Best Practice & Research Clinical Rheumatology 26 (2012) 119–133

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

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Neurologic and other systemic manifestations in FMF: Published and own experience

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Keywords:
FMF (familial Mediterranean fever)
Neurologic manifestations
Demyelinating diseases
Stroke
Aseptic meningitis
Seizures
PRES (posterior reversible leukoencephalopathy)
Central nervous system vasculitis
Colchicine
Cognitive impairment

Objective: Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease, presenting with recurrent episodes of fever and polyserositis. Neurologic involvement in FMF is rare and usually considered fortuitous. The aim of this article is to review the spectrum of possible neurologic manifestations, which can be encountered in FMF patients, and to establish their relation to FMF.

Methods: We reviewed the literature based on Pubmed search to find neurologic manifestations, which were reported in FMF patients. To that we added our own experience on the subject, abstracted from our computerised FMF registry of 12000 FMF patients of the National FMF Center and the computerised database of Sheba Medical Center.

Results: A wide range of neurologic manifestations involving FMF patients was noted. A large part of these manifestations could be directly related to FMF, its complications, associated diseases and treatment adverse effects. The remaining were incidental, or of uncertain association to FMF.

Conclusion: A physician, taking care of an FMF patient, can face various neurologic manifestations and should be aware of their origin. The current chapter provides an insight to this association of FMF.

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doi:10.1016/j.berh.2012.01.004

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease, presenting with recurrent episodes of febrile peritonitis, synovitis and pleuritis. More than 60 disease-associated mutations have been identified in the MEditerranean FeVer gene, designated (MEFV), which encodes for an inflammation regulatory protein, termed pyrin [1–3]. Pyrin seems to comprise a part of the inflammasome NLRP3, that regulates the level of IL-1β (interleukin 1-β) and thereby the degree of inflammation [4]. The devastating complication of FMF is amyloidosis that eventually may lead to end-stage renal failure and other organ dysfunction. Treatment with colchicine effectively prevents the FMF attacks as well as the development of amyloidosis [5].

Neurological manifestations unequivocally related to FMF include headache, as a constitutional symptom that accompanies FMF febrile attacks, and four various types of muscle pain. The first two are the short-term (1–5 days) and protracted (8–12 weeks) attacks of myalgia, affecting the muscles of the upper and lower extremities. The pain in the limbs is excruciating and is further increased by motion. The creatine kinase (CPK) and electromyography (EMG) are normal. The temperature and the acute phase reactants are significantly elevated. The protracted muscle pain is considered to be a form of vasculitis and is often associated with a macular rash and homozygosity for the M694V MEFV mutation, the most 'severe mutation' in FMF [6,7]. Exertional muscle pain, the third type of myalgia, affects the calf and thigh muscles and is precipitated by exertion, usually prolonged standing or walking, and is relieved by bed rest. This manifestation is quite typical of FMF and forms a minor criterion in FMF [8]. Recently, using magnetic resonance imaging (MRI) imaging, this type of myalgia was related to tenosynovitis (Eshed I et al. data in preparation for publication). The fourth type is the constitutional muscle pain, which may go along with FMF febrile attacks. This manifestation particularly refers to leg muscle pain, occurring during abdominal attacks. Other forms of muscle involvement that may be encountered in FMF or related to FMF-allied diseases or to treatment complications will be mentioned and discussed in the following (Table 1).

The occurrence of other forms of nervous system manifestations in FMF is rare, and the relation of most of them to FMF is still uncertain. Nevertheless, a wide range of additional neurologic disorders has been reported in FMF. These include seizures [9], sinus vein thrombosis [10], pseudotumour cerebri [11], optic neuritis [12], central nervous system (CNS) complications of systemic vasculitidis (Henoch–Shonlein purpura (HSP) [13], polyarteritis nodosa (PAN) [14], Behcet's disease (BD) [15] and others [16]), demyelinating lesions and multiple sclerosis (MS) [17–19], ischaemic stroke [20] and recurrent aseptic meningitis [21,22]. Aside from that, the neurologic manifestations in FMF may reflect side effects of medications, to which FMF patients have been exposed.

The aim of this chapter is to review current knowledge on the neurologic diseases associated with FMF, combining our experience with published data. For that purpose, we reviewed all papers, which could be obtained using Pubmed search, looking for the association of the term FMF with neurological manifestations, CNS disease, neurologic involvement, autonomous nervous system, stroke, aseptic meningitis, demyelination, cognitive impairment, neurologic manifestations of vasculitis, neuropathy, myopathy, Creutzfeldt–Jakob disease (CJD), posterior reversible leukoencephalopathy (PRES) and seizures. To this we added our own experience with neurological involvement of our patients, based on

Table 1
Various types of muscle involvement in FMF.

As a manifestation of FMF	Myalgia as a constitutional symptom, during the abdominal/chest/fever only attacks
	Myalgia as an additional type of FMF attack
	Exertional leg pain
	Protracted febrile myalgia
Treatment adverse effects	Colchicine-induced myopathy or myoneuropathy
	Steroid-induced myopathy
As a manifestation of FMF-allied diseases	Myalgia as a manifestation of polyarteritis nodosa, Henoch-Schonlein purpura and Behcet's disease
	Myalgia as part of fibromyalgia