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Abstract

We report a 16-year-old female patient with a severe course of multiple sclerosis and concomitant symptoms suggestive of a hereditary autoinflammatory disease. Genetic analyses revealed that she inherited a TNFRSF1A R92Q mutation from her mother and a pyrin E230K mutation from her father. To our knowledge, this is the first report of a patient with severe childhood multiple sclerosis and mutations in two genes which predispose to hereditary autoinflammatory disorders. We speculate that these mutations contribute to early multiple sclerosis manifestation and enhance the inflammatory damage inflicted by the autoimmune response.

Keywords

childhood, demyelinating autoimmune diseases, Familial Mediterranean Fever, genetics, multiple sclerosis, receptors, tumor necrosis factor, type I

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Background

Tumor necrosis factor receptor 1-associated periodic syndrome (TRAPS) and Familial Mediterranean Fever (FMF) belong to the group of hereditary auto-inflammatory syndromes which are characterized by recurrent episodes of inflammation and are variably associated with fever, abdominal and thoracic pain, arthralgia, myalgia, rashes, and headache.

A few cases of central nervous system (CNS) involvement have been reported in association with TRAPS^{1–2} and FMF,³ and Jewish multiple sclerosis (MS) patients carrying one Mediterranean fever gene (*MEFV*) mutation showed a tendency towards a more severe disease course.⁴ We previously described a group of adult MS patients who carried a TNFRSF1A R92Q mutation and showed, in addition to the typical MS features, symptoms compatible with TRAPS.^{5,6} Very recently, the *TNFRSF1A* gene was identified as a new susceptibility locus for MS.⁷

Here, we report a patient with childhood MS and coexisting mutations in the *TNFRSF1A* and *MEFV* genes.

Case report

Course and diagnosis of MS

At the age of 14, the girl had a first episode of left-sided paraesthesias and impaired hearing. Three months later, she presented with double vision, nystagmus, and impaired balance. A cerebral magnetic resonance imaging (MRI) scan performed at that time showed multiple hyperintense lesions involving also the brainstem, some of them with gadolinium (Gd)

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enhancement. Cerebrospinal fluid (CSF) analysis revealed positive oligoclonal bands. The diagnosis of MS was made according to the McDonald criteria. During the following year, she had three more relapses before immunomodulatory treatment with intramuscular interferon beta (IFN β) was started, initially with a quarter of the adult dose. When the dose was increased to half of the adult dose, she experienced several side effects such as extensive flu-like symptoms, myalgias, headaches, chest pain, and on one occasion a minimal pericardial effusion. All these symptoms did not respond well to anti-inflammatory medication. Repeated MRI scans revealed new, partially Gd-enhanced lesions as well as spinal cord lesions (Figure 1). Immunomodulatory treatment was changed to glatiramer acetate, which is tolerated better and is applied as her current medication.

Symptoms of TRAPS and FMF

Our patient had repeated episodes of pharyngitis in childhood. Attacks of thoracic pain and myalgia occurred before the diagnosis of MS and initiation of immunomodulatory treatment. In addition, she had experienced frequent headaches since early childhood. In contrast, no rashes or episodes of fever were reported. None of these symptoms was brought to medical attention before the diagnosis of MS was made.

Genetic testing revealed heterozygosity for an arginine₉₂ (CGG) \rightarrow glutamine (CAG)/R92Q substitution encoded by exon 4 of the *TNFRSF1A* gene and a glutamic acid₂₃₀ (GAA) \rightarrow lysine (AAA)/E230K mutation encoded by exon 2 of the *MEFV* gene. Her laboratory workup revealed a mild increase of serum amyloid A and a mildly elevated anti-nuclear antibody

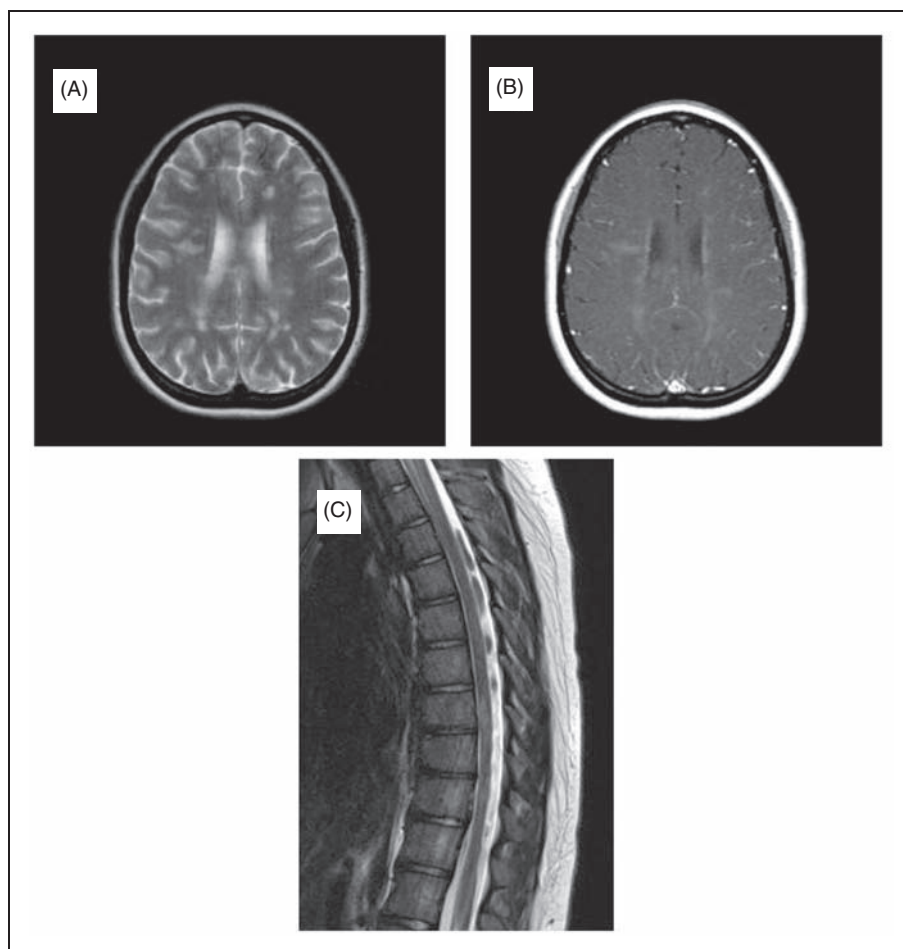


Figure 1. MRI of our patient A) T2-weighted sequence, axial plane, demonstrating multiple hyperintense lesions periventricular, cortical, and juxtacortical, B) corresponding T1-weighted sequence with Gd-enhanced lesions, C) T2 spinal sequence with multiple hyperintense lesions.

titre of 1:60. There was no evidence of an additional rheumatologic disease or a pathologic renal function.

Family members

The patient inherited the *TNFRSF1A* R92Q mutation from her mother, who had a past history of episodic arthralgia, but no further complaints. Her father was the carrier of the pyrin E230K substitution. A detailed medical history revealed severe migraine as the only symptom attributable to FMF. Her sister had a long-standing severe migraine as well as intermittent abdominal pain with constipation. She also tested positive for the pyrin E230K exchange. A maternal grandmother had an unclassified rheumatologic disorder with arthralgia/arthritis (see Figure 2A).

Discussion

Our patient inherited two point mutations, one in the *TNFRSF1A* gene from her mother and the other in the *MEFV* gene from her father. Her past medical history revealed symptoms attributable to TRAPS and FMF, including headaches and myalgias as well as episodes of thoracic pain and recurrent pharyngitis in childhood. Interestingly, she lacked the typical fever episodes.

The *TNFRSF1A* R92Q mutation is known to be associated with a more heterogeneous spectrum of symptoms with or without typical fever flares.⁸ Nine patients with a heterozygous pyrin E230K mutation have been reported in the literature, one described as a clinically severe phenotype.⁹ For the remaining eight patients, no such information is available.

Our patient met the criteria of McDonald and had the typical CSF changes. Her disease course is highly active with seven relapses in 2 years. She had to discontinue the first immunomodulatory treatment with IFN β at half of the adult dosage because of severe side effects, similar to some adult MS patients carrying the *TNFRSF1A* R92Q mutation.⁶

The severe MS course was aggravated by concomitant symptoms of TRAPS and FMF. For mutations in the *TNFRSF1A* and *MEFV* genes, an augmentation of the inflammatory response leading to a 'hyperinflammatory state' has been suggested (Figure 2B). The pathogenesis of TRAPS is mediated via TNF- α and *TNFRSF1A* signalling pathways. Animal experiments and clinical studies suggest that dysregulation of these complex pathways also plays an important role in the pathogenesis of MS.¹⁰ In addition, the *TNFRSF1A* R92Q variant has been identified as a new susceptibility locus for MS in a recent genome-wide association study.⁷ In FMF, inflammation is supposed to be related to a reduced ability of pyrin, the gene product of *MEFV*, to control interleukin-1 β activation.

An association of FMF with other autoinflammatory diseases, such as Henoch-Schönlein purpura and polyarteritis nodosa, is well established, with earliest reports dating back to the 1950s.³ An interrelation between FMF and demyelinating CNS disease, in contrast, is still debated. In a cohort of Turkish FMF cases, the number of MS patients was about four times higher than expected from the prevalence of MS in Turkey.³ In a cohort of Jewish MS patients, who carried one *MEFV* mutation, a tendency towards a more severe disease course of MS was noted.⁴

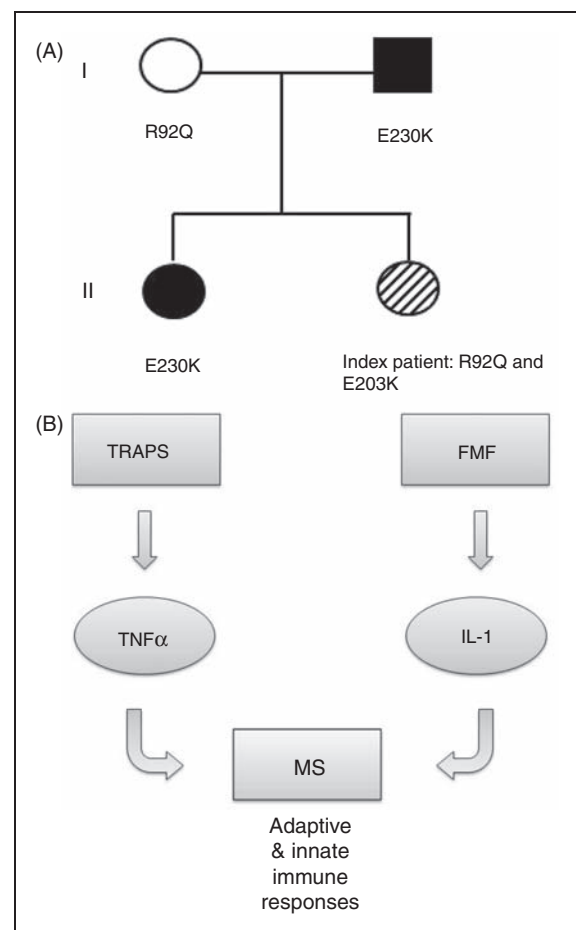


Figure 2. (A) Pedigree of the patient. Filled black symbols: pyrin E230K mutation encoded by exon 2 of the *MEFV* gene; white symbol: *TNFRSF1A* R92Q substitution; black and white symbol: pyrin E230K and *TNFRSF1A* R92Q mutation. (B) TRAPS is associated with mutations in the *TNFRSF1A* gene, which are responsible for increased activity of the proinflammatory cytokine TNF- α . FMF is caused by mutations in the *MEFV* gene (coding for pyrin), which indirectly cause increased production of interleukin-1 β . Both cytokines, TNF- α and interleukin-1 β , could profoundly affect both innate and adaptive immune responses in multiple sclerosis. In the described patient, the combination of mutations might induce a 'hyperinflammatory state', predisposing to MS.

In conclusion, this is the first description of a patient with severe childhood MS and alterations in two auto-inflammatory disease genes. The mutations were associated with additional symptoms such as myalgias, headache and thoracic pain, which could not be attributed to MS and complicated MS treatment. They also may have led to an earlier MS manifestation and could augment the inflammatory response, thereby leading to a very active disease course as observed in our patient.

Conflict of interest statement

T. Kümpfel and R. Hohlfeld disclosed the following relevant financial interest:

They received grant support and lecture fees from Bayer Health Care for a project investigating the effects of TNFRSF1A mutations on side effects of immunomodulatory therapies in MS.

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