

How Frequent is Celiac Disease among Epileptic Patients?

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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 aphthous 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.

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

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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 gastroenterology 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 μ l of serum or plasma was diluted by 1:100 and total incubation time was 60 minutes at room temperature 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 arbitrary 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 aphthous 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

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