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Impact of Serological and Histological Factors on Neurological Manifestations in Children and Adults with Celiac Disease

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: Celiac disease (CD) is a common autoimmune disease with extra-intestinal manifestations, including neurological disorders. There are few reports to assess various factors in increasing the chances of developing neurological disorders in CD, so we designed this study.
Methods: All patients with CD at any age who had been referred to the Celiac Clinic were evaluated for neurological problems. CD was defined as IgA anti-transglutaminase antibodies (anti-tTG) of 18 IU/mL or higher in serology and Marsh type I or more severe in histopathological evaluation. Logistic regression analysis was used to evaluate the impact of various independent variables on the neurological manifestations.
Results: A total of 540 patients enrolled in this study. A 360 (66.7%) of patients were children. A 64.8% and 35.2% were female and male, respectively. Overall, 34.1% of patients had neurological manifestation, including headache, neuropathy, epilepsy, and ataxia. The odds of developing neurological manifestations in children were significantly lower than in adults (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.45–0.96; p=0.03) and in patients with gastrointestinal (GI) symptoms significantly higher than in the group without GI manifestations (OR, 1.77; 95% CI, 1.18–2.63; p=0.005). Other variables, including Marsh classification (OR, 0.44; 95% CI, 0.18–1.11; p=0.08) and anti-tTG levels (OR, 1.00; 95% CI, 0.999–1.001; p=0.59) did not significantly increase the chances of developing neurological disorders.
Conclusion: Our study showed that increasing age and the presence of GI symptoms, but not serological and histological findings, could increase the chances of developing neurological diseases in CD patients.

Keywords: Celiac disease; Neurological manifestations; Serology; Histology; Children; Adults

INTRODUCTION

Celiac disease (CD) is a multifactorial autoimmune disease defined as an inappropriate immunological response to gliadins protein in genetically predisposed persons. The typical CD is defined as the presence of chronic steatorrhea, abdominal pain, and weight loss [1-3].

In the past decades, the clinical manifestations of CD have changed. The prevalence of typical signs and symptoms has decreased, and on the other hand, the atypical ones such as osteopenia, anemia, infertility, intestinal T-cell lymphoma, and neurological presentations have increased [4-6].

Various neurological findings may occur on CD, including gluten neuropathy, ataxia [7-10], migraine headaches, and multiple sclerosis [11-13]. Several studies show that the prevalence of neurological findings is higher in patients with CD than in the general population [8,9,12,14]. To the best of our knowledge, a few research has been done to assess risk factors for increasing the chances of neurological manifestations in children and adults with CD. Therefore, the present study aimed to investigate the types of neurological disorders in children and adults with CD and also to evaluate various factors, including the impact of anti-transglutaminase antibodies (anti-tTG) levels and the severity of histopathological damage, in increasing the chances of these disorders.

MATERIALS AND METHODS

Ethical approval/statement

This study was conducted after obtaining the approval of the Ethics Committee of Shiraz University of Medical Sciences and the institutional review board (IR.sums.med.rec.1398.655) and the Helsinki Declaration of Ethics for Medical Research. Written informed consent was obtained from all CD patients or their legal guardians to review their medical records.

Population

This analytical cross-sectional study was performed to investigate the frequency of various neurological symptoms as well as the impact of various factors in increasing the chances of these neurological disorders in patients with CD from 2016 to October 2019.

All patients with CD at any age who had been referred to the Celiac Clinic, a referral clinic in southern Iran, were evaluated by an internist for neurological problems. Epilepsy was defined as a brain disorder in which the patient has recurrent seizures. Ataxia was defined as a lack of muscle coordination when a person is trying to move voluntarily. Neuropathy was defined as a weakness, numbness, or pain from nerve damage in the feet or hands. If there were doubts about the neurological manifestations, patients were referred to a neurologist for further evaluation including blood test, magnetic resonance imaging, electroencephalogram, and electrodiagnostic assessment to confirm the diagnosis. A checklist was filled out by a physician, including neurological signs and symptoms, physical examination, personal and family medical history, and medication use. On the other hand, an interviewer who was trained before the initiation of the study collected different variables including age, sex, height, weight, histological reports, anti-tTG levels, and other laboratory data in the checklist. Patients were then classified into two groups based on age of CD presentation.

Participants over the age of 19 were considered adults and less than or equal to 19 were classified as children. Finally, the demographic, clinical, serological, and histological findings of the patients with and without neurological manifestations were compared with each other.

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Serological and histological evaluation

Documentation of all CD patients was gathered for serum levels of anti-tTG (IgA) and also immunoglobulin A (IgA) levels. CD patients with IgA level less than 0.006 g/dL were excluded from the study as a condition of selective serum immunoglobulin A deficiency. The estimation of IgA anti-tTG was carried out using the Aeskulisa kit (GA Generic Assays GmbH, Dahlewitz, Germany), along with the ELISA method, for all patients. A titer of 18 IU/mL or higher was considered positive anti-tTG. Documentation of small-bowel biopsies was also gathered in all positive anti-tTG patients. The gap between serology testing and obtaining biopsies was less than one month in all the patients. The histological findings were classified according to Oberhuber-modified Marsh classification; less than 40 intraepithelial lymphocytes (IEL)/100 epithelial cells, normal height of crypts, and normal villous architecture are defined as Marsh type 1; more than 40 IEL/100 epithelial cells, crypt hyperplasia, and normal villous architecture are defined as Marsh type 2; more than 40 IEL/100 epithelial cells, crypt hyperplasia, and mild villous atrophy are defined as Marsh type 3a; more than 40 IEL/100 epithelial cells, crypt hyperplasia, and marked villous atrophy are defined as Marsh type 3b; more than 40 IEL/100 epithelial cells, crypt hyperplasia, and total villous flattening are defined as Marsh type 3c [15]. In patients with elevated anti-tTG levels but normal reporting of duodenal samples by the pathologist, a second pathologist was consulted to re-examine the specimens. The severity of histologic findings was also classified into two subgroups of non-atrophic (Marsh 1 and 2) and atrophic (Marsh 3a, 3b, 3c) for more analysis.

Celiac disease definition

According to previous studies, diagnosis of CD is based on duodenal biopsy as a standard diagnostic method and CD positive serology [16-18], so in our research CD was defined as anti-tTG level of 18 IU/mL or higher in serology and Marsh type I or more severe in histological evaluation.

Exclusion criteria included participants with incomplete records, patients who did not cooperate, IgA deficiency, Marsh type 0 in histology, and the presence of other possible causes of the villous atrophy in the pathologist's report, including infectious, infiltrative, neoplastic, and Crohn's disease.

Statistical analysis

All of the data were gathered in IBM SPSS Statistics for Windows, Version 25.0 (IBM Co., Armonk, NY, USA). Continuous variables were calculated as means and standard deviations (SDs), whereas categorical variables were expressed as percentages. Comparisons between the groups were analyzed by using independent *t*-test and Mann-Whitney U-test for continuous variables and the Chi-square test for categorical variables. Logistic regression analysis was used for estimating odds ratios (ORs) and confidence intervals (CIs) to evaluate the impact of various independent variables on the neurological manifestations. A p-value<0.05 was considered statistically significant.

RESULTS

As shown in **Fig. 1**, out of the patients referred to Celiac Clinic, a total of 540 patients met the inclusion criteria and enrolled in this study. The mean age (SD) of the patients was 19.51 (14.82) and ranged from 2–70 years. A 360 (66.7%) of patients were children. Of the included patients, 350 (64.8%) and 190 (35.2%) were female and male, respectively, with a male-to-

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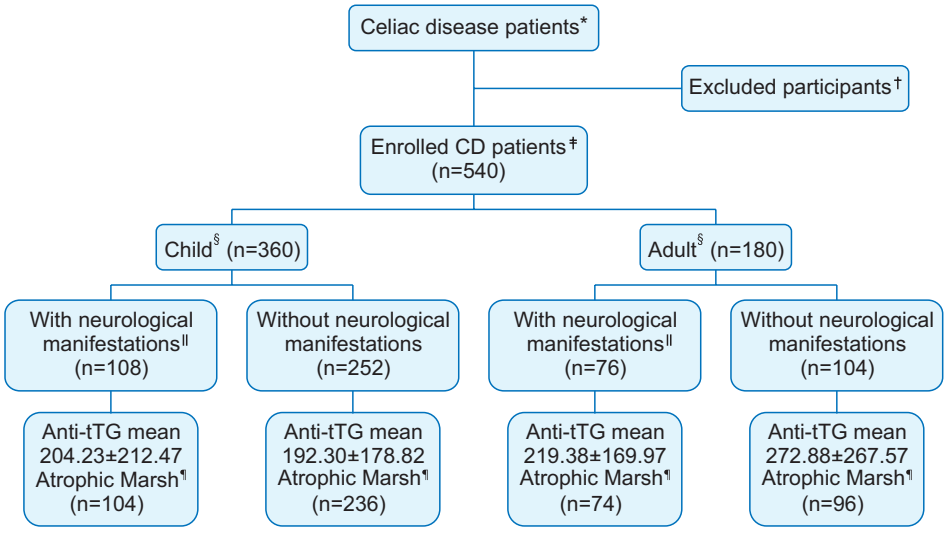

Fig. 1. Flow diagram for the CD participants' selection process. *All CD patients who referred to the Celiac Clinic. †All participants with Marsh type 0 in histology, or the presence of other causes of villous atrophy, incomplete documentation, and uncooperative patients were excluded. ‡CD defined as positive Anti-tTG (IgA) and Marsh type I or more in histology according to Oberhuber-modified Marsh classification. §Participants over the age of 19 were considered adults and less than or equal to 19 were classified as children. ‖The neurological manifestations include headache, neuropathy, epilepsy, ataxia, and others. ¶The histopathological findings of the duodenal biopsies were classified according to Oberhuber-modified Marsh classification, and then the severity of histologic findings was classified into two subgroups of non-atrophic (Marsh 1 and 2) and atrophic (Marsh 3a, 3b, 3c).
CD: celiac disease, Anti-tTG: anti-transglutaminases antibodie levels, IgA: immunoglobulin A.

female ratio of 1:1.8. The mean (SD) serum level of anti-tTG was 214.02 (206.07) mg/dL. **Table 1** summarized the clinical features of the participants. A 348 (64.4%) patients had gastrointestinal (GI) manifestations at the time of diagnosis and 33 (6.1%) participants had a positive family history of CD.

Overall, 184 (34.1%) patients had at least one neurological manifestation, including headache, neuropathy, epilepsy, ataxia, and other diagnosis/syndrome (multiple sclerosis, down syndrome, cerebral vasculitis). The most common neurological findings were headache (26.7%) followed by neuropathy (11.3%) and epilepsy (4.3%). Comparison of demographic and clinical findings in CD patients with and without neurological manifestations shown in **Table 2**. The mean age of patients with neurological findings (23.07±16.16) was significantly higher than that of group without these findings (17.67±13.75). Although the frequency of neurological manifestations was higher in women (36.9%) than in men (28.9%), the difference between the sex was not statistically significant (p=0.064).

The Mann-Whitney U-test was conducted to evaluate the possible mean difference between serum levels of anti-tTG antibodies in these two groups due to the non-parametric feature of the serum level of anti-tTG antibody (Kolmogorov-Smirnov p-value<0.001). Although the mean serum anti-TTG level in patients without neurologic manifestations (215.84±211.49) was slightly higher than the group with neurological manifestations (210.49±195.68), this difference was not statistically significant (p=0.896).

According to Marsh classification, there was no significant difference in the severity of the histological involvement between patients with neurological manifestations compared with participants without neurological findings (p=0.42). Comparison of subgroups of neurological manifestations with regard to demographic and clinical findings in CD patients shown in **Table 3**.

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Table 1. Characteristics of the participants with CD

Variable	Value (n=540)
Age (yr)	19.51±14.82
Sex	
Male	190 (35.2)
Female	350 (64.8)
Ethnicity	
Fars	415 (76.9)
Non-fars	125 (23.1)
Anti-tTG IgA (IU/mL)	214.02±206.07
Gastrointestinal manifestations	348 (64.4)
Neurological manifestations	
Headache	144 (26.7)
Neuropathy	61 (11.3)
Epilepsy	23 (4.3)
Ataxia	18 (3.3)
Other neurological findings	5 (0.9)
Marsh classification*	
Marsh 1	17 (3.1)
Marsh 2	13 (2.4)
Marsh 3a	170 (31.5)
Marsh 3b	212 (39.3)
Marsh 3c	128 (23.7)
CD in the family	33 (6.1)
Cousin marriage in the parents†	55 (10.4)

Values are presented as mean±standard deviation or number (%).
Anti-tTG: anti-transglutaminase antibodies level, CD: celiac disease.
*The histopathological findings of the duodenal biopsies were classified according to Oberhuber-modified Marsh classification. †Cousin marriage means a marriage where the partners are cousins.

Table 2. Comparison of demographic and clinical findings in CD patients with and without neurological manifestations (n=540)

Variable	With neurological manifestations (n=184)	Without neurological manifestations (n=356)	*p*-value
Age (yr)†	23.07±16.16	17.67±13.75	<0.001
Age‡			0.005
Children	108 (30.0)	252 (70.0)	
Adults	76 (42.2)	104 (57.8)	
Sex‡			0.064
Male	55 (28.9)	135 (71.1)	
Female	129 (36.9)	221 (63.1)	
Ethnicity‡			0.166
Fars	138 (33.3)	277 (66.7)	
Non-fars	46 (36.8)	79 (63.2)	
GI manifestations‡	136 (39.1)	212 (60.9)	0.001
CD in the family‡	10 (30.3)	23 (69.7)	0.637
Cousin marriage in the parents‡,§	19 (33.9)	37 (66.1)	0.981
Marsh classification‡,‖			0.417
Marsh 1	4 (23.5)	13 (76.5)	
Marsh 2	2 (15.4)	11 (84.6)	
Marsh 3a	64 (37.6)	106 (62.4)	
Marsh 3b	72 (34.0)	140 (66.0)	
Marsh 3c	42 (32.8)	86 (67.2)	
Anti-tTG (IU/mL)§,¶	210.49±195.68	215.84±211.49	0.896

Values are presented as mean±standard deviation or number (%).
CD: celiac disease, GI: gastrointestinal, Anti-tTG: anti-transglutaminase antibodies level.
†*t*-test. ‡Chi-squared test. §Cousin marriage means a marriage where the partners are cousins. ‖The histopathological findings of the duodenal biopsies were classified according to Oberhuber-modified Marsh classification. ¶Mann–Whitney U-test.

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Table 3. Comparison of subgroups of neurological manifestations with regard to demographic and clinical findings in CD patients (n=540)

Variable	Epilepsy	*p*-value	Neuropathy	*p*-value	Ataxia	*p*-value	Headache	*p*-value	Others	*p*-value
Age (yr)*	22.56±17.7	0.314	32.01±18.00	<0.001	26.16±17.65	0.053	21.36±14.67	0.081	25.6±14.43	0.357
Sex†		0.023		0.324		0.503		0.118		0.576
Male	3 (0.6)		18 (3.3)		5 (0.9)		43 (8.0)		2 (0.4)	
Female	20 (3.7)		43 (8.0)		13 (2.4)		101 (18.7)		3 (0.6)	
Ethnicity†		0.504		0.777		0.593		0.398		0.595
Fars	19 (3.5)		46 (8.5)		14 (2.6)		107 (19.8)		5 (0.9)	
Non-fars	4 (0.7)		15 (2.8)		4 (0.7)		37 (6.9)		0 (0.0)	
CD in the family†	1 (0.2)	0.582	3 (0.6)	0.475	1 (0.2)	0.698	7 (1.3)	0.464	0 (0.0)	0.729
Gastrointestinal manifestations†	16 (3.0)	0.60	53 (9.8)	<0.001	11 (2.0)	0.764	107 (19.8)	0.004	2 (0.4)	0.353
Marsh Severity†,‡		0.631		0.554		0.615		0.202		0.751
Non-atrophic	0 (0.0)		3 (0.6)		0 (0.0)		5 (0.9)		0 (0.0)	
Atrophic	23 (4.3)		58 (10.7)		18 (3.3)		139 (25.7)		5 (0.9)	
Anti-tTG (IU/mL)§	244.02±210.13	0.377	200.62±165.80	0.898	104.08±88.73	0.01	212.56±206.68	0.855	343.20±148.54	0.039

Values are presented as mean±standard deviation or number (%).
Anti-tTG: anti-transglutaminase antibodies level.
*t-test. †Chi-squared test. ‡The histopathological findings of the duodenal biopsies were classified according to Oberhuber-modified Marsh classification, and then the severity of histologic findings was classified into two subgroups of non-atrophic (Marsh 1 and 2) and atrophic (Marsh 3a, 3b, 3c). §Mann–Whitney U-test.
Cousin marriage means a marriage where the partners are cousins.

Logistic regression was run to evaluate the impact of various independent variables such as sex, age, the presence of GI manifestations on the neurological findings (**Table 4**). The odds of developing neurological manifestations in children was significantly lower than in adults (OR, 0.656; 95% CI, 0.448–0.961; *p*=0.030). In addition, the odds of developing neurological manifestations in patients with GI symptoms were significantly higher than in the group without GI manifestations (OR, 1.766; 95% CI, 1.184–2.634; *p*=0.005). Other variables, including Marsh classification (OR, 0.443; 95% CI, 0.176–1.114; *p*=0.083), anti-tTG levels (OR, 1.000; 95% CI, 0.999–1.001; *p*=0.595), sex, and ethnicity did not significantly increase the chances of developing neurological disorders.

Table 4. Impact of various independent variables on neurological manifestations using logistic regression analysis estimating OR and 95% CI

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age				
Children	0.586 (0.404–0.851)	0.005	0.656 (0.448–0.961)	0.030
Adults	1.0		1.0	
Sex				
Male	0.698 (0.477–1.022)	0.065	0.698 (0.474–1.028)	0.069
Female	1.0		1.0	
Ethnicity				
Fars	0.856 (0.564–1.298)	0.463	0.820 (0.534–1.259)	0.364
Others	1.0		1.0	
GI manifestations				
Yes	1.925 (1.301–2.846)		1.766 (1.184–2.634)	
No	1.0	0.001	1.0	0.005
Anti-tTG level	1.000 (0.999–1.001)	0.775	1.000 (0.999–1.001)	0.595
Histological findings*		0.101		0.083
Non-atrophic	0.466 (0.187–1.162)		0.443 (0.176–1.114)	
Atrophic	1.0		1.0	

OR: odds ratio, CI: confidence interval, GI: gastrointestinal, Anti-tTG: anti-transglutaminase antibodies.
*The histopathological findings of the duodenal biopsies were classified according to Oberhuber-modified Marsh classification, and then the severity of histologic findings was classified into two subgroups of non-atrophic (Marsh 1 and 2) and atrophic (Marsh 3a, 3b, 3c). †Cousin marriage means a marriage where the partners are cousins.

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DISCUSSION

Our study showed that the chances of developing neurological diseases in children with CD were significantly lower than in adults. Moreover, the presence of GI symptoms significantly increased the chances of neurological manifestations in these patients. Our results also showed that the severity of atrophy in Marsh classification as well as anti-tTG levels did not change the chances of neurological manifestations.

CD is an autoimmune disease associated with small intestinal atrophic entropy, which can be presented by various types of GI and non-GI manifestations [18,19]. Apart from gluten and genetics, other possible risk factors for CD have been suggested in various studies, but the results were not conclusive [20-23]. The prevalence of CD in the general population is approximately 1%, which is generally higher in women than in men [17]. In some studies, the ratio of men to women has been 1:2 in children and 1:4 in adults [24]. In our study, most of the participants were women, but there was no significant difference between the sexs in terms of neurological manifestations, which, although consistent with Cavusoglu et al. [25] report, did not agree with Aksoy et al. [14] study.

The prevalence of neurological findings is higher in CD patients than in the general population and often progresses slowly and may be irreversible, although there is still disagreement [8,9,12,14]. On the other hand, the association between CD and psychiatric disorders such as depression, eating disorders, and anxiety has been investigated or confirmed [26].

In our study, the mean age in patients with neurological findings was significantly higher than in the group without neurological manifestations. This is in line with study by Mearns et al. [9], which found that neurological findings are more common in adults than in children. This difference may be due to the fact that neurological manifestations in children may be subclinical, so these findings can be missed until adulthood [14]. Therefore, it may be concluded that the development of neurological findings in patients with CD is an age-related process [27].

In our research, about a third of patients had at least one neurological disease, the most common of which was headache and neuropathy. In a population-based study, Lebwohl et al. [13] showed that the prevalence of headache in participants with CD is 2.5 times more than the control group. Similar to our results, headache was the most common neurological problem in Diaconu et al. [28] study. Our results were also consistent with another study by Lionetti et al. [29], which found that 24.8% of their patients had headaches.

A systematic review of the literature showed that the prevalence of neuropathy in patients with CD varies from 0 to 39% and is higher in elderly patients and women [9]. In our results, similar to this review and other studies [24,30,31], neuropathy was seen in about 11% of CD patients, which was more common in older patients and women. Ataxia was observed in about 3% of patients, according to a study by Mearns et al. [9] Showed that the prevalence of ataxia on CD varies from 0 to 6%. Although in some researches ataxia was a common neurological problem [32], it was the least neurological manifestation in our results. The field of autoimmune neurology is advancing rapidly. Radiographic, electrophysiological and laboratory tests are very helpful in diagnosing autoimmune neurological disorders and differentiating them from other diseases [33]. On the other hand, various systemic autoimmune disorders may

be associated with neurological manifestations, including seizures. Possible mechanisms of seizures in these disorders include vascular disease, metabolic disorders, immune complexes, antineuronal antibodies, cytokines, and infection [34].

The exact mechanism of neurological findings in CD was not fully understood, but cross-reaction between gliadin and neurons can lead the gluten-sensitive T-cell lymphocyte to the neuronal tissue [14]. Other possible factors are nutritional and immunological factors [34,35]. In addition, chronic malabsorption leads to a deficiency of vitamins and macroelements such as vitamin E and magnesium. Although many patients with gluten-ataxia improved after administration of vitamin E supplements, vitamin E deficiency was rare in patients with peripheral neuropathy. Therefore, there is still disagreement on this issue [11].

We found that the most common histopathological finding was Marsh type 3b, but none of the histopathological classifications significantly changed the chances of developing neurological manifestations (**Table 2**). In a study by IŞIkay and Kocamaz [36], 40 (13.5%) of the 297 CD patients had neurological findings, in general, the percentage of people with neurological manifestation in this study was lower than our results. They also found that Marsh 3a was significantly higher in patients without neurological manifestations, while Marsh 3b was significantly higher in patients with neurological manifestations, which was completely inconsistent with our results. Interestingly, in our study, the presence of GI manifestations increased the chances of developing neurological diseases by almost 1.8 times, but we do not have a scientific justification for this result, and further studies are recommended to clarify this result (**Table 4**).

One of the strengths of our study was that we compared demographic, neurological, and histological features in detail in the two age groups of children and adults, while the vast majority of previous studies analyzed only one age group in this regard. Another strength of our study was in comparison with similar studies, was the acceptable sample size and appropriate diagnostic evaluation for all participants. Our research also had some limitations. Our results cannot be generalized to seronegative CD patients because we did not evaluate this subgroup. It is recommended to consider patients in this subtype in future study. Another limitation of our research was that there was no control group for comparison and the study was performed in only one center.

In conclusion, our study showed that increasing age and the presence of GI symptoms at the time of diagnosis, but not serological and histological findings, could increase the chances of developing neurological diseases in CD patients. Therefore, Marsh classification as well as anti-tTG levels were not helpful in predicting the chances of developing neurological manifestations, but further research is needed to confirm this results.

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