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OLGU SUNUMU **CASE REPORT**

BRAIN STEM INFARCTION IN A YOUNG PATIENT ASSOCIATED WITH PROBABLE FAMILIAL MEDITERRANEAN FEVER: A CASE REPORT

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ABSTRACT

Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by an autosomal recessive transition, self-limiting, recurrent fever and serositis attacks. Neurological symptoms of FMF are rare. Ischemic stroke, posterior reversible encephalopathy syndrome and demyelinating lesions are shown in FMF patients. A 17-year-old male patient was admitted due to left side weakness for two days. In cranial magnetic resonance diffusion-weighted (MRI-DWI) imaging, an appearance compatible with acute ischemia was detected in mesencephalon right crus cerebri and central localizations. All the young stroke examinations performed for the etiology of the patient who was in remission in terms of FMF were found to be normal. It was thought that the underlying mechanism of young stroke etiology may be the possible subclinical inflammation that causes endothelial dysfunction commonly seen in FMF. A stroke case with this rare complication was found worth presenting.
Keywords: Infarction, familial Mediterranean fever, brain stem, magnetic resonance imaging.

MUHTEMEL AİLESEL AKDENİZ ATEŞİ İLE İLİŞKİLİ GENÇ BEYİN SAPI ENFARKTI OLGUSU: VAKA SUNUMU

ÖZ

Ailesel Akdeniz ateşi (FMF) otozomal resesif geçişli, kendi kendini sınırlayan, tekrarlayan ateş ve serozit ataklarıyla karakterize otoinflamatuvar bir hastalıktır. FMF'nin nörolojik belirtileri nadirdir. İskemik inme, posterior reversibl ensefalopati sendromu ve demiyelinizan lezyonlar FMF hastalarında gösterilmiştir. 17 yaş erkek hasta iki günden beri olan sol yan kuvvetsizliği nedeniyle başvurdu. Kranial manyetik rezonans difüzyon ağırlıklı (MRG-DAG) görüntülemede mezensefalon sağ krus serebri ve santral lokalizasyonlarında akut iskemi ile uyumlu görünüm saptandı. FMF açısından remisyonda olan hastanın etiyolojiye yönelik olarak yapılan tüm genç inme tetkikleri normal bulundu. Genç inme etiyolojisinin altında yatan mekanizmanın FMF'de yaygın olarak görülen endotel disfonksiyonuna neden olan muhtemel subklinik inflamasyon olabileceği düşünüldü. Nadir görülen bu komplikasyona sahip inme olgusu sunulmaya değer bulunmuştur.
Anahtar Sözcükler: Enfarkt, ailesel Akdeniz ateşi, beyin sapı, manyetik rezonans görüntüleme.

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive, self-limiting autoinflammatory disease characterized by recurrent episodes of fever and serositis (1). It is caused by a mutation in chromosome 16 of the Mediterranean fever (MEFV) gene, causing dysfunction of the pyrin protein, which plays a role in regulating inflammation (2).

The central nervous system (CNS) manifestations of FMF are rare and controversial. Although rare, neurological findings associated with FMF can show a wide spectrum.

Studies have shown CNS complications of pseudotumor cerebri, optic neuritis, polyarteritis nodosa (PAN), and Henoch-Schonlein purpura (HSP), recurrent aseptic meningitis, ischemic

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stroke, cranial nerve involvement, subclinical visual evoked potential abnormalities, posterior reversible syndrome, and demyelinating lesions in FMF patients (3). In this study, a young stroke case with brainstem infarction, which was thought to be associated with FMF after excluding all other causes of stroke, is presented after obtaining signed consent for publication from the patient.

CASE REPORT

A 17-year-old male patient presented with a left flank weakness for two days. His history indicated that he had peritonitis, pleuritis, and arthritis attacks accompanied by fever, which started 10 years ago and recurred many times, and that he was diagnosed with FMF and colchicine 0.5 mg 3x1 tablet treatment was started. He was in remission under treatment and had no symptomatic attacks for a long time. There was no parental consanguinity. One brother also had a diagnosis of FMF and died six years ago due to intraparenchymal hemorrhage. Neurological examination revealed left hemiparesis and muscle strength of -5/5. Cranial nerve examination, sensory examination, and cerebellar system examination were within normal limits. The plantar reflex was bilaterally flexor. Ataxia was not detected. Vital signs were within normal values. There was no sign of bleeding in the computerized brain tomography of the patient. Cranial diffusion-weighted magnetic resonance imaging (DW-MRI) imaging and axial T2 FLAIR sequences were consistent with acute ischemia in the mesencephalon right crus cerebri and central localizations (Figure 1a-1b-1c-1d, Figure 2a-2b). The patient was hospitalized in the neurology service and started on dual antiaggregant therapy consisting of acetylsalicylic acid 100 mg and clopidogrel 75 mg. Among the cardiac scans performed for etiology, 24-hour rhythm Holter electrocardiography, transthoracic and transesophageal echocardiography were normal. No pathology was detected in the carotid and vertebral Doppler ultrasonography examination. Brain and neck MR angiography were within normal limits. The 24-hour urine protein level was within normal limits, and amyloidosis was not detected. Serum fibrinogen level was 240 mg/dl, C-reactive protein level (CRP) was 0.8 mg/L, and erythrocyte sedimentation rate (ESR) was 20 mm/h. Homocysteine level, lipid profile, hemogram, urea, creatinine, and other biochemical parameters were normal. ANA, Anti-dsDNA, P-ANCA, C-ANCA, anti-SSA, anti-SSB, anti-phospholipid antibodies, anti-cardiolipin antibodies, and Lupus anticoagulant examined for autoimmune vasculitis panel were within normal limits. No pathology was detected in hypercoagulopathy markers such as protein C, protein S, and antithrombin three levels. No pathology was detected in genetic screenings such as Factor 5 Leiden, methylenetetrahydrofolate reductase, plasminogen activator inhibitor, and prothrombin gene mutation. The patient with a stable clinical condition and completely improved neurological examination was discharged and followed up in the outpatient clinic.

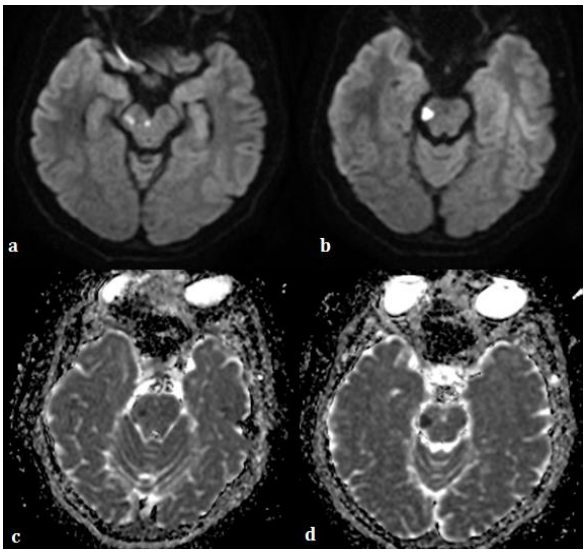

Figure 1a-d. Cranial MRI showed acute ischemic lesions in the mesencephalon right crus cerebri and central locations hyperintense on diffusion-weighted images and hypointense on apparent diffusion coefficient (ADC) sections.

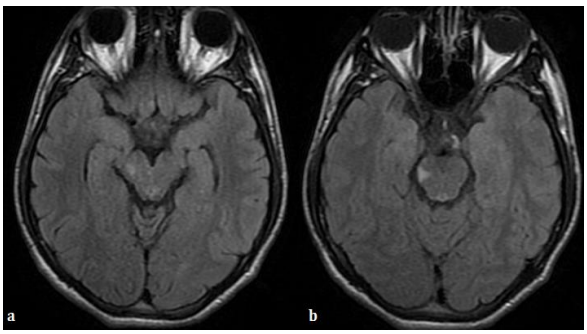

Figure 2a, b. Axial T2 FLAIR MRI sequences showed hyperintense ischemic foci in the mesencephalon right crus cerebri and central locations.

DISCUSSION AND CONCLUSION

FMF rarely causes neurological involvement, and our knowledge on this subject is still limited. Serum fibrinogen level has been accepted as an indicator of ischemic stroke risk in the general population, especially in young and middle-aged men, and is an important inflammatory marker of FMF activity (4). It is also known that intima-media thickness, an atherosclerotic indicator, increases in FMF (5). However, whether FMF constitutes a risk factor for stroke has not yet been elucidated. In a retrospective study investigating neurological involvement in FMF, 18 of 8864 FMF patients were found to have neurological participation, and seven patients had an ischemic stroke. The patients' prevalence of stroke was higher than the general population. Two patients were diagnosed with FMF after a stroke (6).

FMF patients have a significantly widespread and long-lasting subclinical inflammation. As in many autoinflammatory diseases, it is known that there is widespread inflammation in FMF both at the time of the attack and during remission (4). Publications suggest that clinically detectable attacks in FMF are only the tip of the iceberg and that in 30% of patients with FMF, inflammation continues in remission periods without attacks (7). This subclinical inflammation, which continues in the attack-free period, is thought to induce endothelial dysfunction and increase the risk of developing important complications such as atherothrombosis, anemia, splenomegaly, decreased bone mineral density, cardiac involvement, and secondary systemic amyloidosis. Acute phase reactants such as ESR and CRP, serum amyloid A, and fibrinogen, which increase in the attack period, are expected to return to normal in the attack-free period, but these parameters maintain their elevated levels if there is subclinical inflammation (4). Since our case has been clinically asymptomatic for a long time, he did not attend the hospital follow-ups regularly, and blood parameters could not be documented during this period. Therefore, the presence of subclinical inflammation cannot be proven by laboratory values, yet, the possibility of subclinical inflammation cannot be ruled out either, given the presence of long-standing disease. In our case, an ischemic stroke attack developed in a period determined as attack-free by clinical and laboratory findings, and studies on its etiology could not identify a cause. Chronic and widespread subclinical inflammation, a well-known prothrombotic factor, may have resulted in endothelial dysfunction facilitating stroke development.

FMF has been associated with systemic vasculitic diseases such as HSP, PAN, and Behçet's disease (2). The possibility of stroke due to cerebral vasculitis should not be ignored in patients. In our case, no finding that could indicate systemic vasculitis was detected in the angiographic images.

It is well known that homozygous genotype is associated with amyloidosis and a worse prognosis (8). Studies have shown that stroke and other neurological involvements are more common in individuals with homozygous mutations (6). It should be noted that the most common genes are investigated in mutation analysis. No FMF mutation was detected in our case. It is known that mutation negativity is up to 50 percent, even in studies conducted on large case series (9). Therefore, clinical and laboratory findings are of great importance in the diagnosis of the disease. Despite some studies reporting that posterior system circulation is most affected in stroke cases associated with FMF (6), this issue remains clarified. In our case, the posterior system circulation was affected as well.

Colchicine is a widely used and well-tolerated drug with anti-inflammatory properties. First described in 1820, this alkaloid exerts anti-inflammatory activity by inhibiting microtubule polymerization (10). Considering the role of inflammation in the pathogenesis of atherothrombosis, the effect of colchicine on cardiovascular diseases has become appealing. A meta-analysis study determined the incidence of a stroke to be lower in patients treated with colchicine compared to the placebo group, whereas there was no significant difference in cardiovascular disease and overall mortality rates (11). Another systematic review discussed studies with different results. In addition to studies reporting a decrease in the incidence of stroke and transient ischemic attack in patients receiving colchicine treatment compared to the control group, there are also studies in which no significant difference was found compared to the placebo group (12). Despite being treated with

colchicine for a long time, our case had a stroke and was at an effective dose. Recent data on the use of colchicine in stroke prophylaxis are promising, but there is not enough evidence yet.

Although rare, the neurological involvement of FMF disease, which is very common in our country, is noteworthy. The possibility of FMF should be kept in mind in young stroke cases of unknown cause. Considering that there are cases that can be newly diagnosed with FMF even after a stroke attack, it is vital that this disease, which can easily be masked clinically by conditions such as acute abdomen and gastroenteritis, is not missed. It should be known that there may be neurological involvement in the follow-up of the diagnosed cases, and care should be taken in this regard. We believe that large-scale prospective studies investigating the incidence of stroke, stroke subtype, and stroke localization in FMF patients and comparing the relationship between mutation types and stroke will be beneficial.

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Ethics

Informed Consent: The authors declared that informed consent form was signed by the patient.

Copyright Transfer Form: Copyright Transfer Form was signed by the authors.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices: EA, Concept: EA, Design: EA, Data Collection or Processing: İÇ, Analysis or Interpretation: EA, Literature Search: AA, Writing: EA.

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