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Should Children Diagnosed with Cerebral Calcification be Screened for Celiac Disease?

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ABSTRACT:

Should children diagnosed with cerebral calcification be screened for celiac disease?

Objective: In this study, we aimed to examine the prevalence and relationship of celiac disease (CD) in children with cerebral calcifications (CC).

Material and Methods: Children with cerebral calcifications were screened for celiac disease using the anti-tissue transglutaminase IgA antibody.

Results: A total of 129 children with CC (75 boys, 54 girls; age: 6 months to 16 years) were evaluated. Control group consisted of 223 healthy children. The prevalence of CD was significantly higher in patients with CC than control subjects (p=0.01). In three patients pathological examination of duodenal biopsy resulted as total villous atrophy. All three patients had both iron deficiency anemia and short stature problem. Although, no calcification in occipital lobe was detected in computed tomography of these three patients, there were nonspecific calcifications in choroid plexus and pineal gland localizations.

Conclusion: According to results from our study, prevalence of celiac disease being low in patients with intracerebral calcifications suggested that there is not a strong correlation between development of calcification and celiac disease. It suggested that occurrence of calcification in choroid plexus and/or pineal gland might be related to celiac disease.

Keywords: Celiac disease, cerebral calcification, child

ÖZET:

Serebral kalsifikasyon tanısı alan hastalar çölyak hastalığı açısından araştırılmalı mı?

Amaç: Bu çalışmada Çölyak hastalığı ve serebral kalsifikasyon arasındaki ilişki ve prevalansı saptamayı amaçladık.

Gereç ve Yöntemler: Serebral kalsifikasyonu olan çocuklar çölyak hastalığı yönünden anti-doku transglutaminaz IgA kullanılarak tarandı.

Bulgular: Toplamda 129 serebral kalsifikasyonu olan hasta (6 ay-16 yaş arası 75 erkek ve 54 kız) tetkik edildi. Kontrol grubu 223 sağlıklı çocuktan oluşmaktaydı. Çölyak hastalığı olan hastalarda serebral kalsifikasyon anlamlı olarak yüksek bulundu (p=0.01). Üç hastanın duodenal biyopsisinde total villus atrofisi saptandı. Bu hastalarda demir eksikliği anemisi ve boy kısalığı mevcuttu. Bu hastalarda oksipital lobda kalsifikasyon saptanmadı. Koroid pleksus ve pineal glandda nonspesifik kalsifikasyonlar saptandı.

Sonuç: Çalışmamızın sonuçlarına göre, intrakranial kalsifikasyonun çölyak hastalarında az miktarda olması intrakranial kalsifikasyon ve çölyak hastalığı arasında güçlü bir birliktelik olmadığını gösterdi. Pineal gland ve koroid pleksusta kalsifikasyonun olması Çölyak hastalığı ile ilişkili olabilir.

Anahtar kelimeler: Çölyak hastalığı, serebral kalsifikasyon, çocuk

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INTRODUCTION

Intracerebral calcifications are pathologies that develop as a result of accumulation of calcium and various minerals in brain parenchyma. They are usually incidentally detected in computed tomography (CT) scans of the brain. These calcifications may develop primarily or secondarily. They are observed most prevalently in idiopathic, familial, calcium and parathormone metabolism disorders and also, might rarely be seen in celiac disease (CD) (1,2).

Celiac disease, also called gluten-sensitive enteropathy, is an autoimmune inflammatory condition resulting in malabsorption (3). Typical manifestations of CD include steatorrhea, flatulence, bulky stool, and weight loss or complications of severe malnutrition such as anemia and metabolic disorder. On the other hand the incidence of neurological manifestations related to celiac disease has been estimated to be 6-10% (5). The neurological manifestations of CD include ataxia, peripheral neuropathy, epilepsy, cognitive disorders, dementia, tremor, myelopathy, neuropathy, brainstem encephalitis, progressive leukoencephalopathy, vasculitis, occipital calcification, anxiety/depression, and myoclonic syndrome (6).

In recent times, coexistence of cerebral calcification, epilepsy and CD has been designated as CEC syndrome. This syndrome is especially prevalent in Italy, Argentina and Spain; and it has been stated that racial, genetic and environmental factors take part in its development. These calcifications occurring in CEC syndrome are especially bilateral, sub-cortical, roughly symmetrical or asymmetrical, occipital calcifications, with the absence of contrast enhancement, and in the absence of brain atrophy (7).

With the advances in imaging technologies, cerebral calcifications determined in CT incidentally is increasing day by day. It is important to define the clinical importance of these calcifications in those patients. In this study, we aimed to examine the prevalence and relationship of celiac disease in children with cerebral calcifications (CC).

METHODS

Patients and Control Group

A total of 129 children with CC were studied over a period of one year (January 2012–December 2013) in Pediatric Neurology Department of Kahramanmaraş University Hospital, Kahramanmaras, Turkey. Children up to the age of 18 years who had a CT scan for any reasons during the study and who were detected with calcifications in brain parenchyma were included in the study. Patients who were diagnosed with previous infection and/or metabolic diseases were excluded from the study.

The control group consisted of 223 healthy children with minor cranial trauma (130 males and 93 females, aged 0.5-16, mean 10.58±3.24 years) who were examined in the pediatric outpatient clinic. Medical histories of children in the control group were recorded, and their neurological status was evaluated.

All patients were evaluated by a pediatric neurology specialist. Routine hemogram, blood biochemistry, iron parameters, vitamin B12 and folic acid levels were studied. Also, all subjects were screened with anti-tissue transglutaminase IgA (tTG) antibody for CD. All patients were CT scanned in axial plan and radiological images were evaluated by a radiologist. Subjects were grouped according to the localization of calcification.

The study was approved by the Ethics Committee at Gaziantep University Faculty of Medicine. Informed consent was obtained from the parents of all children. Subjects with confirmed positive tTG antibody were offered an endoscopic small intestinal biopsy. Biopsy specimens were assessed according to a modified Marsh classification (8). The 1989 classification of epilepsy by the International League against Epilepsy (ILAE) was used for diagnostic classification of epileptic patients (9). The biopsy proven diagnosis was required for the exact identification of CD.

Laboratory Methods

A commercially available micro-plate enzyme-linked immunesorbent assay (Euroimmune, GmbH,

Lübeck, Germany) was used to test for IgA tTG. The threshold for a positive assay result was set at 20 RU/ml. According the ESPGHAN guideline for the diagnosis of CD, a value of 10x the upper-normal level was accepted as diagnostic (10). To confirm the diagnosis of CD, mucosal biopsy was performed endoscopically from the second part of the duodenum (Olympus GIF P230 videogastroscope, Olympus Optical Corporation, Tokyo, Japan).

Statistical Analysis

Fisher's exact test was used to compare CD prevalence and gender differences between the two groups. χ^2 and student t-test were used for group comparisons. Statistical analyses were performed with SPSS for Windows (Version 11.0; SPSS Inc., Chicago, IL). A p-value of <0.05 was considered as statistically significant.

RESULTS

The study included 129 children with CC and 223 healthy control cases. Age and gender distribution were similar in both groups. A total of 129 children with CC (75 boys, 54 girls; age range: 6 months to 16 years; mean age: 10.58±3.24 years) were evaluated. The neurological complaints of patients as the indication of CT scanning are summarized in Table-1. In computed tomography brain scans; it was determined that cerebral calcification occurs most prevalently in choroid plexus and/or pineal gland localizations (116 patients, 89%). Calcification was also observed in basal ganglions in 6 patients (4.6%), in occipital lobe in 3 patients (2.3%), in periventricular location in 1 patient and in mesencephalon in 1 patient.

Table-1: Evaluation of patients with cerebral calcification (n: 129)

Average age	**10.58±3.09**
Complaints of patients on application	
Headache (n, %)	82 (63.6%)
Seizures (n, %)	37 (28.7%)
Loss of consciousness (n, %)	7 (5.4%)
Speech impediment (n, %)	1 (0.8%)
Disturbance (n, %)	1 (%0.8)
Asymmetry of the face (n, %)	1 (0.8%)
Neurological diagnoses received by the patients	
Sinusitis (n, %)	54 (41%)
Epilepsia (n, %)	31 (24%)
Migraine (n, %)	15 (11.6%)
Upper respiratory tract infection (n, %)	8 (6.2%)
Syncope (n, %)	7 (5.4%)
Down syndrome (n, %)	4 (3.1%)
Breath-holding spell (n, %)	3 (2.3%)
Febrile convulsions (n, %)	2 (1.6%)
Pseudotumor cerebri (n, %)	2 (1.6%)
Conversion (n, %)	1 (0.8)
Mental retardation (n, %)	1 (0.8)
Cerebral palsy (n, %)	1 (0.8)
7th nerve paralysis (n, %)	1 (0.8)

The prevalence of CD was significantly higher in patients with CC than control subjects (p=0.01). Three of the all of patients with CC (2.3%, two girls and one boy, age at onset, 14, 9 and 3 years, respectively) had positive IgA tTG (320, 290 and 300 IU, respectively) (Table-2). Upper gastrointestinal endoscopy and pathological examination of duodenal biopsy resulted as total villous atrophy (Marsh type 3). Two of these patients were diagnosed with childhood epilepsy with occipital paroxysms (CEOP) and one with sinusitis. All three patients had both iron deficiency anemia and short stature problem. In addition to that, one patient with CEOP diagnosis had a sibling with a history of celiac disease diagnosis. The frequency of biopsy-proven CD was 2.3% (3/129) in children with CC. Celiac disease was detected in 6.4% (2/31) of the patients diagnosed with epilepsy. The prevalence of celiac disease in the children with CC was 2.3%. Although no calcification in the occipital lobe was detected in brain CT scans of these three patients, nonspecific calcifications were detected in choroid plexus and/or pineal gland. In right choroid plexus of the 3-year-old patient, who was the youngest of the three, an unusually large (2x1.5x2 cm) focus of calcification was detected (Hematologic and biochemical investigations including plasma levels of vitamin B12, vitamin E, and folate were normal). Following diagnosis, both patients have maintained a gluten-free dietary regimen.

There were four patients diagnosed with Down Syndrome (DS). One of these had generalized brain atrophy and punctate areas of calcification in the occipital lobe, while we detected occipital calcification in only one of the four patients diagnosed

Table-2: Summary of the 3 patients diagnosed with Celiac disesase and with detected calcifications

Case	1	2	3
Gender	Female	Female	Male
Age (years)	14	9	3
Complaints on application	Headache	Seizures	Seizures
Diagnosis	Sinusitis	Epilepsia	Epilepsia
Type of Epilepsia	*	CEOP	CEOP
Iron deficiency anemia	**	**	**
Short stature	**	**	**
Sibling with CD	*	*	**
tTG	320	290	300
Pathology	Marsh 3a	Marsh 3a	Marsh 3a
Localization of calcification	Pineal gland	Pineal gland	Choroid plexus

with DS and in three patients, we detected calcifications in choroid plexuses and/or pineal gland. No basal ganglion calcification was detected in any of them. There were three patients detected with calcifications in the occipital lobe. One of these patients was diagnosed with DS while the other two were diagnosed with epilepsy. Four of the 31 patients diagnosed with epilepsy were classified as CEOP. Two of these four patients were diagnosed with CD. In the other two, calcifications were detected in the occipital lobe.

DISCUSSION

Computed brain tomography is a highly precise method of revealing intracerebral calcifications. With its increasing use in recent years, the number of intracerebral calcifications detected is also rising. Intracerebral calcifications are etiologically divided into two groups. Primary form develops depending on familial or sporadic reasons, while development of secondary form might be due to inflammatory, tumoral, hypoxic and vascular, endocrine, toxic, metabolic, degenerative and other reasons. The most common reason of secondary intracerebral calcifications is hypoparathyroidism (1,2). Celiac disease, on the other hand, is a rare cause of intracerebral calcification. Gobbi et al. defined the association of epilepsy, cerebral calcification and celiac disease as CEC (calcification, epilepsy, celiac disease) syndrome (7). Typical CT features of CEC syndrome consist of bilaterally sub-cortical, roughly symmetrical or asymmetrical, occipital calcifications, with the absence of contrast enhancement, and in the absence of brain atrophy. In some cases additional calcifications may be encountered in the frontal region, and scattered cases of unilateral occipital calcifications are reported. Calcifications are extremely variable in size and at present no definite correlation between the extension of calcifications and the severity of disease has been demonstrated. Small or punctuate calcifications may be sometimes associated with frequent and drug-resistant seizures and/or with progressive intellectual impairment, or, on the contrary, large calcifications may be detected in patients with a benign clinical course (7,11). During our study we detected calcifications in the occipital lobe in very few patients. No CD was detected in these patients.

The cause of association between celiac disease and cerebral calcifications is not clearly understood. Suggested autoimmune mechanisms concentrate on vasculitis and vitamin deficiency. Identification of antitumoral and antiganglioside antibodies in celiac patients with neurological disorders, and clinical improvement with antibody loss in some cases by early start of gluten-free diet suggest that neurological disorders can be caused by antibody-mediated autoimmune mechanisms (7,12). Accordingly, anti-gliadin antibodies cause production of similar antibodies against brain tissue, therefore leading to neurotoxicity. However, previous studies did not show antibodies against brain tissue. Hadjivassiliou et al. reported that neurological symptoms could appear due to neurotoxic effects of gliadin without celiac disease development (13).

In our study we detected calcifications in choroid plexus and/or pineal gland in most of the patients. As the age increases so does the prevalence rate of calcification in choroid plexus. Modiac et al.

investigated choroid plexus calcification with approximately 1000 computed brain tomography scans and determined a rate of 0.5% in the first decade and 86% in the eighth decade (14). We detected punctate calcifications in choroid plexuses and pineal gland in three patients diagnosed with CD. Large areas of calcifications in choroid plexuses are very rarely observed and interestingly we detected an unusually large area of calcification in right choroid plexus in Patient 3.

Calcifications in basal ganglions are incidentally detected with an approximate rate of 0.3-0.6% and are mostly bilateral. In the ethiology of basal ganglion calcifications there are causes such as infectious diseases (TORCH, brusella, Ebstein Barr virus, tuberculosis, HIV), metabolic disorders such as hyper/hypoparathyroidism, tuberous sclerosis, systemic lupus erythematosus, autosomal recessive or dominantly inherited genetic diseases (Fahr disease, Aicardie-Goutières syndrome, Cockayne syndrome, Albright's hereditary osteodystrophy), Celiac disease, anoxia, inhalation of carbon monoxide and head trauma (2). Basal ganglia calcifications have been observed in autopsy material of 7% of children suffering from DS. Basal ganglion calcifications, a very rarely encountered finding in patients with DS, is a complication incidentally detected in 0.6% of all the patients with DS who had a computed brain tomography scan (15, 16). While we detected occipital calcification in only one of the four patients diagnosed with DS, in three patients we detected calcifications in choroid plexuses and/or pineal gland. No basal ganglion calcification was detected in any of them. A prevalence of CD in Down syndrome (DS) was reported as ranging from 4.6%-13% in many studies and it is advised that patients to be evaluated in terms of CD even though they do not have complaints of gastrointestinal system (17). Since the number of patients was small, no significant relation was determined in our study.

The most common neurological disease reported to show the coexistence with CD is epilepsy. Its prevalence varies between 0.5% and 7.2% (18,19). It is more prevalent (8%) in epilepsy cases classified as CEOP (20). In four of the 31 epilepsy patients in this study were diagnosed with CEOP and two of these were also diagnosed with CD.

The most common extraintestinal laboratory finding in CD is iron deficiency anemia and CD prevalence in these patients is 4.4% (21). Moreover, Carroccio et al. determined the prevalence of CD in adult patients with iron deficiency anemia and resistant anemia to be 5.8% and 20%, respectively. Anemia develops as a result of malabsorption of micronutrients such as iron, folic acid and/or vitamin B12 due to inflammatory interventions in the proximal portion of small intestine or as a result of loss of iron due to occult bleedings (22,23). In our study, the most common finding in patients diagnosed with CD was iron deficiency anemia. Also, one of the patients had a history of a sibling with CD. The prevalence of CD in first degree relatives of patients diagnosed with CD is high compared to the community (4.8%) and it is recommended to perform routine screenings (24). Another significant finding that we detected in our CD patients was short stature. It was detected in 8.2% of the patients diagnosed with CD (25). Therefore, iron deficiency anemia, short stature and family history in first degree-relative should be warning signs.

CONCLUSION

In this study, central imaging of patients showed nonspecific calcifications. The observation that central involvement was not reported in similar studies in Turkey but was prevalent in European counties like Italy suggests that racial and individual differences may be associated with central calcification. In our study no strong relation between nonspecific calcifications encountered in computed brain tomography scans and CD was revealed. On the other hand, CD investigation in patients with central calcifications might make sense in the presence of symptoms and findings suggesting CD. Carrying out similar studies in larger groups of patients with occipital lobe calcifications might be useful to prove the relation between CD and cerebral calcification.

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