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Celiac Disease and Associated Neurological Conditions

Çölyak Hastalığı ve Eşlik Eden Nörolojik Durumlar

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ABSTRACT

Objective: Celiac disease has been associated with many neurological disorders. In this report, we discuss 16 patients with both celiac disease and neurological symptoms and evaluate the overall neurological features of celiac disease in the light of the current literature to emphasize the neurological aspects of celiac disease.

Material and Methods: The medical records of all patients diagnosed with celiac disease between 2010 and 2012 were reviewed.

Results: Nine of these 16 cases were female while seven were male with a mean age of 10.34±3.76 years (5-16 years). The reported neurological problems of these 16 children with celiac disease were epilepsy (n=10), mental retardation (n=9), ataxia (n=3), neuropathy (n=1), headache (n=2), febrile seizure (n=1), and neurofibromatosis type 1 (plus headache) (n=1).

Conclusion: Celiac disease may accompany many different neurological conditions. These disorders can share some symptoms such as associated anemia, short stature, and chronic gastrointestinal complaints and the diagnosis of celiac disease may be delayed among patients with neurological disease.

Key Words: Celiac disease, Child, Neurological disease, Epilepsy, Neuropathy

ÖZET

Amaç: Çölyak hastalığı bir çok nörolojik hastalık ile ilişkilendirilmiştir. Bu çalışmada, Çölyak hastalığı ve eşlik eden nörolojik semptomları olan 16 farklı hastayı sunuyoruz. Bu yazıda, Çölyak hastalığının nörolojik yüzüne dikkat çekmek için güncel literatür ışığında Çölyak hastalığının genel nörolojik özelliklerini tartışmayı amaçladık.

Gereç ve Yöntemler: Hastanemizde 2010-2012 yılları arasında Çölyak hastalığı tanısı almış tüm hastaların tıbbi kayıtları geriye dönük olarak incelendi.

Bulgular: Onaltı olgunun dokuzu kız iken yedisi erkek olup yaş ortalamaları 10.34±3.76 yıl idi (5-16 yıl). Çölyak hastalığı olan bu 16 çocukta nörolojik problem olarak epilepsi (n=10), mental retardasyon (n=9), ataksi (n=3), nöropati (n=1), baş ağrısı (n=2), febril konvülziyon (n=1) ve nörofibromatoz tip 1 (n=1) rapor edildi.

Sonuç: Çölyak hastalığı birçok farklı nörolojik duruma eşlik edebilir. Anemi, boy kısalığı ve kronik gastrointestinal semptomlar nörolojik hastalığı olan hastalarda maskelenebilir ve çölyak hastalığı tanısını geçiktirebilir.

Anahtar Sözcükler: Çölyak hastalığı, Çocuk, Nörolojik hastalık, Epilepsi, Nöropati

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune disease seen in predisposed individuals and is associated with gluten-containing cereals such as wheat, rye and barley. Celiac disease has also been associated with many neurological disorders including cerebellar ataxia, polyneuropathy, headache, and epilepsy (1,2). Down syndrome, Turner syndrome, neurofibromatosis (NF), cerebral palsy (CP) and central nervous system (CNS) abnormalities are the other neurological conditions associated with CD (3). In this article, we present 16 different CD patients with neurological symptoms and discuss the overall neurological features of CD in the light of the current literature to emphasize the neurological aspects of CD.

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MATERIAL and METHODS

The medical records of 186 patients diagnosed with CD between January 2010 and December 2012 at the Department of Pediatric Gastroenterology, Gaziantep University, Turkey were evaluated and 16 patients with accompanying neurological disease were determined. The overall data of these 16 patients were investigated. Data extracted from the medical records included year of diagnosis, demographic features, growth parameters, sign and symptoms, complete blood count, liver function tests, serum levels of IgA and IgA anti-tissue transglutaminase antibodies, indication for biopsy, and degree of histopathological injury on samples obtained by upper gastrointestinal endoscopy.

The Gaziantep University Faculty of Medicine Ethics Committee approved the study and the study was then performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Additionally, informed consent was obtained from the parents of all children.

STATISTICAL ANALYSIS

Simple statistical analyses were performed with SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL). The parametric data were presented as arithmetic means ± standard deviation (SD) and non-parametric data were reported as median (minimum-maximum). The Kolmogorov-Smirnov test was used for the descriptive statistics of continuous and restricted variables.

RESULTS

The data of 16 CD cases with accompanying neurological disease were evaluated. Nine of those 16 cases were female while seven were male with a mean age of 10.34±3.76 years (5-16 years). The symptoms of the patients were seizure (n= 11), dizziness (n= 3), failure to thrive (n= 3), headache (n= 2), tingling in the hands and feet (n= 1) and mental retardation (n=9). On physical examination, short stature (n=6), pallor on skin and conjunctiva (n=6), Down syndrome stigma (n=1), ataxia and other cerebellar findings (n=3) and signs of NF-1 (n=1) were present. The reported neurological problems of these 16 children with CD were epilepsy (n=10), mental retardation (n=9), chronic ataxia (n=3), neuropathy (n=1), headache (n=2), simple febrile seizure (n=1), and neurofibromatosis type 1 (plus headache) (n=1).

There were 10 children diagnosed with epilepsy (seven females, three males). Among those 10 children, the epilepsy was idiopathic generalized in four, occipital lobe epilepsy in four and temporal lobe epilepsy in two. All four cases with occipital lobe epilepsy were having childhood epilepsy with occipital paroxysms (CEOP) but only two of them were symptomatic. All cases with CEOP had mental retardation and one of them also had attention deficit hyperactivity disorder (ADHD). Moreover one of the cases diagnosed with epilepsy was also diagnosed with febrile convulsion. In 10 of the children diagnosed with epilepsy, electroencephalography (EEG) showed generalized (n=4), occipital (n=4) (Figure 1), and temporal (n=2) sharp-wave activities. Only the case diagnosed with febrile convulsion and epilepsy had normal EEG. The patients diagnosed with epilepsy were under strict gluten-free diet (GFD) for at least two years. In this period of time, convulsion control had been achieved in all cases after starting GFD; four cases were continuing their anti-epileptic medications while anti-epileptic medications were discontinued in six cases after the complete achievement of convulsion control. Diazepam prophylaxis was advised to the newly diagnosed case with febrile convulsion.

Three patients were ataxic. One patient had cerebellar vermis agenesis and cerebellar hypoplasia; one had neuropathy; and one patient had isolated ataxia with normal brain imaging. The clinical syndrome consisted of stance and gait ataxia in all patients, limb ataxia in two of them, and nystagmus and tremor in one of three patients. After a strict GFD, the case with neuropathy was completely ameliorated on follow- up while the patient with isolated ataxia was cured partially. The signs and symptoms of the patient with cerebellar hypoplasia were still ongoing under GFD.

In two patients, the headache fulfilled the criteria for migraine (4). One of these patients was also diagnosed with NF-1. After starting strict GFD, cyproheptadine treatment has been discontinued in one of the cases. Other case was under topiramate prophylaxis for 6 months and again after starting a GFD, his treatment had also been discontinued.

In this study, there was only one patient diagnosed with Down syndrome. Laboratory evaluations revealed that six cases had iron deficiency anemia. All other biochemical tests including liver function tests, kidney function tests, thyroid hormones and electrolyte levels were normal. None of the children had vitamin B12, vitamin E, folic acid, or IgA deficiencies.

Brain computed tomography and magnetic resonance imaging studies were normal in 13 of these 16 children. There were abnormalities in three cases. The first case, a 14-year-old child with chronic ataxia, exhibited gliosis in the left occipital lobe, which was interpreted as perinatal ischemic injuries. In the second case, a 5-year-old girl with ataxia, cerebellar vermis agenesis and cerebellar hypoplasia were present on brain MRI. The third case had NF-1 and exhibited unidentified bright objects in the globus pallidus, internal capsule, thalamus, cerebellum, and brain stem regions on T2-weighted images.

DISCUSSION

The association of CD, a multisystemic autoimmune disease,

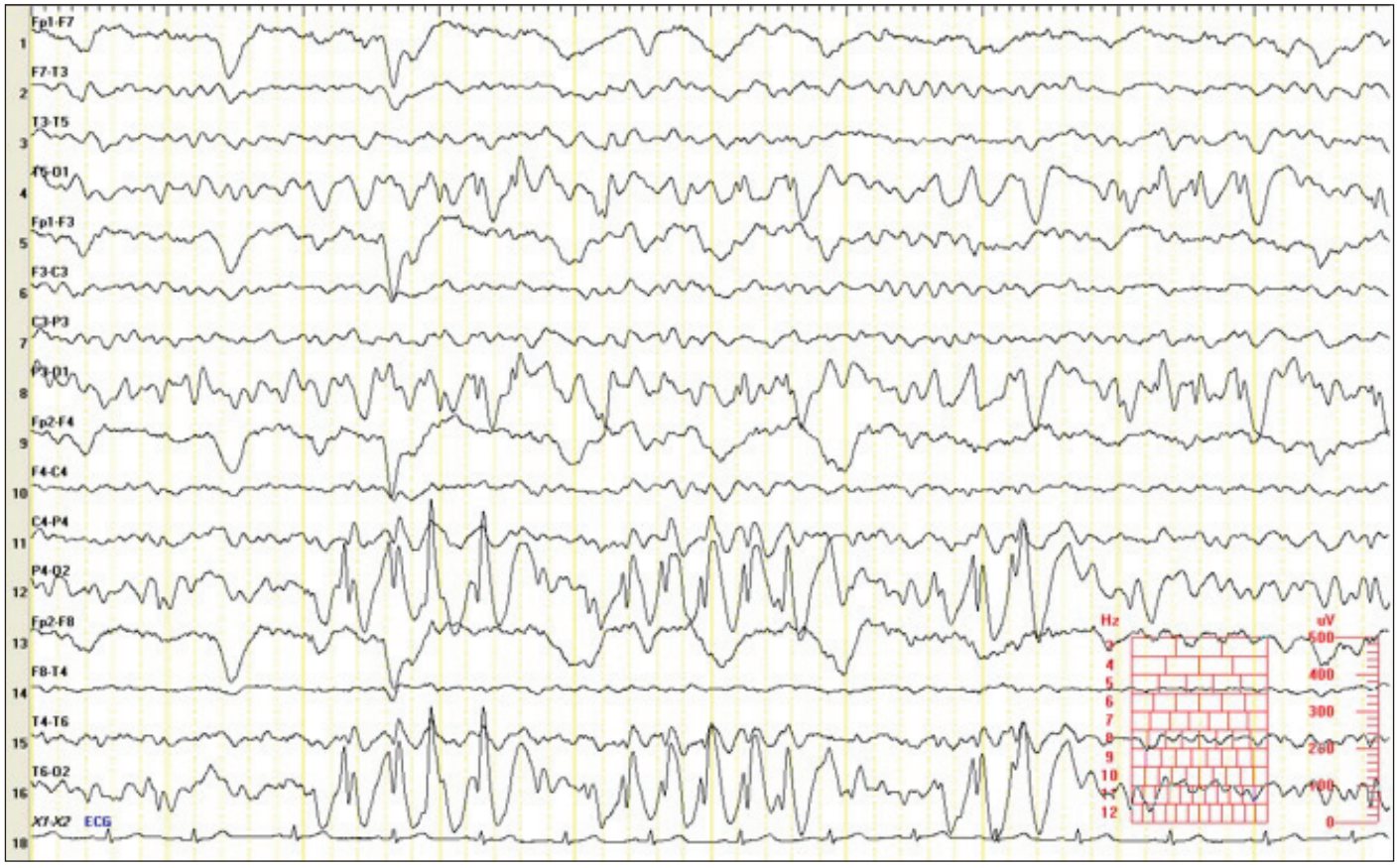

Figure 1: The EEG shows interictal epileptiform discharges of bilateral occipital spike and slow wave complexes, with right predominance.

with neurological involvement has been known for years but still carries many mysteries. We have estimated that 16 (8.6%) of 186 CD patients had an accompanying neurological disease, most commonly epilepsy, in this study.

The overall prevalence of CD is reported as 1:115 in Turkish children (5). There are various ratios for the presence of neurological manifestations in CD in the literature. Finelli et al (6) reported that 10% of patients with CD develop neurological complications. Ruggieri et al. (2) stated that 15 (1.79%) of 835 patients with CD had a neuro-psychiatric disorder. In general. neurological manifestations including epilepsy, dementia, peripheral neuropathy and cerebellar ataxia are estimated to occur in 7-22.5% of CD cases (3,7,8).

The association of CD with epilepsy, ataxia and peripheral neuropathy is obviously known. Nevertheless the cause of these associations has not been clearly understood yet. It has been suggested that these neurological disorders observed in CD may be caused by antibodies against gluten, immune complexes and/or direct neurotoxicity (9). Suggested autoimmune mechanisms concentrate on vasculitis and vitamin deficiencies. Identification of antitumoral and antiganglioside antibodies in celiac patients with neurological disorders, and clinical improvements with antibody loss in some cases by an early establishment of gluten-free diet support that neurologic disorders may be caused by antibody-mediated autoimmune mechanisms (10-12). Accordingly, antibodies against gliadin may cause production of similar antibodies against brain tissue, therefore leading to neurotoxicity. However, antibodies against brain tissue could not be shown in previous studies. Pratesi et al. (10) showed the formation of antibodies against brain blood vessels via the immune fluorescence method. Hadjivassiliou et al. (11) reported that neurological symptoms could appear due to direct neurotoxic effects of gliadin without CD development.

The most common neurological disease associated with CD is epilepsy, as in our report. The epilepsy prevalence among CD patients is reported as 1.2-5% (13). On the other hand, the prevalence of CD among patients with epilepsy is reported to be around 3% to 6% (14,15). Furthermore, Labate et al. (16) have reported that as high as 8% of CPEO patients have CD. The epilepsy cases in our report were mostly occipital or generalized idiopathic in type.

Occipital calcifications and focal white matter changes are observed in central nervous system images of CD patients. Gobbi et al. (17), defined the association of epilepsy, occipital calcifications and celiac disease as the CEC syndrome, and reported that 61% of these cases had occipital epilepsy in their series. Kieslich et al. (18) reported that white matter changes may be more common and more typical than occipital

calcifications. In our series, central nervous system images of three patients was pathological but occipital calcification was not determined in any of the cases.

ADHD was also present in one of the patients with epilepsy. In a study of Güngör et al. (19), the incidence of CD among ADHD patients was similar with the control group and the screening of ADHD patients for CD was not proposed.

Ataxia in CD is thought to develop due to the gluten-associated immunologic response in the central and peripheral nervous system. Lymphocytic infiltration in the cerebellum results in the loss of Purkinje cells and this in turn causes ataxia clinically. Hadjivassiliou et al. (3) have found increased antigliadin antibody levels among patients with sporadic ataxia. It has been determined that a long time after a strict GFD the clinical picture resolves among those ataxic patients. In a recent, interesting study, Guan et al. (20) measured serum levels of anti-gliadin, anti-transglutaminase 2 (TG2), and anti-transglutaminase 6 (TG6) antibodies in 125 patients with ataxia and 51 healthy controls, and determined that the serum concentrations of these antibodies were elevated in ataxic patients but the increase was not statistically significant. However, they determined that TG6-IgA serum levels were significantly higher in sporadic ataxia as compared to those in healthy controls. These results also provide evidence for gluten ataxia (20). There were three cases that presented with ataxia in our report. In the first case, ataxia was due to cerebellar hypoplasia. In the second case the cranial imaging was normal and the ataxia findings were diminished after GFD but not completely resolved. The third case was admitted with imbalance in walking and failure to thrive and there was also accompanying neuropathy.

Peripheral neuropathy has been observed frequently in patients with established CD. The neuropathy may be of the axonal or demyelinating type. In general, neuropathy findings heal completely with a GFD. Vrethem et al. (21) determined slightly more frequent elevated levels of IgA-AGA as well as the anti-tTG and EMA in patients with CIAP (4%) compared to 2.5% in 1866 healthy blood donors. Of course this is a small study to determine an etiological association but may be important to show that these autoantibodies may have a role in polyneuropathy. In our case, neurophysiological assessment was relevant with mild, demyelinating type peripheral polyneuropathy. After the diagnosis of CD, GFD has been started and the control electroneurography was normal at 1st year follow-up in this case.

There was one patient in our report with cerebellar vermis agenesis and cerebellar hypoplasia. Though cerebellar anomalies have been reported to be a cause of chronic ataxia, there is no reported co-existence in the literature to the best of our knowledge. Although there is no common pathogenesis between CD and cerebral palsy (CP), some common problems such as short stature, neuromotor developmental delay, feeding problems and anemia are frequently observed in both diseases. Clinical and laboratory findings of CP may dim out the signs of CD. Stenberg et al. (22, 23) have studied the association between CP and CD in children and did not find any correlation. Although the weight and height of the CP cases were at lower percentiles in our study, there was no sign of malnutrition.

NF-1 is an autosomal dominant neuro-cutaneous disease with the involvement of many systems including the skin and the gastrointestinal and neurological systems. Biagi et al. (24) reported the first co-existence of CD with NF-1 in the literature in a 39-year-old male patient. There was only one case in our study having both NF-1 and CD. Mental retardation is reported in 3-8% of cases with NF-1 and a mild mental retardation was also present in our case.

There were two cases with migraine type headache in our study. The first one also had a diagnosis of NF-1. Gabrielli et al. (25) evaluated 90 patients with a diagnosis of migraine and determined CD in 4 (4.4%) of them. Moreover, it has been reported that the headache attacks of patients with the diagnosis of migraine and co-existing CD diminish with GFD. Dimitrova et al. (26) analyzed 502 subjects: 188 with CD, 111 with inflammatory bowel disease, 25 with gluten sensitivity, and 178 controls. In multivariate logistic regression, CD subjects had a significantly higher prevalence of migraine headache compared with controls (26). Interestingly, no correlation between years on gluten-free diet and migraine severity was determined in that study. On the other hand Inaloo et al. (27) determined that the prevalence of CD was not higher in patients with migraine compared with the control group. In our report, both cases were medicated for a short time for prophylaxis and the headache attacks terminated after GFD during their follow-up.

There was only one patient with Down syndrome in our study. Since CD frequency is six times higher among patients with Down syndrome (22), all cases it is recommended to evaluate all cases for CD even if they have no gastrointestinal system symptom.

The most common extra-intestinal laboratory finding in CD is iron deficiency anemia (IDA) and 12-69% of CD cases have been reported to have IDA at diagnosis (28). The prevalence of CD among patients with IDA and resistant anemia has been determined as 5.8% and 20%, respectively (29). On the other hand, IDA cases are known to be susceptible to febrile convulsions (30). Kieslich et al. (12) reported two febrile convulsion cases in their study on 75 CD patients. Ruggieri et al. (2) reported only three cases of febrile convulsions among 835 CD cases. In our study, there was one patient with febrile convulsion. He also had IDA at diagnosis.

CONCLUSION

Celiac disease may accompany many different neurological conditions. Gluten sensitivity may result in many neurological pictures in CD patients and all cases should be evaluated very carefully for an additional neurological disorder. The main treat-

ment of CD, lifelong GFD, obviously diminishes complications including neurological disorders. Clinicians should be aware of the association of CD with neurological disorders.

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