RESEARCH ARTICLE

RELATIONSHIP BETWEEN CELIAC DISEASE AND REFRACTORY IDIOPATHIC EPILEPSY IN CHILDREN

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Abstract

Objective

Epilepsy occurs with a yearly incidence of 40 per 100,000 children, of which more than 25% are resistant to drug therapy. Epilepsy may occur in autoimmune diseases like lupus, celiac disease and myasthenia gravis. In this study, the relationship between celiac disease and refractory epilepsy was evaluated in children with idiopathic epilepsy.

Material & Methods

Hundred-fifty-five children (mean age, 6.7±3.3 years) with idiopathic and cryptogenic epilepsy referred to the neurology clinic were studied in two groups; drug controlled epilepsy (control, 82 patients) and refractory epilepsy groups (case, 73 patients). Both groups underwent serological tissue transglutaminase antibody measurement by ELISA. In seropositive cases, small intestine biopsy was conducted. Data analysis was performed using student's t test and 2 test.

Results

Seven (0.04%) patients had celiac disease based on a positive tissue transglutaminase antibody and three patients (0.01%) based on a positive biopsy. TWO patients (2.4%) with drug controlled epilepsy (control group) and five with refractory epilepsy (case group) had seropositive celiac disease (p=0.255). In the biopsy survey of six seropositive patients, one patient (1.2%) in the drug controlled epilepsy and two patients (2.7%) in the refractory epilepsy group had positive biopsy for celiac disease (p = 0.604). One seropositive patient did not cooperate for biopsy.

Conclusion

If the relationship between celiac disease and epilepsy, especially in cases of symptomatic or oligosymptomatic celiac is proved, using gluten free diet increases the ability to control epilepsy particularly in refractory cases. We suggest celiac disease survey is not required in patients with idiopathic epilepsy.

Keywords: Epilepsy, celiac disease, children.

Introduction

Epilepsy with the incidence of 40 per 100,000 children in year happens, which more than 25% of the cases are resistant to drug therapy (1). In many cases the cause of seizure is not detectable in brain function (idiopathic-cryptogenic epilepsy) (1). Epilepsy has several causes and can occur in autoimmune diseases such as lupus, celiac disease and myasthenia Gravis (1-3). Celiac disease, a relatively

common autoimmune malabsorption disorder due to a permanent intolerance to gluten and a 1% prevalence, of which 3.5 to 7.5% have seizure attacks (1).

The relationship between epilepsy and celiac disease has been discussed in several studies (2,4). Studies for assessment of the effects of gluten free diet on the control of idiopathic epilepsy are still not enough, but preliminary studies show if this treatment regimen is started early, it is possible to significantly improve seizure control (5-8). On the other hand, because there is no effective treatment for refractory epilepsy, a combined therapy with antiepileptic drugs and a gluten-free diet is very promising (2,4), which may also can be used in the early diagnosis of this disease (4).

As other studies have evaluated the relationship between epilepsy and celiac disease in the adults group, in this study, this relationship has been assessed between celiac disease and epilepsy in children who were suffering from idiopathic epilepsy.

Material & Methods

In this case-control study, the assessed population included 1 to 16-year-old children with idiopathic-cryptogenic epilepsy referred to the pediatric neurology clinic of Mofid university-affiliated hospital of Tehran (Iran) from 2009-2010. Then 155 referred epileptic patients who had the inclusion criteria were studied. The inclusion criteria were:

1. Detection of epilepsy based on the International Association of Epilepsy criteria.
2. History of convulsions at least two non-provoked at least a month away. Patients with idiopathic-cryptogenic epilepsy and or epilepsy associated with stroke.
3.Age between 1-16 years.
4.Seizure onset after the age of 6 months.

In addition, patients with the following conditions were excluded: known etiology for epilepsy or symptomatic epileptic patients, neonatal seizures, seizures beginning before the age of 6 months.

Initially a full history of the patients were taken and in case of having the inclusion criteria, the demographic data of the patients including age, gender and the clinical characteristics of epilepsy including the seizure type, clinical findings, findings of electroenchaphalography (EEG) and brain CT-scan and response to medical therapy were recorded in the information forms.

In this study, according to the limited studies for the evaluation of the association between celiac disease and epilepsy, 155 patients were studied. we devided these patients in two groups.

Control group:82 patients with controlled epilepsy and cases: 73 patients with uncontrolled or refractory epilepsy.

Children continue to have seizure after at least more than 2 standard antiepileptic drugs and one new antiepileptic drug considered as refractory epilepsy groups.

Both control (drug controlled epilepsy group) and refractory epilepsy groups (73 patients) underwent the serological study of tissue transglutaminase antibody measurement by ELISA method. All samples were tested with standard kits manufactured in Wendeisheim (Germany) and titers above headline 20 IU were considered positive. In seropositive cases, a small intestine biopsy was conducted by an expert pediatric gastroenterologist. All the biopsy samples were studied by a pediatric pathologist who had no known serological results (single blinding). Subsequently, data analysis was performed using statistical software SPSS (version 17) and t student's test and χ^2 test. Also, to determine the correlation between quantitative variables Pearson correlation coefficients were used. P values less than 0.05 were considered statistically significant

Results

In this study, 155 children with idiopathic-cryptogenic epilepsy were studied. In the refractory epilepsy group (case), 47 patients (64.4%) were male and 26 patients (35.6%) were female, and in the drug controlled epilepsy group (control), 49 patients (60.5%) were male and 32 patients (39.5%) were female. Statistically significant differences between gender groups in the two studied groups were not observed (p=0.619).

The mean age of the refractory epilepsy patients was 7.6±3.1 years and for the drug controlled epilepsy group this number was 5.9±3.6 years which showed no significant difference between the two groups (P= 0.002) (Fig1). In refractory epileptic patients, the mean age onset of seizure was 2.8±2.3 years which was 4.6±3.3 years in the drug controlled epilepsy group demonstrating no significant difference between the

two groups (p=0.001).

In the refractory epilepsy group, 29 patients had idiopathic epilepsy (39.7%) and 44 patients had cryptogenic epilepsy (60.3%); in the drug controlled epilepsy group 63 patients had idiopathic epilepsy (77.8%) and 18 patients had cryptogenic epilepsy (22.9%). There was no significant differences between the types of epilepsy in the two groups (p=0.052). Regarding neurological development status in the refractory epilepsy group, 30 patients (41.1%) had a normal state and 43 patients (58.9%) had an abnormal state which was 64 patients (79%) and 17 patients (21%), respectively for the drug controlled epilepsy group. Statistically significant differences were observed between the evolution of neurological status in the two groups under investigation (p=0.06).

After the serologic test (anti transglutaminase antibody), two patients (2.4%) in the drug controlled epilepsy group and five patients (6.8%) in the refractory epilepsy group were seropositive, of course there was no significant difference between the two groups (p=0.255) (Table 1).

All patients with positive serology were called for endoscopy and biopsy, except one patient because of the wrong telephone number, communication was not feasible. After arrangement with an expert pediatric gastroenterologist and pathologist, biopsy samples were taken from six patients with seropositive celiac disease and were sent to the laboratory. In the pathologic examination, one patient (1.2%) in the drug controlled epilepsy group and two patients (2.7%) in the refractory epilepsy group were positive for celiac disease. Statistically, no significant differences were observed between positive biopsy results for celiac disease between the refractory epilepsy group and the drug controlled epilepsy group (p=0.604) (Table 2).

It should be mentioned that during the follow-up of patients in our study, a seven-year-old girl with epilepsy resistant to treatment, seropositive celiac disease and positive biopsy for disease, was treated and controlled with combined therapy including celiac diet (gluten-free) and anti-epileptic drugs of which the celiac diet healed her evolutionary criteria.

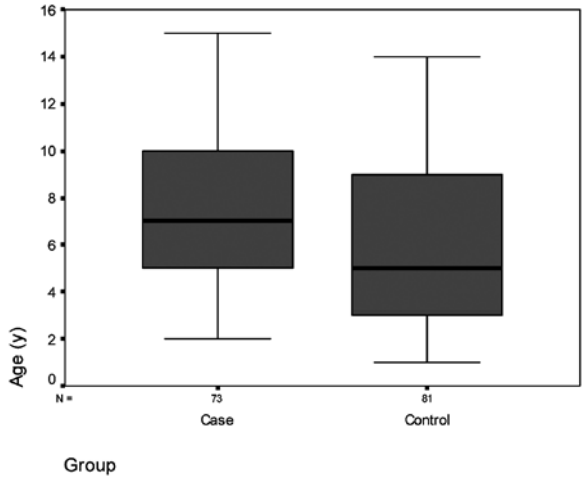

Figure 1. Mean age distribution in the drug controlled epilepsy group (control) and refractory epilepsy group (case)

Table 1: Serologic results for celiac disease in the drug controlled epilepsy group (control) and the refractory epilepsy group (case)

Group	Serologic results		total
	-	+	
Refractory epilepsy	68 (93.2%)	5 (6.8%)	73 (47.4%)
Drug controlled epilepsy	80 (97.6%)	2 (2.4%)	82 (52.6%)
total	148 (96.1%)	7 (3.9%)	155 (100%)

Table 2: Pathologic results for celiac disease in the drug controlled epilepsy group (control) and the refractory epilepsy group (case)

Group	Serologic results		total
	-	+	
Refractory epilepsy	71 (97.3%)	2 (2.7%)	73 (47.4%)
Drug controlled epilepsy	80 (98.8%)	1 (1.2%)	81 (52.6%)
total	151(98.1%)	3 (1.9%)	154 (100%)

Discussion

Celiac disease is an autoimmune disease with the involvement of the gastrointestinal tract, but its spectrum of clinical symptoms is broad and contains various organs including the peripheral and central nervous system (2). The etiology of neurological complications in celiac disease is unknown. But recently many neurological complications including seizures in these patients have been reported (2).

The relationship between celiac and epilepsy is not definite yet, but many studies suggest this relationship particularly symptomatic and oligosymptomatic types of celiac (1,2,4). Neurological symptoms such as learning disorders, ADHD, headache, and cerebellar ataxia in children with celiac have been reported (1,3,7). Neuropathy, sensory ataxia, weakness and decline of DTR, distal axonopathy and stroke are seen in adult patients (1,3). Refractory epilepsy that is commonly associated with calcification in the occipital lobe and white matter brain lesions similar to MS have also been reported worldwide (1,3,8-11). Several studies have reported neurological symptoms among celiac patients even in cases that have been on a gluten free diet. These symptoms include:

1. Epilepsy, especially with partial complex seizures (1,2,4,12)
2. Ataxia (7,8); celiac has been mentioned as the most common cause of sporadic idiopathic ataxia in the literature (3,17)
3. ADHD (5,7)
4. Autism (13)
5. Peripheral neuropathy (1,6)
6. White matter lesions in the brain (1,8)

In a study in 2004 that was performed in Turkey to assess the relationship between celiac disease and epilepsy on 77 children with idiopathic-cryptogenic epilepsy (51.9% of the subjects had generalized epilepsy and 48.1% of them had the partial type), 12 patients (15.6%) (2 male) were positive for tissue transglutaminase antibodies. Due to the lack of cooperation of the children's parents, only seven children had been biopsied of which all (100%) had grade three enteropathy (14).

In Iran, the prevalence of celiac disease in the general population especially children and epileptic patients has not been a comprehensive assay. In our study, of 155 studied epileptic children, seven patients (0.04%) had a positive serology; among which patients with seropositivity one patient was excluded from the study due to lack of cooperation, three patients (50%) had positive biopsy results for celiac enteropathy. One of the cases was in the drug controlled epilepsy group (control), two cases were in the refractory epilepsy group, despite more positive biopsy results in cases of the refractory epilepsy group, based on statistical analysis, no significant difference was observed between the two groups.

In a case control study conducted in Ireland (1998) to investigate the prevalence of celiac in epileptic patients, 177 patients with epilepsy (age 14-80 years) were studied for IgA antiendomesial antibody which were then compared with the control group. In this study, celiac frequency in the idiopathic epileptic group had been reported as one person per 37 patients which indicates a significant relationship between these two diseases. Of four seropositive patients, all of them showed typical pathology of celiac disease in the intestinal biopsy. Although in this study the control group were not matched for age and sex with the epileptic group, it was able to show strong evidence that epilepsy occurs with more frequency than the general population in celiac patients (2).

In the second part of this study, 16 patients (six males, 10 females) who had celiac and epilepsy were evaluated for seizures and neuroradiologic findings that showed a specific syndrome including celiac disease, epileptic seizure and brain calcification (2). Further reports of this syndrome were reported in Italian centers (2). It should be mentioned that in our study in the neuroradiology findings, three patients with positive celiac biopsy had no evidence of this syndrome.

In another study conducted in 2004 in Turkey, 1263 children were studied for celiac disease. The prevalence of celiac disease was 0.87% based on seropositivity tissue transglutaminase antibody and 1.1% based on biopsy results. In addition, in epileptic patients seropositivity was 15.6% and positive biopsy for celiac disease was 9.1%; these findings point out that celiac disease is more common in epileptic children. In this study, contrary to the results of our study, the association between celiac disease and epilepsy had been approved and therefore,

the researchers recommended the evaluation of celiac disease in epileptic children (15).

In 2007, a similar study was conducted in Greece and 255 children with idiopathic epilepsy were assessed for anti-gliadin antibody, tissue transglutaminase antibody and antiendomesial antibody and antireticulin antibody and were then compared with 280 healthy children. In this study, a significant difference for the prevalence of celiac disease had been reported between the two groups (12). In a study in Ankara, Turkey on 70 children, there was a similar report (16), in which both studies suggest that children with idiopathic-cryptogenic epilepsy should be screened for celiac disease (12,16).

In our study, the prevalence of celiac disease in epileptic patients based on seropositive antibody tissue transglutaminase was 0.04% and by positive biopsy was 0.01%, in which the prevalence of celiac disease was much less than similar studies (14,15); in addition, a significant relationship between epilepsy and celiac disease was not observed. Of course, perhaps this discrepancy is because we examined idiopathic-cryptogenic cases, while in similar studies in Turkey only idiopathic epilepsy has been investigated (14,15).

However, in two similar studies in 2005 (Ranua et al.) and 2009 (Giordano et al. in Italy) no significant difference was noted in the prevalence of celiac disease between epileptic patients and healthy children (17,18). In a study by Luostarinem and colleagues in 2001 on 199 patients with epilepsy celiac disease was proved only in five children (0.02%) (19), indicating that the prevalence of celiac disease in these epileptic patients was similar with our study results.

Yet, studies on the effect of gluten-free diet for controlling seizure are not enough; some studies show that if this regime is started early, dramatic improvement will encounter in the patients' seizure status (20). On the other hand, neurologic complications, especially uncontrolled epilepsy and brain calcification occur only in patients who are not on the gluten-free diet (1). Clear remission in gluten ataxia has been reported in cases on very precise gluten-free diet (21). Italian researchers have stated that patients with untreated celiac suffered from hypoperfusion of at least one area of the brain due to vascular injury (22) this problem has been reported especially in the syndrome with calcification of the occipital lobe of the brain and epilepsy, and in one patient it was noted as cortical vascular anomaly (23).

In conclusion, If symptomatic celiac disease is considered as the etiology for refractory epilepsy using gluten-free diet increases the ability to control epilepsy, particularly in refractory cases (1,8,13,20).

Finally, according to study results in our center, we may suggest that in patients with idiopathic epilepsy, a celiac disease survey is not required. Despite this result, we recommend a broad study in different regions of Iran to compare the prevalence of celiac disease and the related factors on the general population and epileptic patients.

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