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INCREASED TISSUE TRANSGLUTAMINASE LEVELS ARE ASSOCIATED WITH INCREASED EPILEPTIFORM ACTIVITY IN ELECTROENCEPHALOGRAPHY AMONG PATIENTS WITH CELIAC DISEASE

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ABSTRACT - ***Background*** **-** Celiac disease is an autoimmune systemic disorder in genetically predisposed individuals precipitated by gluten ingestion. ***Objective*** **-** In this study, we aimed to determine asymptomatic spike-and-wave findings on electroencephalography in children with celiac disease. ***Methods*** **-** A total of 175 children with the diagnosis of celiac disease (study group) and 99 age- and sex-matched healthy children as controls (control group) were included in the study. In order to determine the effects of gluten free diet on laboratory and electroencephalography findings, the celiac group is further subdivided into two as newly-diagnosed and formerly-diagnosed patients. Medical histories of all children and laboratory findings were all recorded and neurologic statuses were evaluated. All patients underwent a sleep and awake electroencephalography. ***Results*** **-** Among 175 celiac disease patients included in the study, 43 were newly diagnosed while 132 were formerly-diagnosed patients. In electroencephalography evaluation of patients the epileptiform activity was determined in 4 (9.3%) of newly diagnosed and in 2 (1.5%) of formerly diagnosed patients; on the other hand the epileptiform activity was present in only 1 (1.0%) of control cases. There was a statistically significant difference between groups in regards to the presence of epileptiform activity in electroencephalography. Pearson correlation analysis revealed that epileptiform activity in both sleep and awake electroencephalography were positively correlated with tissue transglutaminase levels (P=0.014 and P=0.019, respectively). ***Conclusion*** **-** We have determined an increased epileptiform activity frequency among newly-diagnosed celiac disease patients compared with formerly-diagnosed celiac disease patients and control cases. Moreover the tissue transglutaminase levels were also correlated with the presence of epileptiform activity in electroencephalography. Among newly diagnosed celiac disease patients, clinicians should be aware of this association and be alert about any neurological symptoms.

HEADINGS - Celiac disease. Electroencephalography. Transglutaminases. Epilepsy. Child.

INTRODUCTION

Celiac disease (CD) is an autoimmune systemic disorder in genetically predisposed individuals precipitated by gluten ingestion with intestinal and extra-intestinal manifestations. It is caused by an inflammatory reaction to gliadin, a gluten protein found in some cereals, including wheat [14, 23]. A gluten-free diet (GFD) leads to a clinical improvement, while the suspension of a GFD results in a relapse of the clinical symptoms and sometimes biopsy features in intestine[9, 25]. The overall prevalence of CD ranges from 0.4% to 1.3% in children[1, 4, 27]. In recent years, the number of children with atypical CD has increased relatively to typical ones, most probably due to the increased awareness of the atypical symptoms of the disease. Atypical involvement includes dermatological, hematological, endocrinologic, neurological, and skeletal system findings[13].

Several neurological and psychiatric disorders have also been widely described in CD patients; interestingly in 7% of newly-diagnosed cases, such disorders have been reported to precede the diagnosis of CD. These disorders include migraine, febrile seizures, encephalopathy, chorea, brainstem dysfunction, autism, myopathy, neuropathy with

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positive antiganglioside antibodies, cerebellar ataxia, dementia, white matter lesions, depression and, lastly, epilepsy, which is the most frequent disorder associated with CD[6, 15].

There is some evidence suggesting a relationship between CD and epilepsy[3, 17]. However, to the best of our knowledge, there is not any study investigating asymptomatic spike-and-wave findings on electroencephalography (EEG) in children with CD. In this study, we aimed to determine the prevalence of epileptiform activity in EEG among children with CD.

METHODS

This study was carried out in Gaziantep University Hospital, Pediatrics Department, Subdivisions of Pediatric Neurology and Gastroenterology from June 2011 to February 2012. A total of 175 children with the diagnosis of CD (study group) and 99 age- and sex-matched healthy children as controls (control group) were included in the study. None of the CD patients had a history of seizures, convulsions, or diagnosis of epilepsy. The control cases had no gastrointestinal and neurologic disorders and admitted to the Gaziantep University Hospital, Department of Pediatrics for various reasons other than neurological ones. The most common diagnosis of control cases at hospital was upper respiratory system infections, followed by urinary tract infections and acute gastroenteritis.

In order to determine the effects of GFD on laboratory and EEG findings, the celiac group was further subdivided into two as newly-diagnosed and formerly-diagnosed patients. Newly-diagnosed patients were not taking an effective GFD but formerly-diagnosed patients were under effective GFD for at least six months. The data of all newly-diagnosed, formerly-diagnosed patients and control group cases were compared.

Medical histories of all children including age, gender, symptoms, weight, height, physical examination results and laboratory findings including hemoglobin, mean corpuscular volume, platelet count, serum iron, folic acid, vitamin B12 levels were all recorded and neurologic statuses were evaluated. All patients underwent an EEG in Pediatric Neurology EEG Laboratory with a 32 channeled EEG (Nihon Nihon Kohden-9100 Neofax). Incongruous patients were sedated with choralhydrate 50 mg/kg before the EEG. The EEG results were evaluated by the same Pediatric Neurologist who was blinded to celiac status of enrolled patients.

This study was approved by the Ethics Committee of the University of Gaziantep, and written informed consent was obtained from the parents of all children.

Statistical analysis

Statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS for Windows version 16.0, Chicago, IL, USA) program. Chi-square test was used to compare CD and control groups regarding gender. The descriptive data was given as means ± standard deviation (SD). Pearson Chi-square test was used to compare categorical variables. In the comparison of the groups, one way-ANOVA analysis of variance was used in variables with normal distribution, while the Post Hoc test (Tukey-HSD) was used as a secondary test in multiple comparisons. The Kruskal-Wallis test was used for analysis of variables which were not normally distributed, and the Mann-Whitney U test was used in cases showing a statistical difference between the groups. Pearson correlation analysis was performed to determine the correlation of tissue transglutaminase levels and sleeping and awake EEG findings. In the statistical evaluations, a P value of <0.05 was regarded as significant.

RESULTS

The study consisted of 274 subjects; 175 patients with CD and 99 subjects served as controls. The mean ages of the patients with CD and the control subjects were 10.6±3.8 years (34.3% male, 65.7% female) and 10.7±3.5 years (45.4% male, 54.6% female), respectively. There was not any statistically significant difference between the ages and genders of CD and control groups ($P>0.05$) (Table 1). Neurologic examination and intellectual level were normal in all cases.

TABLE 1. General characteristics and laboratory findings of study participants

	Control (n=99)	Newly-diagnosed CD (n=43)	Formerly-diagnosed CD (n=132)	*P*
Gender (F/M)	54/45	27/16	76/56	0.86
Hemoglobin (g/dL)	13.2 ± 1	12 ± 1	12.8 ± 1	0.001
MCV (fL)	82.1 ± 4	77.4 ± 8	80.8 ± 5	0.001
Trombocyte (µL x 1000)	312 ± 66	320 ± 100	300 ± 70	0.69
Serum iron (µg/dL)	68 ± 32	52.8 ± 33	67.1 ± 33	0.02
Serum iron binding capacity	314 ± 64	336.6 ± 80	317.1 ± 63	0.71
Vitamin B12 (pg/mL)	318.4 ± 140	353.8 ± 116	362.5 ± 153	0.61
Folic acid (ng/mL)	9.9 ± 2	7.8 ± 2	9.8 ± 3	0.001

The data are expressed as mean ± standard deviation. F: female, M: male, MCV: mean corpuscular volume.

In CD group the most frequent symptom was failure to thrive (66.3%, n=116) followed by abdominal pain (65.7%, n=115). The other symptoms were chronic diarrhea (46.3%, n=81), abdominal distention (44.6%, n=78), headache (31.4%, n=55), pallor (28%, n=49), vomiting (25.7%, n=45), anorexia (21.1%, n=37), weakness (20%, n=35), and constipation (18.9%, n=33) (Table 2). Short stature as the sole primary symptom was reportedin only 26 (14.8%) patients.

Some clinical characteristics and laboratory results of participants are summarized in Table 1. The differences were all statistically significant regarding hemoglobin, mean corpuscular volume and serum iron levels when the newly-diagnosed CD patients were compared with both formerly-diagnosed CD patients and control subjects (Table 1). Though there was not any statistically significant difference in terms of vitamin B12 levels among groups; folic acid levels were statistically significantly lower in newly-diagnosed CD group than formerly-diagnosed CD and control groups (Table 1).

There was a statistically significant difference between the formerly-diagnosed and newly- diagnosed CD patients in regards to the tTG levels (P=0.001).

Among 175 CD patients, 43 were newly diagnosed while 132 were formerly-diagnosed patients. In EEG evaluation of patients; the epileptiform activity was determined in 4 (9.3%) of new diagnosed and in two (1.5%) of older diagnosed patients (Figure 1-3); on the other hand the epileptiform activity was present in only one (1.0%) of control cases. There was a statistically significant difference between newly-diagnosed and formerly-diagnosed CD patients (P=0.036) and newly-diagnosed CD patients and control cases (P=0.01) in regards to the presence of epileptiform activity in EEG.

In four of the six CD patients who had epileptiform activity in EEG, the epileptiform activity was occipital lobe in origin. The pathological examinations of duodenal biopsy of all these six patients resulted as total villous atrophy (Marsh type 3). All seven patients (six CD, one control) who had epileptiform activity in EEG had normal serum vitamin B12 and folic acid levels (Table 2). The total serum IgA was normal in all patients. In cranial imaging of six patients with CD who had epileptiform activity in EEG, with cranial computed tomography and magnetic resonance imaging; no abnormalities were reported.

TABLE 2. General characteristics of patients with abnormal EEG

Case	Age (Years)	Gender	Group	Sleeping EEG	Awake EEG	Background activity	Spike wave activity in EEG	Vitamin B12 pg/mL	Folic acid ng/mL
1	7	Female	Newly-diagnosed CD	-	+	Alpha-Teta	T3-T5 and P3-O1	436	13.4
2	5.5	Female	Newly-diagnosed CD	-	+	Alpha	O1-O2	298	8.6
3	7	Male	Formerly diagnosed CD	+	+	Alpha	T5-O1 and P3	274	10.6
4	6	Female	Formerly diagnosed CD	-	+	Alpha-Teta	Bilateral Synchrone	341	13.2
5	4	Female	Newly-diagnosed CD	+	-	-	P3-T5	422	9.3
6	5	Female	Newly-diagnosed CD	+	+	Alpha-Teta	O1-T5	403	11.4
7	6	Male	Control	-	+	Alpha	T5-O1 and P3-4	326	14.4

EEG: Electroencephalogram; CD: Celiac disease; Sleeping EEG means: awake EEG means.

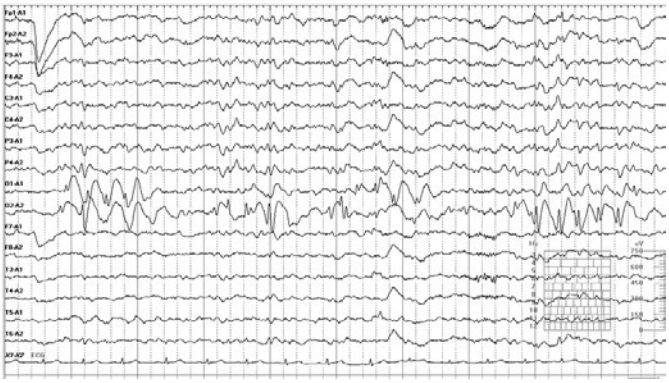

FIGURE 1. Bioccipital spike-waves on unipolar montage in Case 1

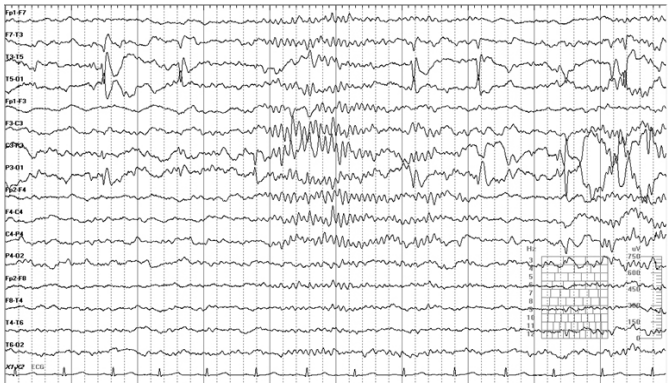

FIGURE 2. Sharp-wave activity of left occipito-temporally and parietally focuses in Case 3

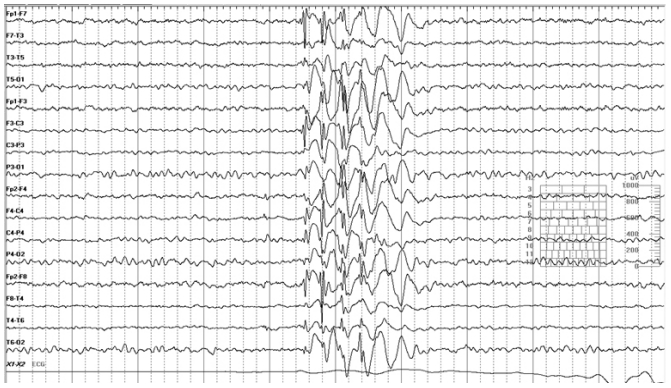

FIGURE 3. Bilaterally synchronous high-amplituted spike-wave complexes on bipolar montage in Case 4

Interestingly, in one of the patients in newly-diagnosed CD group, there were very frequent epileptic activities in EEG (Figure 3). This patient did not have any seizures or seizure history. For a detailed evaluation, 24-hour video EEG documentation was performed but no seizures were recorded.

In this study, though seven cases had epileptiform activities in EEG, only one of them with the high frequency activity was medicated. Since high frequency epileptiform activity may result in some mental changes, valproate was prescribed to the patient. After 3 months of treatment with GFD and valproate, EEG of the patient was normal. All other five CD cases having epileptiform activities in EEG were followed under GFD and in 6th and 12th months' controls, their EEG was normal. The two cases in formerly-diagnosed CD group were re-educated about the GFD. The only case in control group with the epileptiform activity was also followed for 12 months and his EEG returned spontaneously to normal in 6th month control. There was no convulsion or seizure in any of the patients in that period of time.

Interestingly, Pearson correlation analysis revealed that epileptiform activity in both sleep and awaken EEG were positively correlated with tissue transglutaminase levels (P=0.014 and P=0.019, respectively).

DISCUSSION

In this study we have investigated the prevalence of epileptiform activities in EEG among patients with celiac disease and determined that as high as 9.6% of newly-diagnosed CD patients had epileptiform activities in EEG. This prevalence was established as 1.5% in formerly-diagnosed patients under GFD and 1% in control group and the difference was statistically significant between newly-diagnosed patients and other two groups regarding the prevalence of epileptiform activities in EEG. Moreover, tissue transglutaminase levels were correlated with the epileptiform activities in EEG. Though the exact association of celiac disease with epilepsy is not clear; this finding is very important since celiac disease is a treatable disease and elucidating common pathways in epilepsy and celiac disease may help to improve the outcome of these patients.

The association of celiac disease with neurological diseases is obviously known. It has been reported that, 6%-10% of patients with celiac disease also have a neurological disease such as ataxia, myopathy or peripheric neuropathy[13, 15]. The most commonly related neurological disease with the celiac disease is the epilepsy. Epilepsy prevalence among celiac disease patients is reported as 1.2%-5%[6]. On the other hand the prevalence of CD among patients with epilepsy is reported to be around 3% to 6%[3, 17].

Celiac disease is commonly accompanied by ataxia and peripheral neuropathy in adults but accompanied by epilepsy in children. Labete et al. have reported that partial epilepsy cases especially with occipital paroxysms should be evaluated for celiac disease. Dalgic et al. have reported that Ig A tTG positivity was present in 4.7% while biopsy proven celiac disease was present in 1.17% of 170 epilepsy patients. In 2010, Lionetti et al.[16] published a meta-analysis of the few evidence-based data available on these disorders in children. He had determined that the relative risk (RR) of epilepsy in individuals with CD was 2.1 and RR of CD in individuals with epilepsy was 1.7 compared with the general population. The clinical spectrum of epilepsy associated with CD ranges from focal to generalized forms. In the vast majority of these patients, wakefulness EEGs revealed focal abnormalities (spike waves or slow waves), mainly localized in one or both occipital regions[16, 26].

The pathogenesis of neurological manifestations in CD is multifactorial. Such manifestations were initially assumed to be secondary to vitamin deficiencies (foliate, vitamins B12, D and E) due to malabsorbtion since vitamins are known to exert neurotrophic and neuroprotective effects. However, it was determined that neurological manifestations may even arise without enteropathy and malabsorbtion[10, 20]. Therefore, immune mechanisms were suspected to be involved in the pathogenesis of these disorders. This hypothesis was supported by the evidence of lymphocytic infiltration in the central and peripheral nervous systems, as well as by the presence of serum antineuronal antibodies, in CD patients with neurological complications[12]. Antibodies against Purkinje cells and anti-ganglioside antibodies have sometimes been found in CD patients with neurological diseases[11, 21]. The determination of anti-neuronal and anti-ganglioside antibodies in tissue level among CD patients with neurological symptoms and clinical improvement with the loss of antibodies in some cases reveal that neurological defects may be associated with the antibody mediated autoimmune mechanisms. However, the role of these antibodies in the pathogenesis of neurological dysfunction is not yet fully understood and it is still unclear whether CD contributes to the pathogenesis of these disorders or represents an epiphenomenon. Similarly in our study, in newly-diagnosed patients with high positivity rates for auto-antibodies, significantly increased prevalence of epileptiform activities in EEG supports the data that immune system and tTG antibodies may play a central role in association of celiac disease with epilepsy. Moreover, in our study there was not any statistically significant difference between groups regarding the vitamin B12 levels. This data also supports that tTG positivity rather than vitamin B12 levels may play a central role in association of CD with epileptiform activity.

Parisi et al.[19] and Cakir et al.[2] also studied on the subclinical neurological findings in children with CD and reported increased neurological activities in CD cases. In this study we have determined a correlation of tissue transglutaminase levels with the epileptiform activities. In literature, tTG has been reported to play an active role in excitatory amino acid-induced neuronal cell death in an animal study[24]. In a cohort investigating the prevalence of celiac antibodies among patients with epilepsy, only IgA antigliadin antibodies were determined to be more common in epileptic cases but not tTg antibodies. However, in this study the antibody levels were not studied, only the prevalence was reported[22]. Similar with our results; Emami et al.[5] reported that 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%. Defining the exact relationship between tTG levels and epilepsy is essential since it may be helpful in clinical practice to determine the CD patients who are at risk for epileptiform findings. Larger studies are warranted about this topic.

The togetherness of epilepsy, cerebral calcifications and celiac disease was calledas CEC syndrome[6]. Gobbi et al. investigated 43 patients with epilepsy and determined that 29 of them had the CEC syndrome[7]. Among those 29 patients 19 had partial seizures with occipital region involvement while five had generalized seizures. They reported that some patients with CEC syndrome were having seizures resistant to anti-epileptic drugs but gluten-free diet was decreasing or completely stopping their seizures. Since early diagnosis and treatment of celiac disease may change the outcome of these children, pediatricians and pediatric neurologists should be aware of this relationship. On the other hand in a study of Kieslich et al.[12], white matter changes were reported to be more common and more typical than occipital calcifications in CD patients. These changes have been suggested to be due to vasculitis associated ischemia or inflammation coupled demyelination. In cranial imaging of six CD patients with epileptiform activities in our study, no abnormalities have been reported. Similarly in many reports from our country, central nervous system involvement is reported as rare, while it has been reported as common in some European countries, like Italy. This difference may be due to some genetic and environmental factors[7, 18].

Occipital calcifications, occipital lobe seizures and common occipital findings in EEG suggest that occipital lobe involvement is common in celiac disease. It is known that occipital lobe is preferably affected in some metabolic conditions like hypoglycemia and hypoxia. Moreover in histopathological evaluations, occipital lobe has a thinner structure than the other lobes. These factors may result in more susceptibility of this lobe to the antibodies against gliadin. In our study, in four of six CD patients with epileptiform activities; these activities were occipital-lobe in origin. Especially histopathological studies are warranted to explain the concern of celiac disease with occipital lobe.

Of course our study has some limitations. First of all, this study reports the results of a selected, small group of CD patients and does not represent the overall prevalence of epileptiform activities among CD patients. However, very high prevalence of epileptiform activities in newly-diagnosed CD group should alert the clinicians. Secondly, since we do not know the exact mechanisms, we only can speculate about the reasons of this association. Nevertheless, histopathological and molecular studies may help to elucidate the exact causes.

In conclusion; we have determined an increased epileptiform activity prevalence among newly-diagnosed CD patients compared with formerly-diagnosed CD patients and control cases. Moreover the tissue transglutaminase levels were also correlated with the presence of epileptiform activity in EEG. Clinicians should be aware of this association and should be alert about neurological symptoms. On the other hand, celiac disease is a treatable disease but should be suspected especially among patients with convulsions resistant to drugs. Since the early and effective treatment of epilepsy is very important for the life quality and overall outcome of the patients; this relationship should also be kept in mind. Histopathological and molecular studies are warranted to elucidate the association of CD with epilepsy.

Author's contributions

Işıkay S, and Hızlı Ş found the subject and patients; they also wrote the manuscript. Çoşkun S and Yılmaz K helped in finding patients and writing manuscript.

Işıkay S, Hızlı S, Çoşkun S, Yılmaz K. Aumento dos níveis da transglutaminase tecidual está associada ao aumento da atividade epileptiforme em eletroencefalografia entre os pacientes com doença celíaca. Arq Gastroenterol. 2015,52(4):xxx.

RESUMO - ***Contexto*** **-** A doença celíaca é uma doença sistêmica auto-imune em indivíduos geneticamente predispostos, precipitada pela ingestão de glúten. ***Objetivo*** **-** Neste estudo, tivemos como objetivo determinar achados de picos e onda assintomáticos na eletroencefalografia de crianças com doença celíaca. ***Métodos*** **-** Foi incluído um total de 175 crianças com o diagnóstico de doença celíaca (grupo de estudo) com idade e sexo correspondentes a 99 crianças saudáveis como controles (grupo controle) com o fim de determinar os efeitos da dieta livre de glúten nos resultados laboratoriais e na eletroencefalografia. O grupo de doença celíaca é subdividido em dois, com pacientes recém diagnosticados e anteriormente diagnosticados. Foram registrados históricos médicos e resultados laboratoriais de todas as crianças e foram avaliados os estados neurológicos. Todos os pacientes foram submetidos a um eletroencefalografia em sono e acordado. ***Resultados*** **-** Dos 175 pacientes com doença celíaca incluídos no estudo, 43 foram recém diagnosticados, enquanto 132 foram diagnosticados anteriormente. Na avaliação de eletroencefalografia dos pacientes a atividade epileptiforme foi determinada em 4 (9,3%) de recém diagnosticados e em 2 (1,5%) dos pacientes anteriormente diagnosticados; por outro lado, a atividade epileptiforme estava presente em apenas 1 (1,0%) dos casos de controle. Houve uma diferença estatisticamente significativa entre os grupos no que diz respeito à presença de atividade epileptiforme em eletroencefalografia. Análise de correlação de Pearson revelou que atividade epileptiforme na eletroencefalografia tanto no sono como na vigília foram positivamente correlacionados com níveis de transglutaminase tecidual (P=0,014 e P=0,019, respectivamente). ***Conclusão*** **-** Determinamos uma frequência de atividade epileptiforme aumentada entre pacientes recém diagnosticados com doença celíaca em comparação com pacientes anteriormente diagnosticados e casos de controle. Além disso, os níveis de transglutaminase tecidual também foram correlacionados com a presença de atividade epileptiforme na eletroencefalografia. Os clínicos devem estar cientes dessa associação e alertas sobre algum sintoma neurológico entre pacientes recentemente diagnosticados de doença celíaca.

DESCRITORES - Doença celíaca. Eletroencefalografia. Transglutaminases. Epilepsia. Criança.

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