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AN ASSOCIATION BETWEEN MEFV MUTATION AND ANCA-ASSOCIATED VASCULITIS INVOLVING THE CENTRAL NERVOUS SYSTEM AND LUNGS: CAUSALITY UNDER SCRUTINY

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ABSTRACT

Familial Mediterranean fever (FMF) is traditionally associated with biallelic mutations in the MEFV gene; however, heterozygous mutations may also contribute to disease phenotypes. We report the case of a 42-year-old woman with heterozygous p.Met694Ile MEFV mutation, presenting with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis involving the central nervous system and lungs. Her clinical course was marked by immune dysregulation, autoimmunity and inflammatory manifestations, including urticarial neutrophilic dermatoses and IgM deficiency. This case highlights the potential pathogenic role of heterozygous MEFV mutations in ANCA-associated vasculitis, expanding the clinical spectrum of FMF-related inflammatory diseases. Genetic investigation is essential in patients with overlapping autoimmune and autoinflammatory features to guide appropriate diagnosis and management.

KEYWORDS

Pyrin, immune dysregulation, ANCA-associated vasculitis, familial Mediterranean fever

LEARNING POINTS

- Systemic vasculitis may be associated with MEFV mutations as a spectrum of the clinical presentation of familial Mediterranean fever.
- MEFV heterozygous mutations may be associated with manifestations of immune dysregulation.
- Beware of inborn errors of immunity even in adult patients.

INTRODUCTION

The genetic cause of familial Mediterranean fever (FMF) is the mutations in MEFV gene coding pyrin, which has role in the activation of inflammasome, activation of caspase 1 and production of IL-1beta[1]. However, MEFV mutations can have an effect on some other inflammatory

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diseases such as contributing to disease development or increased inflammation or extended disease duration, even in heterozygosity[2-6]. The prevalence of vasculitis in patients with FMF exceeds that of the general population, with IgA vasculitis being the most prevalent, followed by polyarteritis nodosa and Behçet's disease[2-5]. FMF is linked to an with p.Met694Val being the most frequently reported mutation[1,4,7]. To date, only two cases of ANCA-associated vasculitis associated with MEFV mutation have been documented, both in France[8]. We report the case of a patient with a heterozygous p.Met694Ile MEFV mutation, previously diagnosed and treated for ANCA-associated vasculitis.

CASE DESCRIPTION

A 42-year-old woman presented in 2017 with seizures, cortical blindness and decreased consciousness 30 days after bariatric surgery. She was admitted to a tertiary hospital to clinical investigation. No complications of the recent surgery were described. She had a history of primary immune thrombocytopenia (ITP) since the age of 9, treated with splenectomy in 2000. Her family history was significant for a father with sarcoidosis.

Brain and neck magnetic resonance imaging (MRI) revealed hyperintense lesions on T2/FLAIR, asymmetrically involving the periventricular white matter and subcortical regions in both hemispheres, predominantly in the bilateral frontal and especially occipital and left cerebellar hemisphere *(Fig. 1)*. The initial diagnosis considered vasculitis or demyelinating diseases. The patient was treated for acute disseminated encephalomyelitis, receiving methylprednisolone for 5 days, leading to restoration of sight. She had no more seizures events after treatment.

The lower MRI cuts also revealed a lung opacity, so a chest computed tomography (CT) scan was performed *(Fig. 2)* and showed an excavated opacity in the upper segment of the right lower lobe and a smaller non-excavated opacity on the right upper lobe, with a small pericardial effusion. Pulmonary tuberculosis, fungi, and other opportunistic pathogens were ruled out through bronchoalveolar lavage.

Immunological panel results indicated a positive p-ANCA and negative anti-myeloperoxidase (MPO), extractable nuclear antigen (ENA) and viral serologies. She was diagnosed with granulomatosis with polyangiitis involving the central nervous system and lungs, treated with 3 monthly cycles of cyclophosphamide and maintained on azathioprine and glucocorticoids until 2021. During follow-up, she also tested positive for antinuclear antibody (ANA) (nuclear dense fine speckled 1:320) and had persistently low IgM serum levels. Due to the presence of various autoimmune diseases and autoimmune markers from childhood to adulthood, coupled with a family history of sarcoidosis and IgM deficiency, we were prompted to request a genetic panel for the investigation of immune dysregulation.

The genetic panel for Inborn errors of immunity (436 genes) revealed a heterozygous pathogenic variant p.Met694Ile in MEFV gene. The p.Met694Ile mutation in the MEFV gene results in the substitution of methionine by isoleucine at position 694 in the pyrin protein, a variant commonly associated with increased risk and severity of familial Mediterranean fever[1,7].

In 2023, the patient developed urticaria-like skin lesions and bilateral uveitis, which were diagnosed as neutrophilic dermatoses upon biopsy. Colchicine was initiated, resulting in complete resolution of skin lesions. Disease activity remains absent, with residual lesions on subsequent brain MRI.

DISCUSSION

FMF is traditionally considered a monogenic autoinflammatory disease with an autosomal recessive inheritance pattern, associated with mutations in the MEFV gene. However, evidence suggests that heterozygous mutations in the MEFV gene may also be linked to FMF phenotypes or multifactorial forms of the disease[9,10]. Heterozygosity in the MEFV gene have been statistically demonstrated does not account for Mendelian classic FMF but constitutes a susceptibility factor for clinically similar multifactorial forms of the disease[10]. Thus, although FMF is classically associated with biallelic mutations in the MEFV gene, heterozygous mutations may also contribute to FMF phenotypes, albeit frequently in milder or multifactorial forms of the disease.

FMF-associated vasculitis can be a rare phenotype and may

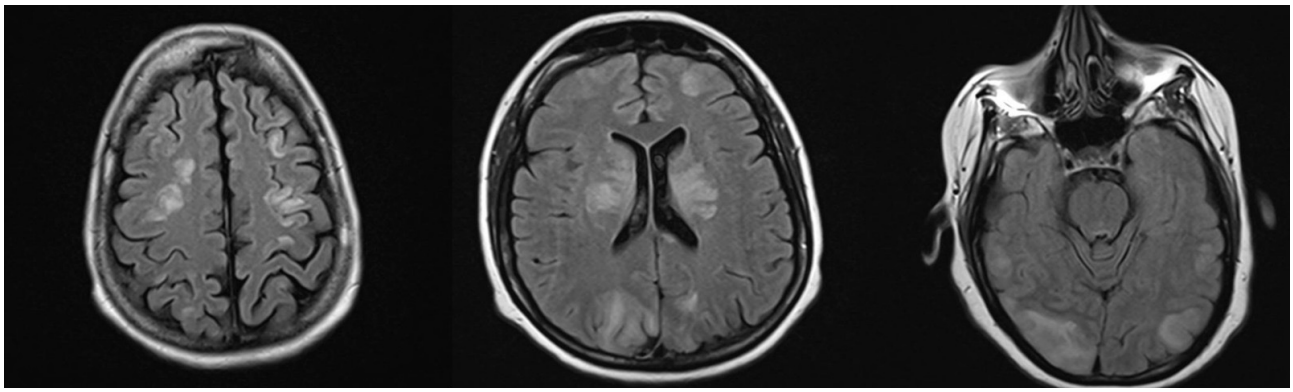


Figure 1. Brain magnetic resonance imaging: hyperintense lesions on T2/FLAIR, involving the periventricular white matter and subcortical regions in both hemispheres, in the bilateral frontal, occipital, left cerebellar hemisphere.

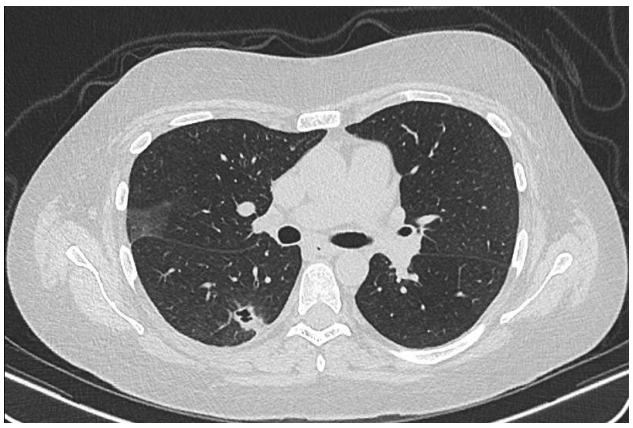


Figure 2. A chest computed tomography scan: excavated opacity in the upper segment of the right lower lobe.

not be seen as a merely coincidental increase in frequency but rather an extension of the underlying pathology of FMF[5,6]. Although the exact pathogenesis is unclear, elevated serum levels of proinflammatory cytokines - particularly IL-1β, as well as IL-6, IL-18, IL-33, and IFN-γ - and subsequent endothelial cell dysfunction appear to play crucial roles in the development of vasculitis in FMF patients[5].

Patients presenting with immune dysregulation, such as polyautoimmunity, immunodeficiency, and/or autoinflammatory manifestations, should undergo a genetic panel that includes MEFV mutations. While ANCA-associated vasculitis is rarely associated with MEFV mutations and FMF, the true significance of this association remains to be elucidated. Until further clarification, clinical features should guide the identification of the predominant phenotype, and appropriate immunosuppression should be initiated when necessary.

REFERENCES

1. Gershoni-Baruch R, Brik R, Shinawi M, Livneh A. The differential contribution of MEFV mutant alleles to the clinical profile of familial Mediterranean fever. *Eur J Hum Genet* 2002;**10**:145-149.
2. Salehzadeh F, Enteshari Moghaddam A. Coexisting Diseases in Patients with Familial Mediterranean Fever. *Open Access Rheumatol* 2020;**12**:65-71.
3. Abbara S, Grateau G, Ducharme-Bénard S, Saadoun D, Georgin-Lavialle S. Association of Vasculitis and Familial Mediterranean Fever. *Front Immunol*. 2019;**10**:763.
4. Schwartz T, Langevitz P, Zemer D, Gazit E, Pras M, Livneh A. Behçet's disease in Familial Mediterranean Fever: Characterization of the association between the two diseases. *Semin Arthritis Rheu*m 2000;**29**:286–295.
5. Aksu K, Keser G. Coexistence of vasculitides with Familial Mediterranean Fever. *Rheumatol Int* 2011;**31**:1263–1274.
6. Migita K, Fujita Y, Asano T, Sato S. The Expanding Spectrum of Autoinflammatory Diseases. *Intern Med* 2023;**62**:43-50.
7. Bernot A, da Silva C, Petit JL, Cruaud C, Caloustian C, Castet V et al. Non-founder mutations in the MEFV gene establish this gene as the cause of familial Mediterranean fever (FMF). *Hum Mol Genet* 1998;**7**:1317-1325.
8. Abbara S, Monfort JB, Savey L, Moguelet P, Saadoun D, Bachmeyer C et al. Vasculitis and familial Mediterranean fever: Description of 22 French adults from the juvenile inflammatory rheumatism cohort. *Front Med (Lausanne)*. 2022;**9**:1000167.
9. Elhani I, Dumont A, Deshayes S, Georgin-Lavialle S, Giurgea I, Aouba A. Typical Familial Mediterranean Fever associated with the heterozygous missense sequence p.T577N variant of the MEFV gene: Report on two Northern European Caucasians relatives in France. *Joint Bone Spine* 2020;**87**:251-255.
10. Jéru I, Hentgen V, Cochet E, Duquesnoy P, Le Borgne G, Grimprel E, et al. The Risk of Familial Mediterranean Fever in MEFV Heterozygotes: A Statistical Approach. *PLoS One* 2013;**8**:e68431.