

## Case report

# Brain stem infarction associated with familial Mediterranean fever and central nervous system vasculitis

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### ABSTRACT

*Familial Mediterranean fever (FMF) is an autoinflammatory autosomal recessive disease caused by mutations of the Mediterranean fever (MEFV) gene on chromosome 16p. Clinically, it is characterised by recurrent episodes of fever and painful polyserositis. An association of FMF with systemic vasculitis, namely Henoch-Schönlein purpura, polyarteritis nodosa and Behçet's disease has been described. Neurological manifestations of FMF occur rarely and include demyelinating (MS-like) lesions, posterior reversible encephalopathy syndrome, and pseudotumour cerebri. Hitherto hardly known, we herein present a young patient with a genetically proven FMF who suffered a brain stem infarction during a typical FMF attack. After a careful diagnostic workup including cerebrospinal fluid analysis, intra-arterial angiography and leptomeningeal biopsy, a FMF-associated central nervous system vasculitis was identified as the cause of stroke. The pathophysiological background and potential therapeutic strategies are discussed.*

### Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory autosomal recessive disease mostly encountered in Mediterranean and Middle Eastern populations affecting about 100,000 people worldwide (1). It is caused by mutations of the **Mediterranean-fever** (MEFV) gene on chromosome 16p resulting in a dysfunction of the pyrin protein. It is suspected that pyrin, which is mainly expressed by neutrophils and monocytes (2), plays an important role in the regulation of inflammation, however its exact function is still not fully understood. The defective pyrin finally leads to activation of caspase-1 and consequently to elevated levels of

IL-1 $\beta$  and several other proinflammatory cytokines (2, 3). Clinically, FMF is characterised by recurrent episodes of fever and painful polyserositis (2, 4). An association of FMF with systemic vasculitis, namely Henoch-Schönlein purpura, polyarteritis nodosa and possibly Behçet's disease has been reported (2, 5-7). Here we present a FMF patient who suffered a brain stem infarction during a fever attack, likely caused by a concomitant central nervous system (CNS) vasculitis.

### Case report

A 34-year-old male of Turkish descent with genetically confirmed FMF (homozygote MEFV-gene mutation M680I) in his past-medical history was admitted to our hospital with a one-week history of headache, abnormal fatigue and exhaustion. The patient complained about an irritation of the right eye, hoarseness, swallowing problems and left-sided hypaesthesia. A few days prior to admission, the patient suffered from recurrent periumbilical pain and febrile temperature, similar to what he typically experienced in the context of the FMF episodes. Neurological examination at admission revealed a right-sided Horner sign, a gaze nystagm, a right-sided glossopharyngeal paresis as well as a left-sided thermhypoaesthesia and hypalgesia (excluding the face). MR-imaging including DWI-sequences confirmed that the incomplete Wallenberg's syndrome was caused by an acute infarction of the right dorsolateral medulla oblongata (Fig.1A). No other lesions suspicious for previous ischaemic events were detected. Laboratory testing showed an increased CRP of 6.5mg/dl and an erythrocyte sedimentation rate of 41mm/h. A mild lymphomonocytic pleocytosis (16 leukocytes/ $\mu$ l) was found in the cerebrospinal fluid (CSF). Due to the headache and fever,

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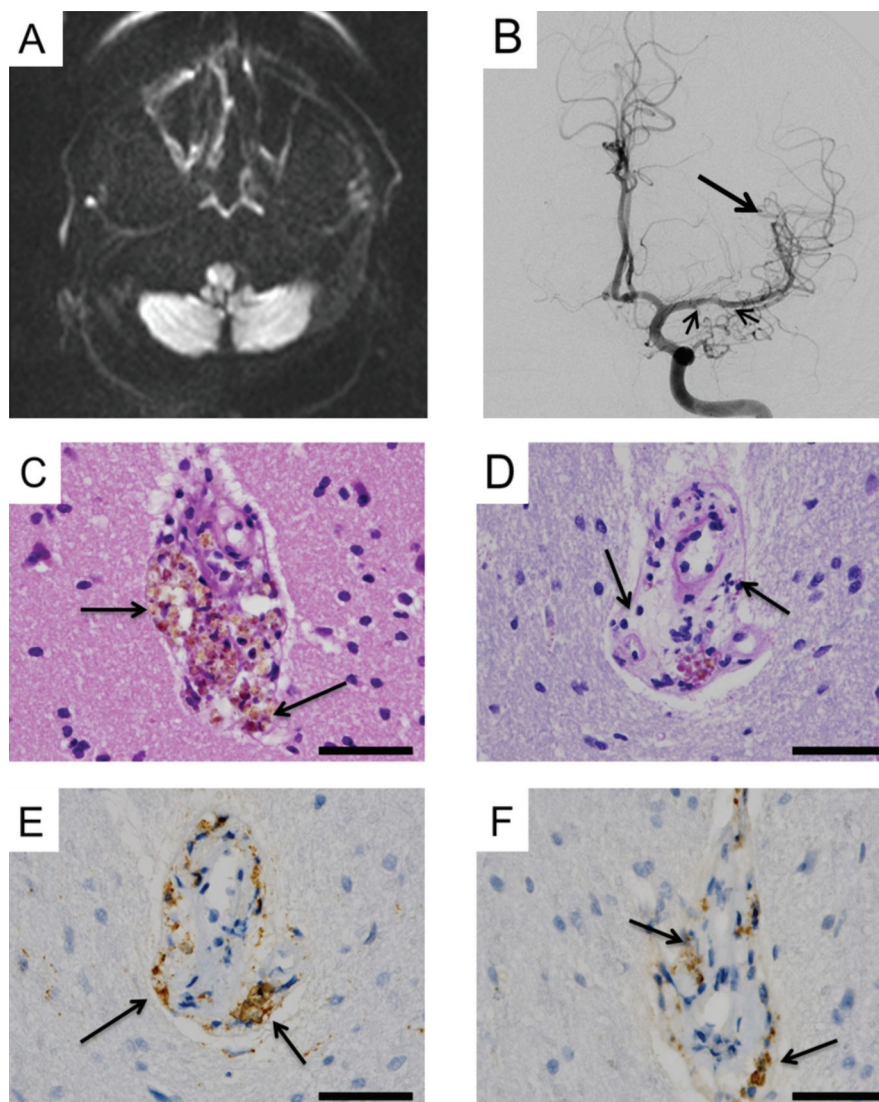
the patient was at first suspected to suffer from meningitis. He was treated with ceftriaxon and aciclovir until negative test results for neurotropic viruses (HSV, CMV, VZV, EBV) and bacteria were obtained.

During the diagnostic work-up sonography of the brain-supplying vessels did not reveal any abnormalities and Holter-ECG and transesophageal echocardiography did not provide evidence for a cardioembolic origin of the stroke. All further laboratory tests were within normal limits, including RA factor, ANA, DNA-antibodies, p-ANCA, c-ANCA, ENA, antiphospholipid-antibodies and lupus anticoagulants. Negative test results were also obtained for *M. tuberculosis*, *HIV*, *Borrelia burgdorferi*, *Treponema pallidum* and *M. Fabry*. Permanent headache, a persisting mild pleocytosis (19 leukocytes/ $\mu$ l) and evidence of oligoclonal bands in a second lumbar puncture were suspicious for cerebral vasculitis. Digital subtraction angiography showed an (apparently asymptomatic) occlusion of a temporal M2-branch and an insular M3-branch of the left middle cerebral artery with sufficient collateralisation (no corresponding infarcts on MRI) (Fig.1B). The vertebrobasilar circulation showed no abnormalities. A leptomeningeal biopsy taken three weeks after the onset of the symptoms revealed perivascular infiltrates consisting of macrophages and cytotoxic T-cells as well as haematoidin pigment (Fig.1C-F).

We finally diagnosed a dorsolateral medulla oblongata infarction resulting from a concomitant cerebral vasculitis during a FMF attack. In addition to colchicine the patient was treated with oral prednisolone (100 mg per day, tapered to a maintenance dosage of 5 mg). Within weeks, fever and most of the neurological deficits resolved. Three months later, clinical examination and brain imaging did not show any new stroke lesions and CSF cell count was normal. Until now there has been no need to initiate a more aggressive immunosuppressive therapy.

### Discussion

Neurological manifestations of FMF occur rarely and include demyelinating



**Fig. 1.** MRI, angiographical and neuropathological findings

**A.** Axial diffusion-weighted MRI shows an infarction of the dorsolateral medulla oblongata on the right side.

**B.** Intraarterial angiography of the left internal carotid artery reveals (clinically asymptomatic) stenosis of the M1 segment of the left middle cerebral artery. Furthermore, occlusions of the proximal temporal M2 segment (with extensive collaterals; short arrows) and a parietal M3 branch (long arrow) are visible. The vertebrobasilar system showed no abnormalities (not depicted).

**C.** HE staining depicts prominent perivascular deposits of yellowish haematoidin pigment (arrows).

**D.** The pigment deposits are accompanied by moderate lympho-monocytic perivascular infiltrates (arrows; PAS staining).

**E, F.** The perivascular cellular infiltrates consist of both **E.** macrophages (immunohistochemistry for CD68, arrows) and **F.** cytotoxic T-cells (immunohistochemistry for CD8, arrows).

Scale bar = 50  $\mu$ m for all images.

(MS-like) lesions, posterior reversible leukoencephalopathy syndrome, pseudotumour cerebri and CNS complications of systemic vasculitis, including ischaemic stroke (7, 8). The vascular comorbidities are fostered by an up-regulation of inflammatory cytokines leading to endothelial dysfunction, platelet activation and consecutive microcirculatory hypoperfusion (9). Fur-

thermore, the coexistence of FMF and other inherited or acquired risk factors such as antiphospholipid syndrome are considered to be predisposing factors for the occurrence of ischaemic stroke (10).

In our patient, however, no evidence for a systemic vasculitis (in particular Henoch-Schönlein purpura, polyarteritis nodosa or Behçet's disease (11)

with obligatory additional characteristic organ manifestations) was found, but clinical findings and examinations suggested a concomitant vasculitis limited to the CNS. First, the brain stem infarction occurred during a FMF attack, following a period of headache, in a patient without vascular risk factors and without other stroke-prone pathologies. Second, although it is suggested that neutrophils are the predominant effector cells of acute inflammatory attacks in FMF (12, 13), in our particular case the lymphomonocytic pleocytosis in the CSF analysis, leptomeningeal biopsy with perivascular infiltrates of macrophages and cytotoxic T-cells and intra-arterial angiography indicated a mild inflammatory affection of cerebral vessels leading to the diagnosis of a CNS vasculitis.

We treated our patient with corticosteroids (14), which was sufficient to control the inflammatory activity, as shown by the amelioration of clinical symptoms and normal CSF findings in the follow-up investigation. However, at this stage it is unclear, whether long-term immunosuppression (e.g. with cyclophosphamide) might be indicated in FMF-associated CNS vasculitis. On the one hand, it is likely that FMF at-

tacks will reoccur; on the other hand, the risk of recurrent cerebral infarcts in this setting remains to be determined in the future.

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