Araştırma Makalesi – Original Article

Can Headache Be a Symptom of Celiac Disease?: A University Hospital Experience*

Baş Ağrısı Çölyak Hastalığının Belirtisi Olabilir mi?: Bir Üniversite Hastanesi Tecrübesi

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ABSTRACT

Aim: The purpose of this study was to determine the prevalence of Celiac disease in pediatric patients presenting with headache. However, little is known about the co-morbidity of Celiac disease and headache. To our knowledge, this is the first prospective pediatric study that systematically reviews this topic.

Method: Two hundred forty four patients referred to the Pediatric neurology clinic of Adıyaman University Training and Research Hospital between January 2021 and November 2022 were examined. Gender, age, type of headache, Celiac serology, and other laboratory parameters of the cases meeting the inclusion criteria were recorded. Upper gastrointestinal endoscopy was performed on patients with positive Celiac serology. Patients whose results were compatible with Celiac disease were placed on a gluten-free diet.

Results: The study group consisted of 202 patients, 123 girls (60.9%). The patients' mean age was 12.67±3.524 years. Tension-type headache was determined in 121 (59.9%) of the patient group, and migraine type in 81 (40.1%). Celiac disease was detected in 5.4%. Vitamin B12 were 211±79.1 pg/ml, ferritin 19.5±13.9 ng/mL, and vitamin D 17.6±9.86 ng/ml (n=193). Interestingly, all patients who were diagnosed with Celiac disease reported that headache complaints decreased with the diet, However, no statistically significant correlation was found between any laboratory finding and headache type.

Conclusion: Although it is still controversial whether headache is common in children with celiac disease, the results of our study showed that neurological symptoms improved after gluten-free diet in children presenting with headache and diagnosed with celiac disease. Celiac disease should be investigated in persistent headache despite pharmacological treatment.

Keywords: Celiac, Child, Migraine, Tension

ÖZ

Amaç: Bu çalışmanın amacı, baş ağrısı ile başvuran çocuk hastalarda Çölyak Hastalığı prevalansını belirlemektir. Çölyak hastalığı ve baş ağrısı birlikteliği hakkında henüz çok az şey bilinmektedir. Bildiğimiz kadarıyla bu çalışma, bu konuyu sistematik olarak gözden geçiren ilk prospektif pediatrik çalışmadır.

Metod: Ocak 2021 ve Kasım 2022 tarihleri arasında Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi Çocuk Nörolojisi kliniğine başvuran iki yüz kırk dört hasta incelendi. Çalışmaya dahil edilme kriterlerine uyan olguların cinsiyet, yaş, baş ağrısı tipi, Çölyak serolojisi ve diğer laboratuvar parametreleri kaydedildi. Çölyak serolojisi pozitif olan hastalara üst gastrointestinal endoskopi yapıldı. Sonuçları Çölyak Hastalığı ile uyumlu olan hastalara glutensiz diyet uygulandı.

Bulgular: Çalışma grubu 123'ü kız (%60.9) olmak üzere 202 hastadan oluşmaktaydı. Hastaların yaş ortalaması 12.67±3.524 yıl idi. Hasta grubunun 121'inde (%59.9) gerilim tipi, 81'inde (%40.1) migren tipi baş ağrısı saptandı. Çölyak hastalığı %5,4 oranında tespit edildi. B12 vitamini 211±79,1 pg/ml, ferritin 19,5±13,9 ng/mL ve D vitamini 17,6±9,86 ng/ml idi (n=193). İlginç bir şekilde, Çölyak Hastalığı tanısı konan tüm hastalar diyetle birlikte baş ağrısı şikayetlerinin azaldığını bildirmiş, ancak herhangi bir laboratuvar bulgusu ile baş ağrısı tipi arasında istatistiksel olarak anlamlı bir korelasyon bulunmamıştır.

Sonuç: Çölyak hastalığı olan çocuklarda baş ağrısının yaygın olup olmadığı hala tartışmalı olsa da, çalışmamızın sonuçları baş ağrısı ile başvuran ve çölyak hastalığı tanısı alan çocuklarda glutensiz diyet sonrası nörolojik semptomların düzeldiğini göstermiştir. Farmakolojik tedaviye rağmen inatçı baş ağrısında Çölyak hastalığı araştırılmalıdır.

Anahtar Kelimeler: Çölyak, Çocuk, Migren, Gerilim

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Introduction

Headache is one of the most common complaints in children and adolescents. Clinical variability in children of different ages can cause difficulty in applying standard headache diagnostic criteria. The diagnosis of primary headache disorders is based on the International Classification of Headache Disorders, 3rd edition (ICHD-3).[1] Children with headaches are brought to family physicians by their parents in case of inability to go to school or take part in social activities or suspicion of an underlying cause such as brain tumor.[2] A detailed physical examination and detailed neurological examination must be performed in addition to a careful history in the evaluation of childhood headaches. Additional diagnostic tests are performed in the presence of a secondary etiology, abnormality, or suspicion following evaluation.

Childhood headaches are rarely caused by a severe underlying disease, although it should not be forgotten that systemic diseases can result in neurological symptoms such as headache. One such entity is Celiac disease. However, few data are available concerning the relationship between Celiac disease and neurological disorders in the pediatric age group. The most common neurological symptoms of Celiac disease include ataxia, headache, and cognitive function disorder.[3,4] Although the underlying mechanism between Celiac disease and neurological system involvement is not yet fully understood, adherence to a gluten-free diet improves neurological symptoms.[5]

This study is presented in order that the incidence of Celiac disease in patients with a headache should not be forgotten and that screening for Celiac disease should be performed in persistent headaches.

Material and method

Patients with headache who were referre to Adıyaman University Training and Research Hospital pediatric neurology clinic, Turkiye, between January 2021 and November 2022 were identified and included in the study. In agreement with the principles of the Declaration of Helsinki, approval for the study was obtained from Adıyaman University center's clinical research ethical committee (Date: 03/11/2022, no. 2022/8-13). In line with the conditions for diagnosis of headache in the ICHD classification, the inclusion criteria were child age 0-18 years, absence of any organic cause of headache, and absence of any organic disease capable of affecting neuromotor development. All patients' files were reviewed retrospectively and data concerning age at presentation to the clinic, sex, type of headache diagnosed, laboratory findings, cases diagnosed with Celiac Disease, and the treatment recommended were recorded. Cases were classified as tension-type headache and migraine-type headache according to ICHD-3 criteria. All patients were given headache diaries. Celiac parameters were examined in cases with headaches that persisted despite first-line treatment. Multiple biopsy specimens were collected from the duodenum and bulb from patients with positive celiac parameters using upper gastrointestinal endoscopy. Patients whose pathology results were compatible with Celiac disease were placed on gluten-free diets. Patients with the diagnosis were re-evaluated for headache at 6 months later. Headache symptoms improved in all our cases receiving a gluten-free diet.

Statistical analysis

Statistical analyses were performed on Statistical Package for the Social Sciences (SPSS) version 26 software. Descriptive statistical methods were applied. The groups were compared using Student's t test. Continuous variables were expressed as both mean ± standard deviation and median (min-max) values. Categorical variables were expressed as number and percentage. p values < 0.05 were regarded as statistically significant.

Results

Files of 244 patients who were referred to Adıyaman University Training and Research Hospital pediatric neurology clinic and were diagnosed with a headache between January 2021 and November 2022 were examined retrospectively. Forty-two patients in whom an organic cause of headache was detected, with another chronic disease capable of affecting neuromotor development, and with deficient file data were excluded. Two hundred two patients with primary headache were thus enrolled in the study.

202 patients in the study group consisted of 123 girls (60.9%) and 79 boys (39.1%). The F/M ratio was 1.5. The patients' mean age at the time of presentation to the clinic was 12.7 ± 3.5 years. One hundred twenty-one (59.9%) patients were diagnosed with tension-type headaches and 81 (40.1%) with migraine-type headaches.

Table 1. Age range, number and percentage values of patients presenting with a headache

Age	4-6 years	7-12 years	Over 12	Total [Migraine-Tension-p value]
Number of patients	11	78	113	202 [81 – 121 – 0.108]
Percentage	5.4	38.6	56	100 [40 – 60]

Table 2. Type of headache and vitamin B12, ferritin, and vitamin D results

	Total number # of migraine-type # of tension-type	Min.	Max.	Mean	Std. Dev.	p-value
Vitamin B12 (pg/ml)	201 81 120	71	480	211	± 79.1	0.637
Ferritin (ng/mL)	200 80 120	1.8	83.6	19.5	± 13.9	0.463
Vitamin D (ng/ml)	192 76 116	3.02	83.09	17.6	± 9.86	0.335

No statistically significant association was determined between type of headache and age (p=0.108). Sixty-six percent (n=113) of the patients were aged ≥ 12 (***Table 1***). No statistically significant association was determined between the type of headache and vitamin B12 (p=0.637), ferritin (p=0.463) or vitamin D (p=0.335). Vitamin B12 levels were 211± 79.1 pg/ml (n=200), ferritin 19.5± 13.9 ng/mL (n=200), and vitamin D 17.6± 9.86 ng/ml (n=193) (***Table 2***).

Table 3. The age, sex, type of headache, laboratory findings, and Marsh scores of the patients diagnosed with Celiac disease

Case no.	Age	Sex	Type of headache	Vitamin B12	Ferritin	D vitamin	Marsh score
1	12	F	Tension	193	1.9	13.0	3C
2	16	F	Migraine	247	11.3	18.8	3C
3	16	F	Migraine	247	1.8	15.3	3A
4	16	M	Migraine	203	31.8	21.8	3B
5	13	M	Migraine	362	21.5	22.5	3B
6	12	F	Migraine	234	6.5	7.2	3B
7	16	M	Tension	165	5	13	3B
8	16	F	Tension	146	4.8	8.9	3B
9	10	E	Migraine	351	5.8	16.4	3B
10	13	F	Tension	298	4.2	12.4	3C
11	16	F	Migraine	95	4.3	4.5	3B

Patients' laboratory normal reference ranges: vitamin B12: >200 pg/ml; ferritin: 23.9-336.2 ng/mL; vitamin D: 10-80 ng/ml

Celiac disease was determined in 5.4% (n=11) of the cases with headache. Multiple biopsy specimens were collected from the duodenum and bulb from patients with positive celiac serology using upper gastrointestinal endoscopy. Patients whose results were compatible with Celiac disease were placed on a gluten-free diet. Patients who were diagnosed and started diet did not have any complaints at 6-month follow-up.

Discussion

Celiac disease, is represented by an autoimmune inflammatory condition with main, but not exclusive, involvement of small bowel. Clinical features are very variable, ranging from typical manifestations of gastrointestinal involvement to neurologic symptom. The most common neurological symptoms reported include headache. Headache is the most common neurological problem in the pediatric population, affecting 88% of children and adolescents.[6] The prevalence of headaches has been shown to increase with age.[2] Headache is also seen more frequently in girls.[7] The prevalence of headaches in the present study also increased with age, particularly during adolescence, and it was similarly more common in girls. Girls represented 59% of cases aged 3-17 years in Yılmaz et al.'s study.[8] In a study of cases of recurrent headaches, Mishra et al. also reported female gender dominance.[9] Female gender also predominated in the present study, with girls representing 123 (60.9%) of the 202 patients and boys 79 (39.1%). In Ahmad et al.'s study, gender differences may be attributed to both biological factors (hormonal influences, particularly estrogen fluctuations) and sociocultural aspects affecting symptom reporting and healthcare-seeking behaviors.[10] The most frequently seen primary headaches in children and migraine type and tension type.[11] Cluster headaches are rarer. There were no cases of cluster headaches in the present study, all headaches being migraine or tension-type. Tension headache was the most common type, followed by migraine. Although tension-type headache is more common than migraine, the epidemiology of tension-type headaches has been less investigated.[12] In addition, although tension-type headache was more common in this study, other publications have reported the opposite.[8,9] Study results concerning estimates of the prevalence of tension-type headaches vary, partly as a result of differences in terms of case definitions, and also of ethnicity and other population characteristics.[13-15] In addition, the less severe symptoms observed in tension-type headaches have been linked to fewer presentations of hospital and less impairment.[16] Tension-type headaches also predominated in the present study.

The human gut microbiome affects human brain health in many ways. Gut microbes can produce hormones and neurotransmitters that are identical to those produced by humans. This can disrupt normal neuroendocrine regulation and cause various disorders linked to abnormal central nervous system function. Changes in the gut microbiome play a primary role in the pathogenesis of Celiac disease, a gluten-sensitive disorder in which the adaptive immune system damages not only the gut but also the brain.[3] The mechanisms explaining how the gut and brain may interact in patients with celiac disease and headache are not entirely clear. However, some studies suggest that this interaction is influenced by multiple factors such as inflammatory mediators (TNF-α, IL-1β, IL-6 and IL-8), gut microbiota profile, neuropeptides and serotonin pathway, stress hormones and nutrients. However, it is thought that altering the composition of the gut microbiota may affect the gut-brain axis and the inflammatory state.[4] It has also been suggested that this condition can be improved by dietary approaches that have beneficial effects on the gut microbiota and the gut-brain axis. Non-pharmacological approaches can be useful in addition to vitamin and iron supplementation in cases of recurring headaches.[2] Positive lifestyle modifications such as regular exercise, adequate fluid intake, regular eating, and avoiding known triggers can reduce the frequency of headaches.[17,18] Sleep generally has a major impact, and sleep duration and quality should be evaluated in all patients with troublesome headaches.[19] In addition, due to its mild or moderate character, tension type

headache generally responds to non-prescription analgesics.[20] All our patients were given headache diaries and followed-up in the light of laboratory results, with lifestyle modifications being recommended. Celiac antibodies were investigated in cases whose headaches persisted despite such advice and follow-up, and the prevalence of Celiac disease in this study was 5.4%.

Delays and difficulties in diagnosis may be encountered when patients with Celiac disease present with atypical complaints including neurological features rather than classic, known malabsorption symptoms such as diarrhea and steatorrhea. A knowledge of atypical symptoms will be useful in establishing the exact prevalence of diseases. Delays in diagnosing Celiac disease also lay the foundation for severe complications. This has been linked to iron and vitamin deficiency associated with intestinal malabsorption.[21] Studies regarding pathogenic mechanisms between Celiac disease and headache is limited. Some mechanisms involved in the deficiency of vitamins or other nutrients due to malabsorption are thought to derive from an immune dysregulation involving neurotransmission disorder with neuronal cells being exposed to an impaired blood-brain barrier response in the brain and intestinal mucosa and gluten peptides crossing the blood-brain barrier.[22,23] The vitamin B12, vitamin D, and ferritin results of the patients with Celiac disease in the present study are shown in ***Table 3***.

According to recent studies of prevalence, the mean frequency of Celiac disease in USA and Europe is estimated around 1% of general population.[5] Cicarelli et al. first employed the term 'gluten encephalopathy' when they observed a greater prevalence of headaches among patients with Celiac disease.[24] Lionetti et al. reported that 5% out of 79 patients with headache were diagnosed with Celiac disease and that improvement in headaches was recorded in 76.4% of children given a gluten-free diet.[25] Despite the low number of studies on the subject, our finding of Celiac disease in 5.4% of our cases is consistent with the previous literature. Headache symptoms improved in all our cases receiving a gluten-free diet. In their 2016 study of cases of recurring headaches, Nenna et al. reported that 2.04% of cases diagnosed with Celiac disease responded to a gluten-free diet.[26] A population-based study reported a greater probability of migraine-type headaches in adolescents with Celiac disease.[27] A meta-analysis from 2018 also emphasized a greater prevalence of headaches in children and adolescents with Celiac disease, particularly in terms of migraine-type headache[28]. Migraine type headache was observed in seven of our 11 cases with Celiac disease aged 10-16. Since the prevalence of headaches increases with age and atypical Celiac disease is more common in older children, it is important to screen patients with persistent headaches in terms of Celiac Disease.

The limitations of this study include its retrospective nature, the low number of patients, and the fact that is based on hospital data. However, the scarcity of previous research on the subject makes our study particularly valuable. The results show the importance of screening for Celiac disease in the complete evaluation of patients presenting with a headache. Complaint of headache in patients with Celiac disease is important in dietary follow-up. Further prospective studies with wider population-based case series are now needed to elicit more detailed results. The lack of a second control group of similar age and gender for comparison is also a notable deficiency. Multicenter studies with larger sample sizes, a control group, and longer follow-up are needed.

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The authors declare that there is no conflict of interest.

Ethical Approval

All procedures conformed with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its subsequent modifications or equivalent ethical

standards. Ethical approval was granted by the institutional review board Adıyaman Universty (Date:03/11/2022, no:2022/8-13).

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