Celiac disease prevalence in epileptic children from Serbia

Zlatko Djurić[1], Aleksandar Nagorni[2], Bosa Jocić-Jakubi[3], Milena Dimić[3], Martin Novak[4], Radovan Milićević[5], Goran Radenković[6],

Departments of [1]Gastroenterology, [3]Neurology, [4]Neuropediatrics, [5]Immunogenetics and Molecular Biology Laboratory, Children's Hospital, [2]Clinic of Gastroenterology and Hepatology, and [6]Department of Histology and Embryology, University of Niš School of Medicine, Niš, Serbia

SUMMARY: Djurić Z, Nagorni A, Jocić-Jakubi B, Dimić M, Novak M, Milićević R, Radenković G. Celiac disease prevalence in epileptic children from Serbia. Turk J Pediatr 2012; 54: 247-250.

Celiac disease (CD) is a genetically determined autoimmune enteropathy, induced by gluten ingestion. To date, different prevalences of CD in children with epilepsy have been reported. The aim of this study was to determine CD prevalence in our patients with epilepsy, using anti-tissue transglutaminase (tTG) antibodies as a screening test.

One hundred twenty-five children (72 girls, 53 boys; age range: 2-18 years, mean age: 10.51±3.53) with idiopathic epilepsy from South East Serbia were tested for immunoglobulin (IgA) tTG antibodies. All positive patients were offered endoscopic small bowel biopsy. Biopsies were examined histopathologically in order to confirm the CD diagnosis. The control group consisted of 150 healthy children.

Three patients with epilepsy were positive for IgA tTG antibodies. In all of them, small bowel biopsy was performed, and only one was proven to have CD by histopathology (Marsh IIIa grade). The prevalence of biopsy-proven CD in children with epilepsy was not significantly higher in the study group compared to controls (0.8% vs.0.6%, p>0.05). The results of this study indicate that children with idiopathic epilepsy from our region should not be routinely tested for CD.

Key words: epilepsy, celiac disease, prevalence, Serbia.

Celiac disease (CD) is a chronic autoimmune enteropathy with a worldwide prevalence in the general population as high as 0.5-1%[1-3]. CD patients can have typical symptoms (chronic diarrhea, malabsorption), extraintestinal symptoms, or can be symptom-free. Extraintestinal clinical signs and symptoms can be diverse. Today, they are increasingly recognized to be common CD clinical manifestations. Neurological manifestations (peripheral polyneuropathy, cerebellar ataxia, myelopathy, dementia, and epilepsy) are estimated to occur in 7-10% of affected patients[4-6]. The cause of neurological manifestations in CD remains unclear. Certain vitamin deficiencies (B_6, B_{12}, folic acid), gluten toxic effects and autoimmune mechanisms can play the main etiologic roles[7-11].

The correlation between CD and epilepsy has been known for more than 30 years[12]. In the last decade, detection of tissue transglutaminase (tTG) antibodies has been proven to be a highly sensitive and specific method for CD testing in patients with epilepsy[13,14]. The clinical significance of CD screening studies in epilepsy patients is to diagnose patients with asymptomatic or atypical manifestations and to prevent serious, long-term CD-related complications (iron-deficient anemia, short stature, osteoporosis, infertility, gastrointestinal malignancy, etc.). Early gluten-free diet (GFD) introduction may have a protective role for other autoimmune disorders in CD patients[15]. Additionally, in some patients, the beneficial effects of GFD have been reported as better seizure control and decrease in antiepileptic medications[16,17].

Celiac disease, epilepsy and cerebral calcifications (CEC) syndrome is a rare clinical condition found predominantly in Italy, Spain

and Argentina[18,19]. Some authors suggest that CEC syndrome might develop later in life in children with CD and epilepsy, and that early introduction of a GFD can diminish the risk of developing cerebral calcifications[20].

The aim of this study was to determine CD prevalence in a sample of Serbian children with idiopathic epilepsy using immunoglobulin (Ig) A tTG antibodies as a screening test.

Material and Methods

Epileptic Patients and Control Group

The investigation involved 125 epileptic children and adolescents (72 girls, 53 boys; age range: 2-18 years, mean age: 10.51±3.53) admitted to the University of Niš Children's Hospital or observed on an outpatient basis in the period from October 2004 to December 2007. Of the 125 patients with idiopathic epilepsy, 48% had generalized tonic-clonic seizures, 34% had simple partial seizures, and 18% had complex partial seizures. Diagnosis of epileptic seizure was based on the revised criteria of the International League Against Epilepsy[21]. Patients with symptomatic epilepsy due to brain damage, cerebral malformation, metabolic disorders, degenerative diseases, tumors, and hemorrhage were not included in the study. Electroencephalography and brain imaging (magnetic resonance imaging [MRI], computerized tomography [CT], or both) were done in all patients. Any coexisting disease and presence of CD symptoms (chronic diarrhea, steatorrhea, anemia, failure to thrive, and failure to grow) were noted for each patient.

To determine CD prevalence in the population of healthy children and adolescents, a control group of 150 healthy children and adolescents (88 girls, 62 boys; age range: 2-18 years; mean age: 10.78±5.22) were selected. The control group participants were defined as healthy on the basis of their medical records and routine physical examinations. Participants from both the study and control groups were from the southeast part of Serbia.

Written informed consent was obtained from the children's parents, and the study was approved by the Ethics Committee of the University of Niš, School of Medicine.

Laboratory Tests

The first step in our study was serum IgA measurement by radioimmunodiffusion in all epileptic patients. Reference values were (g/L): for children aged 6 months to 2 years (0.14-1.08), 2-6 years (0.23-1.90), 6-12 years (0.29-2.70), 12-16 years (0.81-2.32), and ≥16 years (0.60-3.80).

All children with normal serum IgA were tested for IgA tTG antibodies on enzyme-linked immunosorbent assay (ELISA). The kit with antigen substrate based on the human recombinant tTG (Euroimmun, Lübeck, Germany) was used. According to the manufacturer's recommendation, the cut-off was 20 RU (relative units)/ml.

Endoscopy and Histopathology

Celiac disease (CD) was confirmed in accordance with the recommendations of the European Society for Gastroenterology, Hepatology and Nutrition[22]. In the patients with positive titer of IgA antibodies, four endoscopic small bowel biopsies were taken from the distal duodenum using an endoscope Olympus GIF P20. Pathologists unaware of serology results interpreted the biopsies according to the modified Marsh criteria[23,24].

Statistical Analysis

To compare the difference in the number of CD-positive and -negative cases in the study and control groups, Fisher's exact test was used. A value of $p<0.05$ was considered statistically significant.

Written informed consent was obtained from the children's parents, and the study was approved by the Ethics Committee of the University of Niš, School of Medicine.

Results

Laboratory Results

The total serum IgA was normal in all 125 epileptic patients. All of them were tested for IgA tTG antibodies, of whom 3 (2.4%) were found to be positive (Table I). Since serum IgA was found to be normal in all 150 control group participants, they were all tested for IgA tTG antibodies. On testing, only 1 (0.8%) was found to be positive.

Table I. Clinical Characteristics of Epileptic Children Testing Positive for IgA tTG Antibody

Patient	Sex	Age of patients (years)	Type of epilepsy	Other clinical signs and symptoms	IgA tTG antibody titer (RU/ml)	Histopathology
1.	F	8	Benign partial (rolandic)	-	121.7	Marsh IIIa
2.	F	6	Benign partial (rolandic)	-	66.2	Marsh 0
3.	F	13	Generalized (tonic-clonic)	-	38.0	Marsh 0

IgA tTG: Immunoglobulin A tissue transglutaminase. RU/ml: Relative units/ml. F: Female.

Endoscopy and Histopathology

The parents of the 3 IgA tTG-positive study group patients gave their written consent for the endoscopic small bowel biopsy. In 1 patient (0.6%), CD was confirmed on small bowel mucosal histopathology (Marsh grade IIIa atrophy) (Table I). In 2 patients, histopathology was normal (Marsh 0). After initial testing, they both tested negative for IgA tTG in the three subsequent years. In 1 IgA tTG-positive control group participant (0.8%), small bowel biopsy was done, and histopathology indicated Marsh grade IIIa small bowel mucosal impairment.

Symptoms and Clinical Signs

None of the three patients with positive serology had clinical signs of CD. One patient, an eight-year-old girl with positive serology and histopathology, had benign partial (rolandic) epilepsy, which was well controlled with sodium valproate. One of her relatives also had CD.

Statistical Analysis

No significant statistical difference was found in the number of biopsy-proven CD patients between the study (0.8%) and control groups (0.6%) ($p>0.05$).

Discussion

In the last decade, numerous screening studies made in Europe reported an increased CD prevalence (2.1-9.1%) in children with epilepsy[25-28]. The highest CD prevalence (9.1%) in epileptic children was published recently by Turkish authors[26]. Since a significant number of tTG antibody-positive patients (5 out of 12) in that study were not confirmed by small bowel biopsy, the CD prevalence in that group of Turkish epileptic children could have been even higher. In contrast, Italian authors indicated that the prevalence of CD in epileptic children (1.8%) is not significantly different from that in the general pediatric population (1.0%)[28]. In that regard, one new meta-analysis showed that the relative risk of CD in children with epilepsy is 1.7% (95% confidence interval 1.4-2.1)[20].

The difference in the CD prevalence in the epileptic children obtained in the different studies can be attributed not only to genetics, food gluten quantity and difference in serologic tests, but also to differences in the study groups in terms of sample size and types of epilepsy.

The CD prevalence in the general population and in epileptic patients in Serbia has yet to be determined. Only one epidemiological study on CD in Serbia has been published, reporting that the incidence of CD in Vojvodina (Serbian province) in the period 1980-1993 was 1 per 1715 live births[29]. The drawback of this study, however, was the fact that serological screening of children and adults was not done. The incidence was estimated only on the basis of clinically apparent cases in children diagnosed on small bowel biopsy.

In our study, three epileptic children tested positive for IgA tTG antibodies (Table I). None of them had symptoms suggesting CD. One six-year-old girl with benign partial epilepsy, positive serology and CD proven on small bowel biopsy was put on GFD. Potential CD was suspected in two epileptic patients with positive serology and negative histopathology, and they were followed for the next three years since it is known that, in time, patients with potential CD can develop true CD with typical histopathology. However, tTG antibodies finding was negative in both of those subjects in the three subsequent years. They were also CD symptom-free in the same period. On this

basis, potential CD was excluded and their follow-up was discontinued. Their positive IgA tTG antibody tests in the beginning of the study were considered as false-positives.

In accordance with data published in the literature, CD is more commonly associated with partial epilepsy with occipital paroxysms (25). Our study limitation is the absence of cases with this type of epilepsy. Their inclusion might have changed our study results.

In conclusion, the prevalence of CD in children with idiopathic epilepsy was not significantly different from that in a healthy pediatric population in southeast Serbia. The results of this study indicate that children with idiopathic epilepsy from our region should not be tested routinely for CD.

REFERENCES

1. Mearin ML, Ivarsson A, Dickey W. Coeliac disease: is it time for mass screening? Best Pract Res Clin Gastroenterol 2005; 19: 441-452.
2. Carlsson AK, Axelsson IE, Borulf SK, Bredberg AC, Ivarsson SA. Serological screening for celiac disease in healthy 2.5-year-old children in Sweden. Pediatrics 2001; 107: 42-45.
3. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003; 163: 286-292.
4. Luostarinen L, Pirttila T, Collin P. Coeliac disease presenting with neurological disorders. Eur Neurol 1999; 42: 132-135.
5. Hadjivassiliou M, Grunewald RA, Davis-Jones GA. Gluten sensitivity as a neurological illness. J Neurol Neurosurg Psychiatry 2002; 72: 560-563.
6. Djuric Z, Kamenov B, Katic V. Celiac disease manifested by polyneuropathy and swollen ankles. World J Gastroenterol 2007; 14: 2636-2638.
7. Morris JS, Ajdukiewicz AB, Read AE. Neurological disorders and adult coeliac disease. Gut 1970; 11: 549-554.
8. Banerji NK, Hurwitz LJ. Neurological manifestations in adult steatorrhoea (probable gluten enteropathy). J Neurol Sci 1971; 14: 125-141.
9. Harding AE, Muller DP, Thomas PK, Willison HJ. Spinocerebellar degeneration secondary to chronic intestinal malabsorption: a vitamin E deficiency syndrome. Ann Neurol 1982; 12: 419-424.
10. Chin RL, Sander HW, Brannagan TH, et al. Celiac neuropathy. Neurology 2003; 60: 1581-1585.
11. Karponay-Szabó IR, Halttunen T, Szalai T, et al. In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. Gut 2004; 53: 641-648.
12. Chapman RW, Laidlow JM, Colin-Jones O, Eade OE, Smith CL. Increased prevalence of epilepsy in celiac disease. Br Med J 1978; 22: 250-251.
13. Antigoni M, Xinias I, Thedouli P, et al. Increased prevalence of silent celiac disease among Greek epileptic children. Pediatr Neurol 2007; 36: 165-169.
14. Dalgic B, Dursun I, Serdaroglu A, Dursun A. Latent and potential celiac disease in epileptic Turkish children. J Child Neurol 2006; 21: 6-7.
15. Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP study group for autoimmune disorders in celiac disease. Gastroenterology 1999; 117: 297-303.
16. 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.
17. Canales P, Mery VP, Larrondo FJ, Bravo FL, Godoy J. Epilepsy and celiac disease. Favourable outcome with a gluten-free diet in a patient refractory to antiepileptic drugs. Neurologist 2006; 12: 318-321.
18. Gobbi G. Celiac disease, epilepsy and cerebral calcifications. Brain Dev 2005; 27: 189-200.
19. Martinez-Bermejo A, Polanco I, Royo A, et al. A study of Gobbi syndrome in Spanish population. Rev Neurol 1999; 29: 105-110.
20. Lionetti E, Francavilla R, Pavone P, et al. The neurology of coeliac disease in childhood: what is the evidence? A systematic review and meta analysis. Dev Med Child Neurol 2010; 52: 700-707.
21. Dreifuss FE. Classification of epileptic seizures. In: Engel J Jr, Pedley TA (eds). Epilepsy: A Comprehensive Textbook. Philadelphia: Lippincott-Raven; 1998: 517-524.
22. Walker-Smith JA, Guandalini S, Schmitz J, Shmerling DH, Visakorpi JK. Report of Working Group of European Society for Pediatric Gastroenterology, Hepatology and Nutrition. Revised criteria for diagnosis of coeliac disease. Arch Dis Child 1990; 65: 909-911.
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. Oberhuber G. Histopathology of celiac disease. Biomed Pharmacother 2000; 54: 368-372.
25. Labate A, Gambarella A, Messina D, et al. Silent celiac disease in patients with childhood localization-related epilepsies. Epilepsia 2001; 42: 1153-1155.
26. Ertekin V, Selimoglu MA, Tan H, Konak M. Prevalence of celiac disease in sample of Turkish children with epilepsy. Pediatr Neurol 2010; 42: 380.
27. Fois A, Vascotto M, Di Bartolo RM, et al. Celiac disease and epilepsy in pediatric patients. Childs Nerv Syst 1994; 10: 450-454.
28. Giordano L, Valotti M, Bosetti A, Accorsi P, Caimi L, Imberti L. Celiac disease related antibodies in Italian children with epilepsy. Pediatr Neurol 2009; 41: 34-36.
29. Vukavić T, Beselin S, Berger G, et al. The incidence of coeliac disease in children born on the territory of Voyvodina (Serbia): coeliac disease register 1980-1993. Arch Gastroenterohepatol 1995; 14: 1-3.