How Frequent is Celiac Disease among Epileptic Patients?

Mohammad Hasan Emami[1], Hajar Taheri[2], Soheila Kohestani[1], Ahmad Chitsaz[3], Masud Etemadifar[3], Somayeh Karimi[2], Mohammad Amin Eshaghi[2], Marzieh Hashemi[2]

1) Isfahan University of Medical Sciences (IUMS) and Poursina Hakim Research Institute (PHRI); 2) IUMS and PHRI, Isfahan Medical Students Research Center; 3) Isfahan University of Medical Sciences (IUMS), Isfahan, Iran

Abstract

Background. A variety of neurological disorders have been reported in association with celiac disease (CD) including epilepsy, ataxia, neuropathy and multifocal leucoencephalopathy. The purpose of this study was to assess the prevalence of CD among epileptic patients. **Methods**. Our study population consisted of 108 consecutive unexplained epileptic patients from Epilepsy Clinics. Patients who were able to give informed consent were invited to undergo screening for CD in a gastroenterology clinic. The diagnosis of CD was determined by IgA anti-tissue transglutaminase (t-TG) antibodies and by small intestine biopsy. Histopathologic changes were interpreted according to the Marsh classification. **Results**. A total of 108 consecutive epileptic patients (72 females, 36 males) ranging from 2-64 years (mean: 23.44, SD: 12.1) were studied. Positive IgA anti t-TG were detected in 4 of 108 epileptic patients (3.7%), while the known prevalence of CD in the study area was 0.6%.The intestinal biopsy confirmed the diagnosis of CD in three patients and was interpreted as Marsh I. In the other patient, small intestinal biopsy indicated only slightly increased number of intraepithelial lymphocytes. There was a significant difference between patients with CD and without CD for two symptoms: diarrhea and aphtous lesions ($p<0.05$). **Conclusion**. Prevalence of CD was increased among patients with epilepsy of unknown etiology. It is important to investigate CD in any patient with idiopathic epilepsy even in the absence of digestive symptoms.

Key words

Coeliac disease – epilepsy – anti-tissue transglutaminase antibodies.

Received:18.06.2008 Accepted: 06.09.2008
J Gastrointestin Liver Dis
December 2008 Vol.17 No 4, 379-382
Address for correspondence: Hajar Taheri
Medical Student Research Committee,
School of Medicine, Isfahan University
of Medical Science, Isfahan, Iran.
E-mail:taheri@edc.mui.ac.ir

Introduction

Celiac disease (CD) is an immune-mediated small bowel disease that manifests in genetically susceptible individuals after exposure to ingested wheat gluten [1]. Histologically it is characterized by jejunal villous atrophy, crypts hyperplasia and increased number of intraepithelial lymphocytes [2].

The prevalence of CD differs in various countries; different studies estimate its seroprevalence to be 0.3 to 1.1% [3- 5]. This figure is probably underestimated because a number of affected individuals are asymptomatic [6].

Celiac disease has been associated with numerous immune-mediated disorders [7] including dermatitis herpetiformis [8], type I diabetes [9], IgA nephropathy [10], thyroid disease [11] and arthritis [12]. In addition, attention has recently been focused on the association of CD with neurological disorders, such as cerebellar ataxia, peripheral neuropathy, myoclonus, dementia, myelopathy, and epilepsy [13, 14]. During the last decade numerous studies have mentioned the association between CD and epilepsy [15, 16].

The prevalence of epilepsy has been suggested to be high in CD patients [17, 18]. Chapman et al reported a prevalence of epilepsy of 5% in CD patients [17]. In another study, epilepsy was observed in 5.5% of all cases of celiac sprue [19].

On the other hand, the prevalence of CD among patients with epilepsy has been less extensively studied. Cronin et al screened 177 patients with epilepsy and found 4 patients with CD (2.3%) and a prevalence of 0.4 % in control group [16]. The prevalence of CD in another study was 2.3 times higher in epileptic patients [20].

Studies have shown that a prompt diagnosis of CD might improve the evolution of the epilepsy and may improve cognitive status [21]. Starting a gluten-free diet, soon after the diagnosis, leads to progressive epilepsy control, allowing significant decrease in dosage [2, 21] or even discontinuation of anti-epileptic treatment [13].

Antigoni et al concluded that greater attention is required to the possible coexistence of CD in epileptic children. Children with various idiopathic types of epilepsy should

be screened for silent CD in order to prevent irreversible complications [22].

There are no data about this association in our country. Therefore, the purpose of this study was to assess the prevalence of CD in patients with idiopathic epilepsy.

Material and method

Our study population consisted of 108 consecutive epileptic patients who were referred by two neurologists from two separate neurological outpatient clinics between January 2006 and March 2007. Patients who were willing to give informed consent were invited to undergo screening for CD in the gastroentrology clinic (Poursina Hakim Research Institute).

We completed a valid and reliable questionnaire for each patient admitted in the study which included demographic information, basic data of digestive signs and symptoms, neurologic manifestations and type of epilepsy. Separate questionnaires were created for adults and for children.

Screening for celiac disease. IgA anti-tissue transglutaminase (t-TG) antibodies were measured as the first-level screening step in all epileptic patients by an enzyme-linked immunosorbant assay (ELISA) technique, using commercially available kits (ORG540 A, ORGENTEC Diagnostica GmbH). The microplate of t-TG was coated with a human recombinant tissue transglutaminase h(t-TG) as substrate;10 µl of serum or plasma was diluted by 1:100 and total incubation time was 60 minutes at room temprature for both tests. The upper limit of the normal range (cut-off value) for anti-t-TG IgA, as determined by the manufacturer, is 10 u/ml and the result was reported in terms of arbitary units (Au/ml), an IgA t-TG>10 Au/ml was considered positive. Also, serum Ig A antibody level was measured to rule out IgA deficiency.

Endoscopy and intestinal histopathology. All subjects showing an IgA anti-t-TG antibody value >10 u/ml (seropositive) or IgA deficient patients underwent a diagnostic gastrointestinal endoscopy with a standard 110-cm-long video endoscope, during which four biopsy specimens were obtained from the distal part of the second portion of the duodenum. The specimens were processed, stained with H&E, and studied under light microscopy. Patients found to have total, subtotal or partial small bowel villous atrophy with severe intra epithelial lymphocytosis (>30%) were considered as having CD.

Histopathology was expressed according to the Marsh classification of 1992: "infiltrative" lesions with more than 30 lymphocytes/100 epithelial cells were defined as Marsh type I, "infiltrative/hyperplastic" lesions as Marsh II and "partial subtotal villous atrophy" as type III. The latter was further divided into partial villous atrophy (Marsh IIIa), subtotal villous atrophy (Marsh IIIb), and total villous atrophy (Marsh IIIc) [23].

Statistical analysis

Statistical analysis was performed using SPSS 11.0 for Windows. Means, and standard errors (SE) of means were presented for describing variables with continuous distribution. Clinical data were analyzed by t-test (for age) and Fisher's exact test (for sex). Proportion of characteristics of CD and non-CD were compared using Chi-square test or Fisher exact test. All tests were two tailed and $p<0.05$ was considered statistically significant.

Results

A total of 108 consecutive epileptic patients (72 females, 36 males) ranging from 2-64 years (mean: 23.44, SD: 12.1) were studied.

Positive IgA anti-t-TG were detected in 4 of 108 epileptic patients (3.7%), while the known prevalence of CD in the study area was 0.6% [24].

Small intestinal biopsy was performed in the 4 patients with positive serology. The intestinal biopsy confirmed the diagnosis of CD in three patients. It was interpreted as Marsh I. In the other patient, small intestinal biopsy indicated only slightly increased levels of intraepithelial lymphocytes. In one patient, CD had been already diagnosed, but she had mild symptoms and had no history of gluten restriction. The other three patients were not suspected of having CD at the time of screening.

Intestinal histopathologic changes, IgG antigliadin antibodies, IgA antiendomysial antibodies and serum IgA level were determined in the anti-t-TG positive epileptic patients.

Immunologic and histopathologic findings of the 4 celiac patients are summarized in Table I.

Frequency of some symptoms or signs of patients with and without CD is shown in Table II. Abdominal pain was the most common symptom (33.3 %).There was a statistically significant difference between CD and non-CD patients for two symptoms: diarrhea and aphtous lesions ($p<0.05$).

Discussion

The relationship between neurologic symptoms and CD was first described by Cooke and Smith in 1966 [25]. During the last decade, a variety of neurological disorders have been reported in association with CD, and more especially with epilepsy [22, 26].

The mechanism of the association remains unknown [27]. There are many hypotheses to explain it: autoimmune mechanisms [22], malabsorption [28], hereditary and gluten toxicity (7) have been suggested as possible mechanisms.

Previous studies on the prevalence of CD among epileptic patients have reported conflicting results [29]. Gobbi et al [15] reported the association of epilepsy, occipital cerebral calcifications, and CD as a distinct syndrome. Pratesi et al [13] who screened 255 epileptic patients (119 children and 136 adults) for CD found increased prevalence of CD in this sample (2.3 times higher in epileptic patients than in control subjects). Fois et al [30] reported a frequency of CD of 1 in 87 among patients attending an Italian paediatric epilepsy clinic. Luostarinen et al [31] reported five cases of CD in 199 consecutive patients with epilepsy (2.5%), while the known

Table I. Immunologic and histopatologic findings in four epileptic patients

				Immunologic findings				
Patient	Sex	Age (yr)	Type of epilepsy	IgA/tTG (U/mL)	EMA	IgG/AGA (U/mL)	Immunoglobulin IgA (g/L)	Intestinal biopsy*
1	F	27	GTCS	57	+	65	1.2	Marsh 1
2	M	11	GMS	45	-	80	1.3	Marsh 1
3	F	31	GTCS	109	+		1.8	Marsh 1
4	M	13	GTCS	38.11	+	280	1.7	-
				IgA/tTG Negative <10 U/mL Positive >10 U/mL	EMA: (−) Or (+)	IgG/AGA Negative <12 /mL Equivocal 11-17 U/mL Positive >12 U/mL	Serum IgA level Adult:0.6-3.3 3-8 years:0.6-1.7 8-12 year: .6-2	

Abbreviations: EMA-IgA antiendomysial antibodies; GTCS-Generalized tonic-clonic seizures; GMS: Generalized myoclonic seizure IgA/tTG-IgA antitissue transglutaminase antibodies; IgG/AGA-Immunoglobulin G antigliadin antibodies; SPS-Simple partial seizures
* Intestinal biopsy: Marsh criteria [11]: infiltration of intraepithelial lymphocytes (Marsh I), increase in crypt length (Marsh II), flattening (atrophy) of the villi (Marsh III).

Table II. Frequency of some symptoms or signs of patients with and without CD

Symptoms	Celiac disease		p-value
	Positive %	Negative %	
Abdominal pain	75	31	0.1
Abdominal disconfort	50	17	0.1
Aphtous lesions	50	11	0.04
Constipation	25	30	0.6
Depression	25	30	0.6
Diarrhea	25	9	0.03
Flatulence	25	15	0.5
Malodor stool or gas	25	7	0.2
Weekness or fatigue	25	31	0.6

prevalence of CD in the study area was 0.27%. In another study, 177 teenagers and adults with various types of seizures were screened for serum antibodies for CD. Four patients (2.25%) were positive. All had small-bowel histology typical of CD. In a control group of 488 pregnant patients, two serum samples were positive (0.04%) [16].

In contrast, other studies demonstrated that the prevalence of CD-associated antibodies did not differ between patients with epilepsy and control subjects [29]. However, the prevalence of antigliadin antibodies (AGA) was higher in patients with primary generalized epilepsy when compared with the reference population. This may implicate a common genetic predisposition. Also another study has shown a strong association between CD and various neurologic manifestations, with the exception of tic disorders and marginally epileptic disorders [32]. In a study by Mäki et al [29] the prevalence of CD in patients with epilepsy (1.2%) was very similar to its prevalence in the reference population (0.9%).

In the present study, positive IgA anti-t-TG were detected in 4 of 108 epileptic patients (3.7%). The known prevalence of CD in the study area was 0. 6% [24]. Intestinal biopsy confirmed the diagnosis of CD in three patients and was indicative for CD in the other patient. Symptoms or signs of CD in three of these cases were not previously referred or observed.

The mucosal lesions and clinical gastrointestinal symptoms of CD recover on gluten-free diet [33]. However, the effect of gluten elimination on neurological manifestations is not very clear. The duration of gluten exposure may be important [34]. In support of this hypothesis, Cicarelli et al found a significant correlation between the duration of the disease preceding the diagnosis (and treatment) and the neurological findings as detected even years after the diagnosis [35, 36].

Systematic screening for CD in all epileptic patients, however, is not practical or cost-effective at the present time. Nevertheless, it seems reasonable to screen those with intractable seizures [26]. Serologic screening was suggested not only in children with partial epilepsy, but also in all patients with intractable epilepsy [13]. Celiac disease should be ruled out in the differential diagnosis of neurological dysfunction of unknown cause [29]. The long diagnostic delay of CD or poor dietary compliance may be harmful for the overall outcome and lead to severe complications.

Conclusion

According to previous studies, prevalence of celiac disease is increased in patients with epilepsy of unknown etiology. It is of vital importance to screen for celiac disease in any patient with idiopathic epilepsy even in the absence of digestive symptoms.

Conflicts of interest

Nothing to declare.

References

1. Wills AJ. The neurology and neuropathology of coeliac disease. Neuropathol Appl Neurobiol 2000; 26: 493-496.
2. Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and

Nutrition. Arch Dis Child 1990; 65: 909-911.
3. Cook HB, Burt MJ, Collett JA, Whitehead MR, Frampton CM, Chapman BA. Adult coeliac disease: prevalence and clinical significance. J Gastroenterol Hepatol 2000; 15: 1032-1036.
4. Hansson T, Dahlbom I, Rogberg S, et al. Recombinant human tissue transglutaminase for diagnosis and follow-up of childhood coeliac disease. Pediatr Res 2002; 51: 700-705.
5. Trier JS. Celiac sprue. N Engl J Med 1991; 325: 1709-1719.
6. Misra S, Ament ME. Diagnosis of coeliac sprue in 1994. Gastroenterol Clin North Am 1995; 24: 133-143.
7. Pengiran Tengah DS, Wills AJ, Holmes GK. Neurological complications of coeliac disease. Postgrad Med J 2002; 78: 393-398.
8. Weinstein WM, Brow JR, Parker F, Rubin CE. The small intestinal mucosa in dermatitis herpetiformis. II. Relationship of the small intestinal lesion to gluten. Gastroenterology 1971; 60: 362-369.
9. Collin P, Salmi J, Hallstrom O, et al. High frequency of coeliac disease in adult patients with type-I diabetes. Scand J Gastroenterol 1989; 24: 81-84.
10. Fornasieri A, Sinico RA, Maldifassi P, Bernasconi P, Vegni M, D'Amico G. IgA-antigliadin antibodies in IgA mesangial nephropathy (Berger's disease). Br Med J (Clin Res Ed) 1987; 295: 78-80.
11. Midhagen G, Jarnerot G, Kraaz W. Adult coeliac disease within a defined geographic area in Sweden. A study of prevalence and associated diseases. Scand J Gastroenterol 1988; 23: 1000-1004.
12. Lubrano E, Ciacci C, Ames PR, Mazzacca G, Oriente P, Scarpa R. The arthritis of coeliac disease: prevalence and pattern in 200 adult patients. Br J Rheumatol 1996; 35: 1314-1318.
13. Pratesi R, Gandolfi L, Martins RC, Tauil PL, Nobrega YK, Teixeira WA. Is the prevalence of celiac disease increased among epileptic patients? Arq Neuropsiquiatr 2003; 61: 330-334.
14. Boscolo S, Baldas V, Gobbi G, et al. Anti-brain but not celiac disease antibodies in Landau-Kleffner syndrome and related epilepsies. J Neuroimmunol 2005; 160: 228-232.
15. Gobbi G, Bouquet F, Greco L, et al. Coeliac disease, epilepsy, and cerebral calcifications. The Italian Working Group on Coeliac Disease and Epilepsy. Lancet 1992;340: 439-443.
16. Cronin CC, Jackson LM, Feighery C, et al. Coeliac disease and epilepsy. QJM 1998; 91: 303-308.
17. Chapman RW, Laidlow JM, Colin-Jones D, Eade OE, Smith CL. Increased prevalence of epilepsy in coeliac disease. Br Med J 1978; 2: 250-251.
18. Magaudda A, Dalla Bernardina B, De Marco P, et al. Bilateral occipital calcification, epilepsy and coeliac disease: clinical and neuroimaging features of a new syndrome. J Neurol Neurosurg Psychiatry 1993; 56: 885-889.
19. Essid M, Trabelsi K, Jerbi E, et al. Villous atrophy and idiopathic epilepsy. Tunis Med 2003; 81: 270-272.
20. Arroyo HA, De Rosa S, Ruggieri V, et al. Epilepsy, occipital calcifications, and oligosymptomatic celiac disease in childhood. J Child Neurol 2002; 17: 800-806.
21. Cernibori A, Gobbi G. Partial seizures, cerebral calcifications and celiac disease. Ital J Neurol Sci 1995; 16: 187-191.
22. Antigoni M, Xinias I, Theodouli P, et al. Increased prevalence of silent celiac disease among Greek epileptic children. Pediatr Neurol 2007; 36: 165-169.
23. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102: 330-354.
24. Shahbazkhani B, Malekzadeh R, Sotoudeh M, et al. High prevalence of coeliac disease in apparently healthy Iranian blood donors. Eur J Gastroenterol Hepatol 2003; 15: 475-478.
25. Cooke WT, Smith WT. Neurological disorders associated with adult coeliac disease. Brain 1966; 89: 683-722.
26. Mavroudi A, Karatza E, Papastavrou T, Panteliadis C, Spiroglou K. Successful treatment of epilepsy and celiac disease with a gluten-free diet. Pediatr Neurol 2005; 33: 292-295.
27. Green PH, Alaedini A, Sander HW, Brannagan TH, III, Latov N, Chin RL. Mechanisms underlying celiac disease and its neurologic manifestations. Cell Mol Life Sci 2005; 62: 791-799.
28. Peltola J, Kulmala P, Isojarvi J, et al. Autoantibodies to glutamic acid decarboxylase in patients with therapy-resistant epilepsy. Neurology 2000; 55: 46-50.
29. Ranua J, Luoma K, Auvinen A, et al. Celiac disease-related antibodies in an epilepsy cohort and matched reference population. Epilepsy Behav 2005; 6: 388-392.
30. Fois A, Vascotto M, Di Bartolo RM, Di Marco V. Celiac disease and epilepsy in pediatric patients. Childs Nerv Syst 1994; 10: 450-454.
31. Luostarinen L, Dastidar P, Collin P, et al. Association between coeliac disease, epilepsy and brain atrophy. Eur Neurol 2001; 46: 187-191.
32. Zelnik N, Pacht A, Obeid R, Lerner A. Range of neurologic disorders in patients with celiac disease. Pediatrics 2004; 113: 1672-1676.
33. Farrell RJ, Kelly CP. Celiac sprue. N Engl J Med 2002; 346: 180-188.
34. Siqueira Neto JI, Costa AC, Magalhaes FG, Silva GS. Neurological manifestations of celiac disease. Arq Neuropsiquiatr 2004; 62: 969-972.
35. Cooke WT, Smith WT. Neurological disorders associated with adult coeliac disease. Brain 1966; 89: 683-722.
36. Muller AF, Donnelly MT, Smith CM, Grundman MJ, Holmes GK, Toghill PJ. Neurological complications of celiac disease: a rare but