ORIGINAL ARTICLE

Evaluation of Frequency of Celiac Disease in Children with Idiopathic Epilepsy

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ABSTRACT

Objectives

Extra gastrointestinal symptoms in celiac disease (CD), such as neurological manifestations, might be common in pediatrics. The present study aimed to evaluate the frequency of CD in children with idiopathic epilepsy.

Materials & Methods

In a cross-sectional study, signs and symptoms of CD were evaluated in 40 children aged 2-14 years with idiopathic epilepsy who were referred to the Pediatric Neurology Clinic of Shahid Sadoughi Medical Sciences University, Yazd, Iran. Then, serum levels of tissue transglutaminase antibody (tTG) and total IgA were measured in them. Upper gastrointestinal endoscopy and small intestine biopsy were recommended for patients with abnormal serum IgA Anti-tTG.

Results

Eighteen girls and 22 boys with a mean age of 5.29±2.4 years were evaluated. In this study, only three patients (7.5%) with epilepsy had abnormal serum IgA Anti-tTG and serum Total IgA. Upper gastrointestinal endoscopy and pathological examination of duodenal biopsy of those three children reported total villous atrophy (Marsh type 3). The age of onset of seizures in children with CD was more than three years, while in children without CD, 62.2% of cases were less than three years. These results indicate that CD is associated with the age of onset of seizures in children.

Conclusion

Due to the accompaniment of celiac with neurological manifestations, patients with neurological symptoms and gastrointestinal symptoms should be examined for celiac.

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Introduction

Celiac disease (CD) is an immune-mediated enteropathy that was early known as a food hypersensitivity disorder, happening in genetically susceptible individuals through the ingestion of cereal gluten proteins (1). It affects approximately 1% of the population worldwide (2). The significant inclining genes, the HLA-DQ2 and DQ8 genes, present in more than 95 percent of celiac patients, are located on chromosome 6 of the HLA system. Gluten is a complex mixture of diverse wheat proteins essential to most world populations (3). According to the reports, the fraction of wheat gluten containing gliadin polypeptides induced Small intestinal mucosal damage. Although the mechanism of this toxic reaction in susceptible individuals is unknown, strong evidence is available for an immune component (4). Clinically, CD is classified into two categories: symptomatic and asymptomatic. The symptomatic form of the disease, which is much rarer, can be differentiated into classical and atypical clinical presentations. Chronic diarrhea followed by malabsorption and secondary malnutrition are the classical form of the disease, while the clinical features of the atypical form are characterized by extra intestinal indexes (5-9). The classical form of the disease is more common in infants and children, and the non-classical form is mainly found in later ages and adults (10, 11). Neurological complications often affect patients with CD, even if they do not show any gastrointestinal symptoms. The most common neurologic disorders in patients with CD are cerebellar ataxia, epilepsy, and peripheral neuropathy (12). Recently, previous studies describe an increased epilepsy risk in CD patients, but with considerable variability from 0% to 7.9% in the prevalence (13, 14). A recent cohort study used about 28,885 celiac patients and 143,166 control subjects, and the results revealed a 1.43-fold increased risk of epilepsy in patients with CD (15). In these studies, one association has been found between some key points, such as CD, peripheral neuropathy, brain white matter lesions, and autism, while the highest risk of disease is in childhood (16).

There are some CD diagnostic procedures (or methods), such as history, clinical symptoms, serology, HLA testing, slight intestinal biopsy examination, and response to a gluten-free diet (GFD), but more is needed. Thus, a reliable diagnosis depends on combining them (8). The only treatment currently available for CD is to follow a strict lifelong GFD, eliminating all food products containing barley, wheat, and rye. While GFD is generally effective, it is associated with several drawbacks: high cost, restrictive nature, and impaired quality of life. As a result, alternative treatment forms are necessary, and several drug pipelines are currently being developed (17). Most recent guidelines have recommended using IGA anti-tTG antibodies screening to diagnose CD among children because of the high accuracy of the essay (18). The best serologic approach to evaluating CD is to use IgA endomysial antibodies (IgA-EMA) and deamidated gliadin peptide AGA (DGP-AGA). The sensitivity and specificity for IgA DGP-AGA are 84.3 % and 79.8%, respectively, while the sensitivity and specificity for IgG DGP-AGA are 82.3 % and 98.9%, respectively (19). Although novel serological tests are highly precise and sensitive, a small bowel biopsy is the “golden standard” for CD diagnosis (20). According to the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines, small bowel biopsy indications included symptoms and signs

of CD, anti-TG levels ten times higher than the ULN, and a positive EMA test (12, 13). This study aimed to assess the prevalence of CD among children with idiopathic epilepsy referring to the Pediatric Neurology Clinic of Shahid Sadoughi University of Medical Sciences in Yazd, Iran, since October 2020.

Methods & Materials

In a cross-sectional descriptive study, all consecutive 2 to 14-year-old children diagnosed with idiopathic epilepsy based on history, physical examination, and clinical judgment of a pediatric neurologist who referred to the Pediatric Neurology Clinic of Shahid Sadoughi Medical Sciences University, Yazd, Iran, in 2020 and was treated with levetiracetam for six months, were enrolled in the study. Classification of seizure types and definition of idiopathic epilepsy in this study were based on the ILAE Commission on Therapeutic Strategies Consensus. Initially, the parents of the children who met the criteria to enter the study were interviewed by the researcher, and after receiving their consent, their children entered the study.

Information on study variables, including age, sex, age of seizure onset, type of seizure, weight, height, body mass index (BMI), and symptoms and signs of CD (based on history and physical examination) were reviewed. Then, serum levels of transglutaminase antibody (tTG) and total IgA were measured. Venous blood samples were tested for IgA anti-tTG antibodies using a commercially available enzyme-linked immunosorbent assay (AESKU 7503, Germany) with commercially available diagnostic kits (Quanta Lite tTG, Inova Diagnostics Inc., San Diego, CA, USA) and tTG IgA value greater than 10 IU/mL were considered abnormal (positive serology). Upper gastrointestinal endoscopy and small intestine biopsy were recommended for patients with positive serology. The slides were examined under an optic microscope by a single pathologist who was experienced in diagnosing CD. The duodenal biopsies were classified according to the criteria defined by Marsh (21). 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 (22). The diagnosis of CD was based on the criteria defined by the American Gastroenterological Association (7), with a bowel biopsy of at least Marsh IIIa. The data were analyzed using Statistical Package for the Social Sciences version 26 (SPSS, Chicago, IL, USA) statistical software. The chi-square test was used for data analysis of qualitative variables, and mean values were compared using a paired T-test. Informed consent was obtained from the children's parents before enrolling in the study, and the study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Results

Forty children, including 18 girls (45%) and 22 boys (55%), with a mean age of 5.29 ± 2.46

years, were evaluated. Seven patients (17.5%) had a positive family history of epilepsy. The frequency of seizure types was as follows: tonic-clonic seizure (72.5%), tonic seizure (5%), clonic seizure (5%), and partial seizure 17.5%.

Three patients (7.5%) with epilepsy had abnormal serum IgA Anti-tTG and serum Total IgA. Upper gastrointestinal endoscopy and pathological examination of duodenal biopsy of those three children reported mild villous atrophy (Marsh type 3a). Hence, the frequency of CD in children with idiopathic epilepsy was 7.5%.

The frequency distribution of CD based on some patients' characteristics is shown in Table 1, indicating that no statistically significant differences were seen regarding sex distribution, type of seizure, family history of epilepsy, and mean age of patients in both groups. However, CD was more frequent in children over three years old.

Table 2 compares the mean age, weight, height, and BMI of children, indicating that no statistically significant differences were seen between the groups from these viewpoints. Table 3 shows the frequency distribution of positive serology (tTG IgA > 10 IU/mL) in children with idiopathic epilepsy based on some patients' characteristics. This indicates that no association was found between positive serology in children with idiopathic epilepsy with these variables.

Table 1. Frequency distribution of celiac disease based on some patients' characteristics

Data \ Celiac disease		Yes	No	P. Value
Sex	Girl	2 (66.7%)	16 (43.2%)	0.42
	Boy	1 (33.3%)	21 (56.8%)	
Seizure type	Partial	1 (33.3%)	6 (16.2%)	0.44
	Generalized	2 (66.7%)	31 (83.8%)	
Family history of epilepsy	Yes	0 (0%)	7 (18.9%)	0.55
	No	3 (100%)	30 (81.1%)	
Type of generalized seizure	Tonic	1 (33.3%)	9 (24.3%)	0.91
	Clonic	0 (0%)	1 (2.7%)	
	Tonic -clonic	2 (66.7%)	27 (73%)	
Onset age of seizure in year	Less than 3 years	0 (0%)	23 (62.2%)	0.03
	More than 3 years	3 (100%)	14 (37.8%)	
Anthropometric status	Under weight	1 (33.3%)	19 (51.4%)	0.77
	Normal	2 (66.7%)	17 (45.9%)	
	Over weight	0 (0%)	0 (0%)	
	Obese	0 (0%)	1 (2.7%)	
Age group	Less than 5 years	2 (66.7%)	19 (51.4%)	0.21
	5- 8 years	0 (0%)	15 (40.5%)	
	More than 8 years	1 (33.3%)	3 (3%)	

Table 2. Comparison of mean of age, weight, height and BMI in both groups

Data \ Celiac disease	Yes	No	P. Value
Age in year (mean ±SD)	6.33 ± 3.21	5.21 ± 2.43	0.21
Weight in kilogram (mean ±SD)	19.60 ± 9.02	17.02 ± 6.51	0.10
Height in centimeter(mean ±SD)	118.66 ± 19.55	107.51 ± 19.24	0.33
BMI (mean ±SD)	13.24 ± 2.04	14.39 ± 2.71	0.77

Table 3. Frequency distribution of positive serology (tTG IgA > than 10 IU/mL) in children with idiopathic epilepsy based on some patients' characteristics

Data \ Positive serology		Yes	No	P. Value
Sex	Girl	3 (60%)	15 (42.9%)	0.47
	Boy	2 (40%)	20 (57.1%)	
Seizure type	Partial	1 (20%)	6 (17.1%)	0.87
	Generalized	4 (80%)	29 (82.9%)	
Family history of epilepsy	Yes	0(0%)	7 (20%)	0.23
	No	5(100%)	28 (80%)	
Type of generalized seizure	Tonic	1 (20%)	9 (25.7%)	0.88
	Clonic	0 (0%)	1 (2.9%)	
	Tonic -clonic	4 (80%)	25 (71.4%)	
Onset age of seizure in year	Less than 3 years	1 (20%)	22 (62.9%)	0.07
	More than 3 years	4 (80%)	13 (37.1%)	
Anthropometric status	Under weight	2(40%)	18 (51.4%)	0.8
	Normal	3(60%)	16 (45.71%)	
	Over weight	0 (0%)	0 (0%)	
	Obese	0(0%)	1 (2.85%)	
Age group	Less than 5 years	4 (80%)	17 (48.6%)	0.17
	5- 8 years	0 (0%)	15 (42.9%)	
	More than 8 years	1 (20%)	3 (8.6%)	

Discussion

In recent years, some studies have reported the association of epilepsy with CD. Previous studies have reported different rates, from 0.78% to 9.1% of CD in epileptic children (23, 24). This variation in prevalence may be related to different epilepsy definitions or regional variations of CD prevalence (14, 25). In a retrospective population-based study, the relationship between epilepsy and some autoimmune diseases has been investigated, and the risk of epilepsy was determined to be significantly increased among patients with autoimmune diseases, including CD (26). In Turkey, Ertekin et al. (23) and Dalgıç et al. (27) have reported 9.1% and 1.17% of CD in epileptic children, respectively. A 1.43-fold increased risk of epilepsy among patients with CD was reported by Ludvigson et al. (28). On the other hand, a population-based cohort study consisting of 213,635 individuals born during 1989–2011 confirmed the positive association between CD and epilepsy (29). Due to the small number of papers investigated in Iran, this study was performed to investigate the prevalence of CD in children with idiopathic epilepsy. In the present study, the frequency of CD in children with idiopathic epilepsy was 7.5%, and no correlation was found between CD and gender, BMI, age, type of seizure, family history of epilepsy, and the duration of epilepsy. In contrast, the age of onset of seizures in children with CD was more than three years, while in children without CD, in 62.2% of cases, it was less than three years. These results indicate that CD is associated with the age of onset of seizures in children. Shahramian et al. at Zabol's Amir Al-Momenin Hospital in 2016 showed that CD affects 5% of children with epilepsy, and generalized tonic-clonic seizures were more common in children with CD (30). In addition, 60% of children were under five years old, which is consistent with the present study. As mentioned before, the prevalence of CD in this study and Shahramian et al. was calculated at 7.5 % and 5%, respectively, and these results were consistent with those of Bashiri et al. (31) and Casciato et al. (32). However, these findings were different from Fois (33) and Vascotto's (34) results which can be due to difference in sample size. For example, in Vascotto et al.'s study, 1210 patients with seizures were evaluated. Bashiri et al. reported a 6% prevalence of CD in patients with seizures, which was lower than the current study, and GFD was reported to reduce the incidence of seizures in patients. Of 113 studied patients, seven (6%) were diagnosed with CD. After five months of instituting a GFD, six patients' seizures were completely under control, and antiepileptic drugs were discontinued. In one case, anticonvulsant drugs were reduced by half, and seizures were controlled (31). Similarly, in the current study, GFD -controlled seizures in one-third of patients with CD. Gobbi et al. (35) described the link between epilepsy, CD, and cerebral calcification as CEC syndrome and determined that 61% of their cases with CD and cerebral calcifications had occipital epilepsy. Believingly, central nervous system folic acid deficiency may play a role in this syndrome. Seizure control can be improved by introducing a GFD with folic acid supplements in these patients (36, 37). In contrast, in a cross-sectional study, Husby S et al. concluded that the study could not prove a link between CD and epilepsy (38). In their study, it was estimated that 100 cases of CD in children and adolescents had idiopathic or cryptogenic epilepsy**.** 3 (3.0%) patients tested anti-tTG-positive, two with normal duodenal mucosa (Marsh 0) and one with intraepithelial

infiltrate (Marsh I). No villous atrophy of the duodenal mucosa (Marsh III) CD was reported. Equally, Djuric et al. examined the anti-tTG IgA antibodies of 125 children with idiopathic epilepsy. They concluded that the prevalence of biopsy-confirmed CD in children with epilepsy in the study group was not significantly higher than that in the control group (24). In another study by Camilo VIEIRA et al., the association between CD and epilepsy was refused (39). The cause of the relationship between epilepsy and CD is not fully understood. The proposed autoimmune response focuses on vasculitis and victuals deficiency. The determination of anti-tumor and anti-ganglioside antibodies in CD patients with neurological disorders suggests that antibody-mediated autoimmune mechanisms may cause neurological disorders. In addition, clinical improvement with loss of antibodies was observed in some cases due to early initiation of a GFD (16, 40). Therefore, anti-gliadin antibodies can induce the production of similar antibodies against brain tissue, causing neurotoxicity. Pratesi et al. (41) showed the formation of antibodies against brain blood vessels via the immune fluorescence method. Hadjivassiliou et al. (42) reported that due to the neurotoxic effect of gliadin, neurological symptoms can occur without the occurrence of CD. Therefore, due to the prevalence of celiac disease in children with epilepsy, it is crucial to identify celiac disease in epilepsy patients to prevent its long-term complications, and a GFD has also been suggested to play a protective function in autoimmune diseases and seizure control.

In Conclusion

According to the present study, the prevalence of CD among patients with seizures was 7.5%. The obtained results showed that there was no correlation between CD and gender, age, type of seizure, family history of epilepsy, and duration of epilepsy. Unexpectedly, the age of onset of seizures in children with CD was more than three years, while in children without CD, in 62.2% of cases, it was less than three years. These results indicate that CD is associated with the age of onset of seizures in children. Finally, this study suggests that due to the accompaniment of celiac with neurological manifestations, patients with neurological symptoms and gastrointestinal symptoms should be examined for celiac.

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Authors' Contribution

Roohollah Edalatkhah, Razieh Fallah conceived the study, participated in the study design and supervision of project. Bahareh Dehghani firouzabadi participated in data collection, data analysis. Bahareh Dehghani firouzabadi, Majid Aflatoonian assisted in preparing manuscript and revision. All the authors have read and approved the final submitted manuscript.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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