

## Celiac Disease in Patients with Neuropathy

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### ABSTRACT

#### Background:

Neuropathy means nerve damage, which interferes with the functioning of the peripheral nervous system. It has been mentioned as one of the extra-intestinal manifestations of celiac disease. This study aimed to investigate the prevalence of celiac disease in patients presented with idiopathic neuropathy.

#### Materials and Methods:

A cross-sectional study was done in patients with idiopathic neuropathy at Shariati Hospital, Tehran. Serological tests including endomysial IgA, tissue transglutaminase (TTG) IgA and IgG, and DGP (deamidated gliadin peptide) IgA, and genetic assessment for HLA DQ2 and DQ8 (human leukocyte antigen) were done for all patients and those who had positive celiac serology and HLA DQ2/DQ8 underwent endoscopy and adequate biopsy samples were taken. Diagnosis was made based on histopathological report of celiac disease.

#### Results:

101 patients with idiopathic neuropathy were enrolled. The mean age was  $43.56 \pm 10.66$  years (range 70-18 years). The prevalence of HLA-DQ2 and HLA-DQ8 positivity in patients with idiopathic neuropathy was 36.6% and 9.9%, respectively. The most common neuropathy subtype in patients with positive HLA-DQ2 and DQ8 was demyelinating PN (Polyneuropathy). One patient (1%) was diagnosed as having celiac disease.

#### Conclusion:

Although the prevalence of celiac disease in patients with idiopathic neuropathy was similar to the general population, having considered the prevalence of celiac disease, treating this condition with gluten-free diet is of importance.

**Keywords:** Celiac disease, Neuropathy, Serological test

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#### INTRODUCTION

Celiac disease is a disorder in genetically vulnerable patients due to sensitivity to gluten (1). Its estimated prevalence of 1% makes it a prevalent disease in the general population (2). Tissue transglutaminase (tTG) has an important role in celiac disease as an auto-antigen. This enzyme acts in glutamine to acid glutamic conversion process and leads to higher affinity of peptide molecule to its target site on HLA-DQ2 molecule in the surface of antigen presenting cells. Gliadin binds to antigens on DQ2 and DQ8 molecules on the surface of immune cells and triggers immune and humoral immunity mechanisms (3,4).

Manifestations of celiac disease are categorized into intestinal and extraintestinal, with ataxia and peripheral neuropathy as the most common extraintestinal manifestations (5,6). Peripheral neuropathy is also a prevalent condition in the general population with distal symmetric polyneuropathy as the most common type (7-10).

The relationship between neuropathy and celiac disease was described in 16 patients with concomitant celiac disease and neurological disorders. Among neurological disorders, the most common condition was peripheral neuropathy in 10 patients (11). Another study revealed that 39% of the patients suffering from celiac disease had neuropathic symptoms (12). A report has declared that while the prevalence of polyneuropathy in general population is 1%, its prevalence in celiac disease is estimated to be from 2.5% to 8% (13). Another study also indicated that neurophysiological evidence of peripheral neuropathy was found in 23% of the patients with proven celiac disease (14).

In this study we aimed to evaluate the prevalence of celiac disease in patients with idiopathic neuropathy.

## MATERIALS AND METHODS

This cross-sectional study was conducted in Shariati Hospital affiliated to Tehran University of Medical Sciences, in 2015. Patients with idiopathic neuropathy who were diagnosed at neurology clinic were enrolled in our study.

Neuropathy is defined when nerve damage interferes with the functioning of the peripheral nervous system. When the cause cannot be determined, it is called idiopathic neuropathy. There is no single definite test for neuropathy. Evaluations begin with a physical examination and a complete medical history.

Diagnostic tests may include:

- blood tests
- urinalysis
- nerve conduction studies (NCS)
- electromyography (EMG)
- skin, nerve, and muscle biopsies and
  - Imaging tests that may include computed tomography, radiography, or magnetic resonance imaging (MRI).
  - Our exclusion criteria were the presence of

any of these conditions: diabetes mellitus, uremia/liver failure, cancer, amyloidosis, multiple trauma, benign gammopathy, hypothyroidism, vitamin B12 and folate deficiency, alcohol abuse, chemotherapy, heavy metal toxicity, acquired immunodeficiency syndrome (AIDS), acromegaly, chronic obstructive pulmonary disease (COPD), and polycythemia vera. Patients' recruitment was based on convenience or availability sampling method. Informed consent was obtained from all the eligible patients. The demographic data and ethnicity of the patients were recorded using a questionnaire. Neuropathy characteristics were thoroughly evaluated. Gastrointestinal and extraintestinal manifestations, celiac-related serological tests, genetic tests, and upper endoscopy were also conducted and documented.

Celiac serological evaluations including endomysial IgA, tTG IgA (Euroimmune, Germany kit, with cut-off value > 20 IU/mL as positive), AGA (Anti-gliadin antibodies) IgA, and AGA IgG were performed. HLA DQ2/DQ8 was also tested for all the patients. Patients with positive HLA DQ2/DQ8 and serological celiac evaluations, underwent upper endoscopy and biopsy samples were taken from the second part of the duodenum (D2) to identify histopathological patterns.

The diagnosis of celiac disease is based upon histological findings in duodenal or jejunal biopsies. Histological features supporting the diagnosis of the disease architectural changes of the villi and/or crypts, an increase in lamina propria cell density, and an increase in IEL (intraepithelial lymphocytes) counts. For diagnostic purposes and for monitoring the patients with celiac disease an exact histological classification of the histological findings has to be given. This has become possible by using a modified Marsh classification.

Patients with definite diagnosis of celiac disease, based on Marsh classification, were provided with gluten-free diet for 6 months and then were re-assessed for the presence of neuropathies. Our study protocol was approved by the Ethics Committee of Digestive Diseases Research Institute of Tehran University of Medical Sciences, and all ethical codes were respected throughout the study.

**Table 1: Overall characteristics of the patients with idiopathic neuropathy**

Variables		N (%)
Age groups	19-40 years	37 (36.6)
	41-65 years	59 (58.4)
	Over 65 years or below 18	5 (5)
Ethnicity	Fars	44 (43.6)
	Turk	27 (26.8)
	Kurd	15 (14.8)
	Others	15 (14.8)
Female/male N (%)		45/56 (44.5/55.5)
Neuropathy	AMAN <sup>1</sup>	5.9%
	AMSAN <sup>2</sup>	1%
	Demyelinating PN <sup>3</sup>	58.4%
	Axonal symmetric PN	15.8%
	Small fiber neuropathy	11.9%
	Mononeuritis multiplex	4%
	Autonomic neuropathy	3%
Gastrointestinal (GI) symptoms	Diarrhea	5.9%
	IBS	25.7%
	Other	68.3%
Non GI symptoms	Iron deficiency anemia	15.8%
	Osteoporosis	4%
	Other	80.2%

1.Acute motor axonal neuropathy; 2.Acute motor and sensory axonal neuropathy;  
3.Polyneuropathy

## RESULT

101 patients with idiopathic neuropathy were enrolled in our study. The mean age of the patients was  $43.56 \pm 10.66$  years (range: 18-70 years). Sex distribution was in favor of men (56.55%). The most common ethnicity among our patients was “Fars” (43%). Family history of celiac disease was present in 7% of the patients. IBS (26%)(Irritable bowel syndrome) and chronic diarrhea (6%) were among the most common gastrointestinal (GI) symptoms, while iron deficiency anemia (16%), and osteoporosis (4%) were the most prevalent non-GI symptoms.

Neuropathy symptom was sensory in 57.56% of the cases while sensory-motor form was detected in 44.44% of the patients. The results of nerve conduction velocity test (NCV) were categorized as chronic in 91% and acute in 8% of the patients. The most common neuropathy subtype was demyelinating polyneuropathy (58.4%). The overall characteristics

of the patients with idiopathic neuropathy are listed in table 1.

Serologic markers of patients with idiopathic neuropathy are displayed in table 2.

HLADQ2 and HLADQ8 were detected in 36.6% and 9.9% of the patients, respectively. The most common type of neuropathy in patients with positive HLADQ2 and HLADQ8 was demyelinating polyneuropathy (48.6% and 40%, respectively).

There was only one patient (1%) diagnosed as having celiac disease with serum tTG level = 32 IU/mL and Marsh classification grade of 3b. Characteristics of the patient are described in table 3.

## DISCUSSION

In the present study, we found no difference between the prevalence of celiac disease in general population and subjects with idiopathic neuropathy. Only one patient was diagnosed as having celiac

**Table 2: Measurements of celiac serological markers in the patients**

Variables	N (%)
<b>tTG1 (IgA) (U/mL)</b>	3.34 ± 2.57
< 10	99%
10 - 20	0%
> 20	1%
<b>AGA2 IgA (U/mL)</b>	4.53 ± 2.03
< 12	99%
12 - 24	1%
> 24	0%
<b>AGA IgG (U/mL)</b>	4.64 ± 2.29
< 12	99%
12 - 24	1%
> 24	0%
<b>Total IgA (mg/dL)</b>	212.61 ± 73.88
< 70	5%

1. Tissue Transglutaminase; 2. Antigliadin antibody

**Table 3: Characteristics of idiopathic neuropathy in the patient with celiac disease**

Age	69 years
Sex	Male
Ethnicity	Fars
Neuropathy subtype	Axonal symmetric polyneuropathy
GI symptoms	Other
Non-GI symptoms	Other
Family history of celiac disease	Negative
AGA IgG	18.30
AGA IgA	16.50
TTG (IgA)	24.70
HLA-DQ2	Positive
HLA-DQ8	Positive
Neuropathy response to gluten-free diet	Positive

GI: Gastrointestinal ;AGA: anti gliadin antibodies

disease in endoscopic and pathological evaluations (approximately 1%). This prevalence rate is equal to the prevalence of celiac disease in general population (15,16). Even the assessment of the first-degree and the second-degree relatives of the patients could not reveal any higher prevalence rate for celiac disease (17). Neuropathy of the patient with celiac disease showed remarkable improvement after two months of receiving gluten-free diet.

There is abundant evidence regarding the different neurological manifestations of the celiac disease in the literature. Briani and colleagues have reported that neurological complications occur in 22.5% of the patients with celiac disease (18). Patterson and co-workers have found that there is no association between neuropathy in patients with celiac disease and copper deficiency (19). Some studies have declared that gluten-free diet has led to improvement of non-progressive polyneuropathies and has resolved muscle fasciculation in gluten-sensitive patients (20,21).

On the other hand, in the study of Luostarinen and others (14), patients did not show any signs of peripheral neuropathy and there was only an elevated antibody titer against gangliosides. In some patients, the evidence of neuropathy was seen prior to the diagnosis of celiac and patients were first evaluated for the causes of neuropathy and diagnosis of celiac disease has been established in this process (13).

In a study in Iran, 97% of patients with celiac disease and 58% of controls were carriers of HLA-DQ2 and/or HLA-DQ8 heterodimers, either in the homozygous or heterozygous states. The prevalence of DQ8 in our patients was higher than that reported in other populations (25.4%). As reported in other populations, these results underline the primary importance of HLA-DQ alleles in the Iranian population's susceptibility to celiac disease (22).

Neurological manifestations of the patients with celiac disease have shown a wide range of variety and maybe determining a dominant subtype of neuropathy in such patients is not feasible. In the current study, several subtypes of neuropathy including Demyelinating polyneuropathy (DPN), symmetric axonal, small fiber neuropathy, Acute Motor Axonal Neuropathy (AMAN), mononeuritis multiplex, autonomic neuropathy, and Acute Motor and Sensory Axonal Neuropathy (AMSAN) were detected. In the study by Chiara Briani and colleagues (18), three patients showed peripheral neuropathy with Deep Tendon Reflex (DTR) deterioration. Two of them suffered from lower limb cramps and distal paresthesia while the third patient had subclinical neuropathy. Cicarelli and co-workers (23) have detected 52% hyporeflexia, 18% reduction in vibration sense, 44% paresthesia, and 31% weakness in 176 patients with celiac disease.

There have been some efforts to track the changes in neurological manifestations after the initiation of treatment in patients with celiac disease. Even in the affected patients with long-term gluten-free diet, there was a 35% rate of paresthesia and 23% rate of present evidence of chronic electromyographic neuropathy (14).

Overall, the trend of studies regarding this issue follows a path. Initial studies on the prevalence of neurological manifestations in patients with celiac disease did not reveal any significant difference with other types of diseases. Then the type of manifestations became the topic of studies, which showed a wide range of variety in these symptoms and lack of a dominant type of neuropathy in such patients. Improvement of these symptoms after treatment of celiac disease was investigated later, which did not show any significant improvement in the studies. Following the previous reports, the current study evaluated idiopathic neuropathy cases, which revealed identical prevalence of celiac disease in such patients and general population.

Our study is the first study evaluating celiac disease in patients with neuropathy in Iran, which can be one of the strengths of our study. Meanwhile small sample size is a major limitation of the study, so further studies with more patients with neuropathy are suggested.

#### CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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