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Familial Mediterranean fever and multiple sclerosis

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Abstract Central nervous system (CNS) manifestations of familial Mediterranean fever (FMF) are extremely rare. These include pseudotumor cerebri, optic neuritis, CNS complications of polyarteritis nodosa type vasculitis, or hypercoagulable states secondary to renal amyloidosis, recurrent aseptic meningitis, and amyloid ophthalmoplegia. We present three patients with FMF whose neurological findings and magnetic resonance imaging (MRI) abnormalities resembled multiple sclerosis (MS). These two conditions in the same patient could arise from either coincidence or an unknown pathophysiological relationship. Both explanations are equally speculative and this matter needs further study, especially to investigate MRI features in FMF patients without CNS symptoms.

Key words Familial Mediterranean fever · Neurological complications · Multiple sclerosis

Introduction

Familial Mediterranean fever (FMF) is an inherited disorder affecting several ethnic groups in the Middle East and in Mediterranean countries. FMF, also known as periodic disease or recurrent polyserositis, is an autosomal recessive disorder characterized by recurrent attacks of fever, synovitis, peritonitis, or pleuritis. Less frequent manifestations include skin rash, myalgia and systemic amyloidosis [6, 18]. The cause of the disease is unknown. Recent genetic studies have shown that the gene for FMF is located on chromosome 16p [22, 25]. The diagnosis of FMF is usually made on clinical grounds, typically when recurrent attacks of abdominal pain, fever, and arthritis are observed in a patient with an appropriate ethnic background and family history [3]. So far, there is no specific diagnostic laboratory test for FMF [6].

Central nervous system (CNS) manifestations of FMF are very rare and remain controversial. We describe a previously unreported association of FMF and multiple sclerosis (or multiple sclerosis-like syndrome [8, 23]).

Case reports

Patient 1 was a 34-year-old man who had been admitted 3 years previously because of a 1-month history of numbness and hypaesthesia on the lower extremities. He had been followed up with the diagnosis of FMF for 23 years and had used colchicine (1.5 mg/day) during that time (Table 1). Neurological examination did not reveal any abnormalities except for hypaesthesia below the T10 level. Cranial MRI showed multiple hyperintense lesions in the deep and periventricular white matter on the T2 weighted images (Fig. 1). MRI of the spinal cord was normal. CSF investigations, including a search for protein and oligoclonal bands were normal. A visual evoked potential (VEP) study showed normal P100 latency and amplitude. Brain-stem auditory evoked responses (BAER) and somatosensory evoked potential (SEP) were abnormal. Other laboratory tests showed normal values (Table 2). A diagnosis of non-compressive cord syndrome was suggested and treatment with methyl-prednisolone was given. Repeated brain MRI showed considerable resolution in the size and number of the lesions, and the SEP study became normal. The neurological findings did not change. He had been well during follow-up for 3 years. However, 3.5 years later he was evaluated for painless right monocular visual loss, which developed over a few days. On examination, the visual acuity in his right eye was reduced to 20/800 with decreased red colour perception and a right relative afferent pupillary defect. No optic disk pallor was present on ophthalmoscopic examination. Visual field examination disclosed a moderate

Table 1 Clinical data

Patient	Age (years)	Sex	Age at diagnosis of FMF (years)	Age at the beginning of symptoms ascribed to MS	Time interval (years)	Family history
1	30	Female	18	30	12	(+)[a]
2	25	Male	20	24	4	(–)
3	34	Male	23	34	11	(–)

[a] FMF were diagnosed in two of four siblings; one of them also had PAN like vasculitis

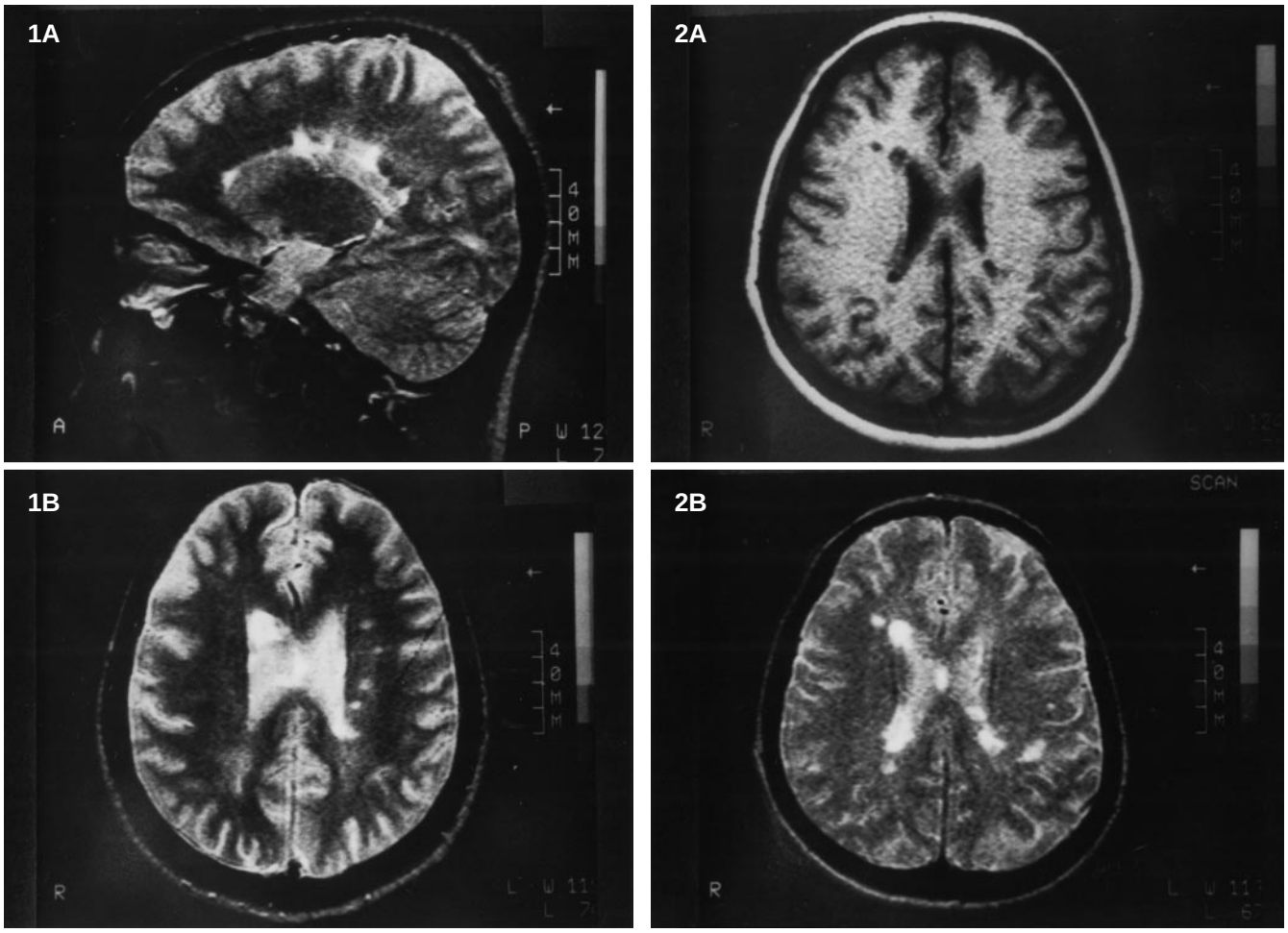

Fig. 1 Sagittal (**A**) and axial (**B**) T2-weighted MRI of the brain in patient 1 showing multiple hyperintense signal changes in the periventricular white matter

Fig. 2 Transversal T1 (**A**) and T2 (**B**)-weighted MRI of the brain in patient 2 showing multiple white matter lesions consistent with demyelinating plaques

right visual field constriction, beginning with a superior altitudinal defect. His physical and neurological examinations were otherwise unremarkable. Routine blood tests including serological tests for syphilis and brucellosis were normal. P100 wave latency, on pattern reversal VEP study, was prolonged over the right eye. His repeated MRI showed no significant changes compared with the previous one. A demyelinating optic neuritis was considered and he was given methylprednisolone therapy. Over a 3-week period the patient's visual acuity gradually returned to normal. No cases of optic neuritis were reported in the family.

Patient 2 was a 30-year-old female with 3-month history of gait difficulty, diplopia, fatigue, and depression. She had mild gait ataxia, titubation, up-beat nystagmus, bilateral Babinski sign, and a bilateral moderate intention tremor on neurological examination. Age at diagnosis of FMF was 18 years. Since then, she had been given colchicine therapy (0.5 mg/day) and the abdominal pain attacks were well controlled. FMF was diagnosed in two of her four siblings. Her brother had also PAN-like vasculitis. As shown in Table 2, laboratory tests showed high ESR and fibrinogen level. The markers of collagen tissue disorder were normal except for nonspecific and slightly high titre of ANA. Multimodal evoked potential studies were abnormal, and CSF IgG index was high. A diagnosis of demyelinating disease on the basis of brain MRI findings suggestive of MS (Fig. 2) was considered and treatment with methyl-prednisolone was given. A slight improvement in gait ataxia was noted at the end of the therapy.

Patient 3 was a 25-year-old male. Acute monoparesis of the left lower extremity which resolved spontaneously within 2 weeks had been documented in another neurology centre 3 years previ-

Table 2 Results of laboratory testing

	Patient 1	Patient 2	Patient 3
Haematological and urinary			
Erytrocyte sedimentation rate (ESR; mm/h)	24	85	100
BUN/Cre	12/0.9	8/0.52	11/1.2
Urine protein (mg/l)	(–)	(–)	200
Creatinin clearance (ml/min)	120	?	148
Serum albumin/protein	3.9/6.9	4.2/7.4	2.6/4.6
Cerebrospinal fluid			
Cells	5 RBC/mm^3	(–)	(–)
Glucose (mg/dl)	64	56	56
Protein (mg/dl)	40	42	22
Ig G Index	0.4[a]	2.6[a]	1.98[a]
Oligoclonal band	(–)	(–)	(+)
Immunological and Serological			
Anti-nuclear antigen	(–)[c]	(+)[b]	(–)
Anti-double-stranded DNA (IU/ml)	1.2	5.2	0.2
Rheumatoid factor	(–)[c]	(–)	(–)
Anti-cardiolipin antibodies (IgG/IgM)	(–)[c]	(–/–)	(–/–)
Antineutrophil cytoplasmic antibodies (c-/p-)	(–)[c]	(–/–)	(–/–)
VDRL	(–)	(–)	(–)
Brucella antigen	(–)	(–)	(–)
Fibrinogen (mg/dl)	390	580	521
Electrophysiologic			
VEP	Normal[d]	Abnormal	Abnormal
SEP	Abnormal	Abnormal	Abnormal
BAEP	Abnormal	Abnormal	Abnormal

[a] Reference value: 0.2–0.5
[b] 1/40 titre and speckled pattern
[c] Obtained in second attack
[d] Abnormal in second attack

ously. He had been treated with 1.5 mg daily colchicine with the diagnosis of FMF for 5 years. He also had proteinuria due to renal amyloidosis, which was proven by biopsy. Two years later he was admitted to our hospital because of acute paraparesis. MRI of brain and spinal cord revealed multiple lesions compatible with MS (Fig. 3). The results of laboratory tests are summarized in Table 2. No therapy was recommended except continuation of colchicine because of spontaneous complete recovery of the symptoms.

Discussion

FMF is rarely complicated by neurological symptoms. Pathological findings are those of a non-specific acute inflammation. Amyloid may be deposited in intima and media of the arterioles and in the subendothelium of venules in all major organs. Liver, heart and brain are believed to be characteristically spared. In the literature, there have been reports of pseudotumor cerebri [7], optic neuritis [13], CNS complications of polyarteritis nodosa type vasculitis [9], or hypercoagulable states secondary to renal amyloidosis [26], headaches, nonspecific electroencephalographic changes during attack [13], recurrent aseptic meningitis [1, 24], ischaemic stroke due to coincidental reasons [27] and amyloid ophthalmoplegia [12] among the spectrum of neurological involvement in patients with FMF. However, FMF has not previously been reported in association with MS.

The association between FMF and MS may arise from a simple co-occurrence. This seems highly speculative because of the low incidence of these disorders in the Turkish population; nevertheless, we cannot rule out this possibility. The first and the third patients had two separate attacks. According to Poser's criteria [21] the first and third patients could be classified as clinically definite MS, while the second patient had laboratory supported definite MS. Establishing these diagnoses requires exclusion of other diseases by appropriate tests. Moreover, multifocal white matter lesions as seen in T2 weighted MRI are known to be not unique to MS [5]. A variety of neurological conditions can cause white matter abnormalities, but this has not been documented for FMF to date. Most of the conditions resulting with MRI white matter abnormalities, especially neurosarcoidosis, Behcet's syndrome, Sjögren syndrome, polyarteritis nodosa, ADEM, SLE and ageing, can be ruled out by age, clinical and laboratory features. Behcet's syndrome, which is more prevalent in Turkey, was easily excluded with the absence of any of the major diagnostic criteria including oral aphthous ulcers, genital ulcerations, typical eye or skin lesions, and positive pathergy test [11].

The serological tests for syphilis and brucellosis were performed, but not for Lyme disease, which is extremely rare in Turkey. We know CT and MRI display multifocal and periventricular cerebral lesions in the chronic phase

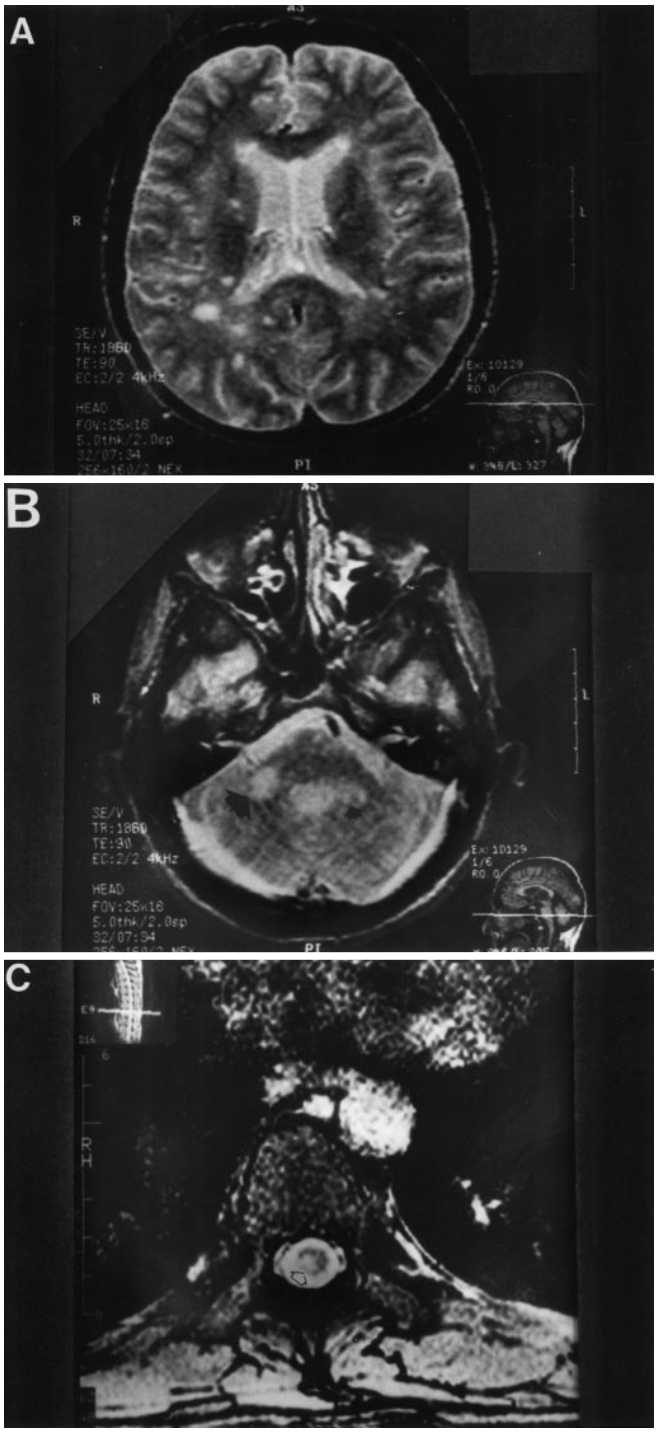

Fig. 3 Axial T2-weighted MRI images of the brain and spinal cord in patient 3 reveal multiple hyperintense lesions in periventricular white matter (**A**), in brachium pontis (**B**) and in medulla spinalis (**C**)

of Lyme disease [4]. However, none of the presented cases had the usual pattern of systemic or neurological involvement of Lyme disease. Neither meningoencephalitis, cranial or peripheral neuritis, radiculitis as the most common neurological manifestations nor systemic symptoms and skin lesions as systemic involvement were observed. There was no mild lymphocytosis or mild elevation of protein levels in the CSF.

FMF is not a systemic vasculitic disease. However, PAN-like vasculitis may rarely develop [9]. The diagnosis of this type of vasculitis remains largely dependent on visceral angiography and peripheral nerve biopsy. On the basis of the absence of the distinctive clinical and serological features of PAN, this possibility could be excluded [10, 19].

Colchicine-induced neurotoxicities causing vitamin B_{12} deficiency have been reported [20]. None of the patients presented here had low B_{12} levels and there has been no colchicine-associated optic neuritis or MS reported in the literature. However, the direct toxic effect of colchicine is not excluded. It has not been described before, but colchicine has never been used before on a young population continuously for many years, and our knowledge of its mode of action and long-term effects is limited.

The “decreased anti-inflammatory response’’ hypothesis [3, 14–17] and other putative mechanisms such as FMF-associated chronic antigenaemia, oxygen radical-mediated chromosome damage, or FMF-related immunological mechanism including relative bone marrow plasmocytosis, T-cell dysfunctions, and lymphocytotoxins [2, 6, 16] may all be relevant, but inadequate explain the exact pathophysiology of this disease. Whether or not the underlying mechanism is immunologically mediated and whether CNS involvement takes place in FMF owing to those inflammatory changes may be revealed by further experience.

All the mechanisms proposed above remain speculative. A study designed to investigate MRI features in FMF patients without CNS symptoms is necessary to understand the nature of MRI appearances in FMF. This seems to be the only way to learn whether the observed MRI lesions are related to FMF or to MS.

All of the presented patients had already been treated with colchicine (0.5–1.5 mg/day) at the time of commencement of CNS-related symptoms. We continued with this therapy and added intravenous methyl prednisolone in two patients, and a slight improvement was noted in one. If we consider the two diseases as two different entities without any pathophysiological relationship, colchicine alone seems ineffective in the treatment of neurological disease and corticosteroids are recommended.

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