ORIGINAL PAPERS

Adv Clin Exp Med 2016, **25**, 4, 751–754
DOI: 10.17219/acem/43585

ISSN 1899–5276

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Celiac Disease and Epilepsy: The Effect of Gluten-Free Diet on Seizure Control

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Determining the true prevalence of celiac disease (CD) is difficult because of many atypical symptoms. Although CD primarily affects the gastrointestinal tract, patients may be asymptomatic or have extra intestinal symptoms.
Objectives. In this study, we assessed the prevalence of CD in patients with epilepsy and the effect of a gluten-free diet on seizure control in these patients.
Material and Methods. Patients with epilepsy in Imam Reza and Farabi Hospitals, Kermanshah, Iran, were studied. At first, the patients were screened by means of measuring the immunoglobulin A antiendomysial (IgA) antibodies. In the patients testing positive for IgA antibodies, 2–3 endoscopic small bowel biopsies were taken from the distal duodenum to confirm CD changes. People with CD received a gluten-free diet for 5 months and their seizure activity was recorded.
Results. During the study period, we studied 113 patients with epilepsy. Seven patients (6%) were diagnosed with CD. After 5 months of instituting a gluten-free diet, in 6 patients seizures were completely under control and antiepileptic drugs were discontinued. In one case, anticonvulsant drugs were reduced by half and seizures were controlled.
Conclusions. Our results showed that about 6% of epileptic patients were positive for CD. Institution of a gluten-free diet is useful for seizure control in these patients (**Adv Clin Exp Med 2016, 25, 4, 751–754**).

Key words: celiac disease, epilepsy, gluten-free diet.

Celiac disease (CD) is an immune-mediated enteropathy precipitated by the ingestion of gluten in genetically susceptible individuals [1]. CD was primarily apparent to be a pediatric disorder; however, now it is being diagnosed with increasing frequency in the adult population [2]. Determining the true prevalence is difficult because of the many patients presenting atypical symptoms [1]. Although CD primarily affects the gastrointestinal tract, patients may be asymptomatic or have extra intestinal symptoms [2]. Studies have shown that neurologic or psychiatric dysfunctions develop in up to 22% of patients with CD [3], and about 57% of people with neurologic or psychiatric dysfunction with unknown origin are positive for anti-gliadin antibodies [4] and many patients with neurological symptoms with unknown origin were established to have gluten sensitivity [1]. Cerebellar ataxia, epilepsy, neuropathy, dementia, depression and multifocal leucoencephalopathy have all been described in CD [4–6]. Neurological symptoms like epilepsy have been associated with CD but the cause is unclear, while an immune-mediated mechanism has been often suggested. Obviously, seizure activity was better managed in the patients who received the earliest gluten-free diets. In a few studies, alleviation of seizure activity symptoms has been often successfully attained with a gluten-free diet [7, 8].

The purposes of this study, therefore, were (i) to assess the prevalence of CD in epileptic patients and (ii) to determine whether symptoms of seizure

activity have subsided as a result of administrating a gluten-free diet.

Material and Methods

This prospective study was approved by the Kermanshah University of Medical Sciences (KUMS) ethics committee and was conducted from April 2012 to February 2014. Epileptic patients who were referred to the neurology clinic at Imam Reza and Farabi hospitals, Kermanshah, were recruited to participate in this study. All participants provided written informed consent in compliance with the KUMS review board.

The definitions of seizure type and epilepsy syndrome were *as per* the International League Against Epilepsy (ILAE) that was proposed by Nordli (2005) [9]. Patients with acute and remote symptomatic seizures, evidence of abnormality in neuroimaging as the cause of seizures, neurodegenerative or metabolic disorders with epilepsy, non-epileptic attack disorders, patients with symptomatic epilepsy due to brain damage, cerebral malformation, metabolic disorders, degenerative diseases, tumors, and hemorrhage were not included in the study. All patients were asymptomatic from gastrointestinal disturbances.

Measuring immunoglobulin A antiendomysial antibodies by indirect immunofluorescence was used to screen for CD. In the patients testing positive for IgA antibodies, 2–3 endoscopic small bowel biopsies were taken from the distal duodenum. CD has been simplified and was based on the demonstration of immunoglobulin A antiendomysial antibodies and an intestinal biopsy showing pathologic changes typical of CD.

Following the diagnosis of CD, the patients began a strict gluten-free diet for five months, while the antiepileptic treatment was maintained. About 3 months after commencing the gluten-free diet, intestinal biopsies were repeated and improved intestinal pathological changes were recorded to determine the patient's response to treatment. The diagnosis was confirmed when the antiendomysial antibodies disappeared during the gluten-free diet. The patient's seizure activity was recorded during the course of five months.

Statistical Analysis

Data is presented as mean ± SD or frequency and percent, using descriptive statistics. To compare the difference in the IgA levels of CD-positive and -negative cases Student's t-test was used. A value of $p < 0.05$ was considered statistically significant.

Results

One hundred thirteen epileptic patients (48% male) between the age of 35.7 ± 14.9 (range 16–42 years) who were referred to the neurology clinic of KUMS were evaluated during the study period.

The mean age of epilepsy onset was 16.2 ± ± 10.6 years (range 1–36 years). Of the 113 patients, 46% had generalized tonic-clonic seizures, 38% complex partial, and 16% complex partial with secondary generalization. Twenty-five patients had one attack per week (22.1%), sixty-two patients had one attack per month (54.9%) and twenty six patients had once in three months (23%).

After laboratory assessments, seven patients (4 males and 3 females) tested positive for the endomysial antibody (three patients had one attack per week and four patients had one attack per month). All of these IgA positive patients were also positive for CD in intestinal biopsies. Mean serum level of IgA in CD patients was 2.8 ± 1.1 μg/mL and in CD negative patients was 0.4 ± 0.2 μg/mL ($p < 0.0001$). After five months of instituting a gluten-free diet, seizure activity in six of seven patients was successfully controlled and anticonvulsant drugs were discontinued. Seizure activity in one case was controlled by half a dose of Carbamazepine (200 mg orally twice a day). Characteristics of epileptic patients with CD are shown in Table 1.

Discussion

The relationship of CD and neurological complications has been observed during the past decades [8]. Neurological complications seen in patients with CD may be the prime presentation of this disease. Therefore, CD may easily go unrecognized and untreated.

Several studies have suggested an association between CD and epilepsy [10, 11]. The prevalence of celiac cases in people with epilepsy ranges from approximately 0.8–6% [8, 12]. In our study we found 7/113 patients (6%) diagnosed with CD, which is comparable with previous studies. Also, in Isfahan, Iran, Emami et al. found that 4 of 108 epileptic patients (3.7%) were positive for IgA anti t-TG [13].

The mechanisms underlying the association between CD and epilepsy are unknown, but several mechanisms are suggested. CD is an immune-mediated condition associated with sensitivity to a gluten diet. On the other hand, many immunological abnormalities have been labeled in patients with epilepsy. Studies have shown that epilepsy

Table 1. Characteristics of epileptic patients with celiac disease

Patient	Sex	Age (year)	Age at diagnosis of epilepsy (year)	Epilepsy type	Anticonvulsant drugs	Seizure control
1	male	26	21	complex partial	carbamazepine (400 mg/d)	seizure-free
2	male	29	17	generalized tonic-clonic	valproate (500 mg/d) phenytoin (400 mg/d)	seizure-free
3	female	32	18	generalized tonic-clonic	carbamazepine (400 mg/d) phenytoin (300 mg/d)	seizure-free
4	male	38	14	generalized tonic-clonic	carbamazepine (400 mg/d) phenytoin (300 mg/d)	seizure-free
5	female	25	9	generalized tonic-clonic	carbamazepine (800 mg/d) phenytoin (300 mg/d)	controlled by carbamazepine (400 mg/d)
6	female	29	23	complex partial	carbamazepine (400 mg/d)	seizure-free
7	male	33	16	generalized tonic-clonic	valproate (500 mg/d) phenytoin (300 mg/d)	seizure-free

develops in several immune-mediated conditions such as SLE, myasthenia gravis and IgA deficiency [11, 14] Several immunoglobulin abnormalities which are described in patients with epilepsy, in part associated with anti-convulsant therapy, as well as a high prevalence of anticardiolipin and antinuclear antibodies have been seen in patients with epilepsy [11, 15]. Therefore, epilepsy in a number of patients may be due to an immune process, and the association between CD and epilepsy may be the susceptibility of immune-mediated conditions to occur together. Another suggested mechanism is that the antibodies related to CD may be themselves neurotoxic or may be a marker for a neurotoxic immunological process [6].

Furthermore, several studies have demonstrated autoantibodies such as anti-tissue transglutaminase (TTG), antiendomysium and antireticulin in epileptic patients [13, 16, 17]. Calcium and magnesium deficiency, genetic factors and drug malabsorption, oxidative stress and free radical reposition were included in other elucidations [2, 18].

According to these interpretations, there is a high suspicion that CD should be suspected in patients with epilepsy [11]. It is suggested that an epileptic patient with gastrointestinal symptoms, or with any evidence of malabsorption, should be tested for CD. Untreated CD may result in seizure control difficulty, through impaired drug absorption as well as nutrients and vitamins malabsorption [11].

As expected, in the patients with CD who adhere to a gluten-free diet, seizure activity was better managed [7]. Delay in diagnosis of CD in epilepsy patients may adversely affect the overall outcome and result in unfavorable complications. It seems that early intervention with administration of combination of a gluten-free diet with anticonvulsant treatment is useful in patients with treatment-resistant epilepsy.

Previously, some studies suggested that gluten-free diet have a lucrative effect on seizure control [11, 19, 20]. In this study, we found that seizure activity successfully controlled in six of seven patients and in one patient anticonvulsant drugs reduced to half. In a small study by Hernandez et al. on four patients with epilepsy, bilateral occipital calcifications and latent CD, it was reported that three of four patients had significant reduction of seizure frequency after going on a gluten-free diet [20]. Also, a number of case studies have reported dramatic improvement in patients with refractory epileptic seizures that treated with a gluten-free diet plus antiepileptic therapy [16, 21].

In conclusion, accumulating evidence suggests that CD is frequent in epileptic patients and it is suggested that epileptic patient with gastrointestinal symptoms are screened for CD. Administration of a combination of a gluten-free diet with anticonvulsant treatment is useful in patients with treatment-resistant epilepsy.

Acknowledgements. The authors thank the neurology clinic members and Imam Reza hospital laboratory members for their kind cooperation.

References

[1] **Siqueira Neto JI, Costa AC, Magalhães FG, Silva GS:** Neurological manifestations of celiac disease. Arq Neuropsiquiatr 2004, 62, 969–972.
[2] **Das G, Baglioni P**: Coeliac disease: Does it always present with gastrointestinal symptoms? QJM 2010, 103, 999–1000.
[3] **Briani C, Zara G, Alaedini A, Grassivaro F, Ruggero S, Toffanin E, Albergoni MP, Luca M:** Neurological complications of celiac disease and autoimmune mechanisms: A prospective study. J Neuroimmunology 2008, 195, 171–175.
[4] **Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, Davies-Jones GA, Gibson A, Jarratt JA, Kandler RH, Lobo A:** Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet 1998, 352, 1582–1585.
[5] **Chin RL, Sander HW, Brannagan TH, Green PH, Hays AP, Alaedini A, Latov N:** Celiac neuropathy. Neurology 2003, 60, 1581–1585.
[6] **Hadjivassiliou M, Gibson A, Davis-Jones GAB, Lobo JA, Stephenson TJ, Milford-Ward A:** Does cryptic gluten sensitivity play part in neurological illness? Lancet 1996, 347, 369–371.
[7] **Arroyo HA, De Rosa S, Ruggieri V, de Davila MT, Fejerman N:** Epilepsy, occipital calcifications, and oligosymptomatic celiac disease in childhood. J Child Neurol 2002, 17, 800–806.
[8] **Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL:** Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. Psychiatr Q 2012, 83, 91–102.
[9] **Nordli DR Jr:** Idiopathic generalized epilepsies recognized by the International League Against Epilepsy. Epilepsia 2005, 46, 48–56.
[10] **Fois A, Vascotto M, Di Bartolo RM, Di Marco V:** Celiac disease and epilepsy in pediatric patients. Childs Nerv Syst 1994, 10, 450–454.
[11] **Cronin CC, Jackson LM, Feighery C, Shanahan F, Abuzakouk M, Ryder DQ, Whelton M, Callaghan N:** Coeliac disease and epilepsy. QJM 1998, 91, 303–308.
[12] **Chin RL, Latov N, Green PH, Brannagan TH, 3rd, Alaedini A, Sander HW:** Neurologic complications of celiac disease. J Clin Neuromuscul Dis 2004, 5, 129–137.
[13] **Emami MH, Taheri H, Kohestani S, Chitsaz A, Etemadifar M, Karimi S, Eshagi MA, Hashemi M:** How frequent is coeliac disease among epileptic patients? J Gastrointestin Liver Dis 2008, 17, 379–382.
[14] **Aarli JA:** Immunological aspects of epilepsy. Brain Dev 1993, 15, 42–50.
[15] **Verrot D, San-Marco M, Dravet C, Genton P, Disdier P, Bolla G, Harle JR, Reynaud L:** Prevalence and signification of antinuclear and anticardiolipin antibodies in patients with epilepsy. Am J Med 1997, 103, 33–37.
[16] **Labate A, Gambardella A, Messina D:** Silent coeliac disease in patients with childhood localization related epilepsies. Epilepsia 2001, 42, 1153–1155.
[17] **Mavroudi A, Karatza E, Papastavrou T, Panteliadis C, Spriroglou K:** Successful treatment of epilepsy and coeliac disease with a gluten free diet. Pediatr Neurol 2005, 33, 292–295.
[18] **Neto JIS, Costa ACL, Magalhaes FC, Silva GS:** Neurological manifestations of coeliac disease. Arq Neuropsiquiatr 2004, 62, 969–972.
[19] **Bardella MT, Molteni N, Prampolini L, Giunta AM, Baldassarri AR, Morganti D, Bianchi PA:** Need for follow up in coeliac disease. Arch Dis Child 1994, 70, 211–213.
[20] **Hernandez MA, Colina G, Ortigosa L:** Epilepsy, cerebral calcifications and clinical or subclinical coeliac disease. Course and follow up with gluten-free diet. Seizure 1998, 7, 49–54.
[21] **Canales P, Mery VP, Larrondo FJ, Bravo FL, Godoy J:** Epilepsy and celiac disease: Favorable outcome with a gluten-free diet in a patient refractory to antiepileptic drugs. Neurologist 2006, 12, 318–321.

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Conflict of interest: None declared

Received: 10.05.2015
Revised: 1.06.2015
Accepted: 11.06.2015