enteropathy (8 coeliac disease, 1 increased intraepithelial lymphocytes).

3.2. QoL compared to controls

Table 1 summarizes the scores in all SF-36 subdomains in patients with GN and controls. Patients with GN showed significantly worse scores compared to controls in the following quality of life modalities; physical functioning ($p<0.001$), role limitations due to physical health ($p<0.001$), energy/fatigue ($p=0.045$) and general health ($p=0.029$). A trend for statistical significance ($p=0.094$) was observed in the pain modality of the SF-36 questionnaire.

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	GN (n=53)	Controls (n=53)	P value
Demographics			
Age, in years (SD)	68.2 (9.3)	66.8 (10.0)	0.440
Male gender (%)	39 (73.6)	38 (71.7)	0.828
Quality of life modalities			
Physical functioning	50.8 (32.8)	78.0 (23.0)	**<0.001**
Role limitations due to physical health	53.9 (34.0)	77.4 (25.8)	**<0.001**
Role limitations due to emotional problems	76.7 (29.4)	83.3 (25.5)	0.219
Energy/Fatigue	48.0 (21.8)	56.3 (20.1)	**0.045**
Emotional well-being	75.5 (15.9)	74.2 (16.7)	0.677
Social functioning	70.2 (30.5)	79.2 (25.9)	0.104
Pain	59.4 (27.9)	68.5 (27.3)	0.094
General Health	54.8 (23.6)	64.3 (20.1)	**0.029**
Health change	42.9 (19.8)	49.1 (18.3)	0.101

Table 1. Demopgraphics and quality of life parameters of patients with gluten neuropathy and controls.

3.3. The role of GFD (self-reported) on QoL

Based on the self-reported adherence to GFD (Biagi score equal to or greater than 3), 31 patients (58.5%) were on a GFD. Table 2 summarizes the demographic, clinical and quality-of-life related characteristics of patients with GN reporting being on GFD versus patients with GN reporting being on a gluten containing diet. The two groups did not differ significantly in age, gender, disease duration, neuropathy severity or neuropathy type. A trend of statistically significance (p=0.094) was observed on the overall health change subdomain of the SF-36.

After adjusting for age, gender and disease severity, being on GFD (self-reported) is positively correlated with better SF-36 scores on the overall health change domain of the SF-36 (beta 0.258, p=0.047).

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	Gluten free diet (n=31)	**Gluten containing diet (n=22)**	**P value**
Demographics			
Age, in years (SD)	68.6 (8.3)	67.6 (10.8)	0.702
Male gender (%)	20 (64.5)	19 (86.4)	0.115
Clinical characteristics			
Disease duration, in years (SD)	13.8 (8.0)	11.0 (10.2)	0.259
Type of neuropathy			0.690
Symmetrical length dependent PN (%)	21 (67.8)	15 (68.2)	
Sensory ganglionopathy (%)	9 (29.0)	7 (31.8)	
Mononeuritis multiplex (%)	1 (3.2)	0 (0.0)	
Neuropathy severity			
Total ONLS score (SD)	3.1 (1.7)	3.2 (1.8)	0.814
Quality of life modalities			
Physical functioning	53.5 (34.3)	47.0 (31.0)	0.482
Role limitations due to physical health	56.0 (32.6)	50.9 (36.5)	0.589
Role limitations due to emotional problems	79.6 (25.2)	72.7 (34.7)	0.409
Energy/Fatigue	49.2 (23.5)	46.3 (19.5)	0.640
Emotional well-being	76.5 (16.1)	74.1 (15.9)	0.599
Social functioning	70.4 (27.4)	69.9 (35.1)	0.951
Pain	63.6 (28.0)	53.5 (27.3)	0.197
General Health	56.5 (22.9)	52.7 (24.9)	0.576
Health change	46.8 (19.1)	37.5 (20.0)	0.094

Table 2. Demographic, clinical and quality-of-life related characteristics of patients with gluten neuropathy reporting being on a gluten free diet versus patients with gluten neuropathy reporting being on a gluten containing diet.

3.4. The role of strict GFD on QoL

Twenty-two patients have managed to eliminate the antigliadin, endomysial and transglutaminase antibodies after being on GFD. This population, which accounted for 41.5% of the total GN study group and 71% of those GN patients self-reporting as being on a GFD, was considered to be on a strict GFD.

Table 3 summarizes the demographic, clinical and quality-of-life related characteristics of patients with GN being on a strict GFD versus patients with GN not being on a strict GFD. The two groups did not differ significantly in age, gender, disease duration, neuropathy severity or neuropathy type. Patients on a strict GFD had significantly higher scores (indicating better QoL) on the pain sub-domain of the SF-36 (p=0.03). A trend of statistically significance (p=0.066) was also observed on the overall health change subdomain of the SF-36.

After having adjusted for age, gender and disease severity, being on a strict GFD (serologically proven) is positive correlated with better SF-36 scores on the pain domain of the SF-36 (beta 0.317, p=0.019) and the overall health change domain of the SF-36 (beta 0.306, p=0.017).

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	On strict GFD (n=22)	**Not on strict GFD (n=31)**	**P value**
Demographics			
Age, in years (SD)	69.7 (8.5)	67.2 (9.9)	0.329
Male gender (%)	14 (63.6)	25 (80.6)	0.166
Clinical characteristics			
Disease duration, in years (SD)	13.9 (8.1)	11.7 (9.6)	0.385
Type of neuropathy			0.462
Symmetrical length dependent PN (%)	14 (63.6)	22 (71.0)	
Sensory ganglionopathy (%)	7 (31.8)	9 (29.0)	
Mononeuritis multiplex (%)	1 (4.5)	0 (0.0)	
Neuropathy severity			
Total ONLS score (SD)	3.2 (1.8)	3.0 (1.7)	0.695
Quality of life modalities			
Physical functioning	58.4 (35.7)	45.5 (30.0)	0.160
Role limitations due to physical health	58.5 (33.9)	50.6 (34.2)	0.409
Role limitations due to emotional problems	81.8 (23.7)	73.1 (32.8)	0.293
Energy/Fatigue	50.0 (26.1)	46.6 (18.5)	0.578
Emotional well-being	76.8 (18.2)	74.5 (14.2)	0.608
Social functioning	69.6 (28.4)	70.6 (32.4)	0.916
Pain	69.2 (26.6)	52.5 (27.1)	**0.030**
General Health	56.4 (23.9)	53.9 (23.7)	0.708
Health change	48.9 (21.1)	38.7 (18.1)	0.066

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Table 3. Demographic, clinical and quality-of-life related characteristics of patients with gluten neuropathy being on a strict gluten free diet versus not being on a strict gluten free diet (serologically confirmed, by having eliminated the anti-gliadin antibodies).

4. Discussion

This case-controlled study demonstrates that patients with GN have significantly worse QoL compared to age and gender matched controls in the SF-36 modalities of physical functioning, role limitations due to physical health, energy/fatigue and general health. This finding adds to the existing literature that the main impact of peripheral neuropathy on patients' QoL is on the modalities affecting their dys-functioning (i.e. impaired activities of daily living) [7]. To our knowledge, this is the first study to investigate the QoL of patients with GN.

Another novelty of the current study is examining the role of GFD on QoL. For this we conducted two separate analyses; based on what the patients report and based on the evidence of elimination of all gluten sensitivity-related antibodies.

In their study, Lee et al found that patients with coeliac disease report that GFD has a negative impact on their quality of life, as it restricts their social activities such as travelling or dining out [20]. In our study, patients on a GFD had higher scores in seven out of eight domains of SF-36 (Table 2), with the scores of the overall health change subdomain of the SF-36 being significantly different compared to patients not being on a GFD. There are possible explanations for such disparity. Firstly, awareness of gluten sensitivity and coeliac disease has increased over the last decade with improved availability and better range of gluten free products. Furthermore, dining out or travelling is much easier as many restaurants and hotels do have gluten free menus. Secondly, the heterogeneity of the study populations as Lee et al included patients with different gender distribution (female predominance), different age (younger) and a different clinical picture (coeliac disease with gastrointestinal symptoms) versus our cohort of patients presenting with a neuropathy.

When comparing patients who are truly strict with GFD (i.e. elimination of all circulating gluten sensitivity-related antibodies) with patients either not being on a GFD or not being strict with GFD we showed that the former have significantly better scores in the pain and the overall health change domain. This is in keeping with the current literature, which shows that patients with GN benefit from a GFD with evidence of improvement of the neuropathy [6, 20]. Moreover, this finding highlights the importance of serological monitoring in an attempt to improve adherence to GFD. Interestingly, from our cohort, 29% of patients on GFD still had positive serology.

Our results should be interpreted with some caution, given the limitations of our design. This is a cross-sectional study based on patients attending a specialized clinic, and the results may not be generalizable to other settings. Furthermore, our cohort included patients with large fiber axonal peripheral neuropathies only. Pure small fiber neuropathy associated with gluten sensitivity, is another area that merits further consideration, as it is a particularly painful condition and therefore can affect patients' QoL.

In conclusion, in patients with GN physical dysfunctioning is the major determinant of QoL compared to control subjects. Contrary to previous observations in patients with classical CD, for patients with GN, being on a GFD does not have a negative effect on social functioning. Clinicians are advised to regularly monitor the strictness of the GFD diet by serological testing for gluten sensitivity-related antibodies because strict GFD ameliorates the overall pain and health change scores, indicating better QoL.

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Conflict of interest

None

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