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MEFV gene analysis in PFAPA

To the Editor:

The PFAPA syndrome is a chronic disease of unknown etiology characterized by Periodic episodes of high Fever accompanied by Aphthous stomatitis, Pharyngitis, and cervical Adenitis, sometimes associated with headache and/or abdominal or joint pain.¹⁻³ This syndrome belongs to the group of recurrent fever syndromes, which includes systemic onset juvenile rheumatoid arthritis, cyclic neutropenia, and the group of hereditary fevers, ie, familial Mediterranean fever (FMF), hyperimmunoglobulinemia D syndrome (HIDS), TNF receptor-1-associated syndromes (TRAPS), Muckle-Wells syndrome (MWS), and familial cold urticaria (FCU).² As with other recurrent fevers, the diagnosis of this disease is difficult to establish because: (a) none of the clinical symptoms is pathognomonic of PFAPA; (b) there is no specific biologic abnormality; and (c) the symptomatology may mimic other recurrent fevers. However, regarding the latter point, molecularly-based diagnostic tests are now available for several of the hereditary recurrent fevers: *MEFV* gene analysis has been proved to provide an objective diagnostic criterion for FMF⁴; HIDS has been shown to result from mutations in the mevalonate kinase gene^{5,6}; mutations in the gene encoding the tumor necrosis factor receptor-type 1 (*TNFRSF1A*) have been identified in patients with TRAPS⁷; more recently, it has been shown that MWS and FCU are both related to mutations in the *CIAS1* gene.^{8,9} The phenotypic similarities between PFAPA and FMF prompted us to test the involvement of *MEFV* in PFAPA. Indeed, given the recent demonstration that different hereditary inflammatory disorders may be related to mutations in a single gene, eg, mutations in *CIAS1* and *NOD2* accounting for MWS or FCU,^{8,9} and Crohn's disease or Blau syndrome,^{10,11} respectively, one cannot exclude the possibility that, depending on the nature of the molecular defect, the *MEFV* gene may be involved in clinically related diseases. We have, therefore, searched for *MEFV* mutations in six unrelated children with PFAPA by means of an exhaustive molecular analysis of all coding sequences and intronic boundaries.⁴ All patients met the clinical criteria for FMF defined by Livneh et al.¹²

Among the twelve independent alleles studied, only one was found to carry a *MEFV* gene mutation: the M694V substitution (nucleotide 2080 ATG>GTG), which was identified in a girl of Sephardic Jewish origin, a population in which the frequency of healthy carriers for the M694V substitution reaches one sixth. Therefore, our patient may actually be a simple carrier, a hypothesis further strengthened by the fact that this patient was successfully treated with cimetidine, a drug known to be efficient in several patients with PFAPA.¹³ The similar existence of *MEFV* mutations in

the heterozygous state has also been reported by Padeh et al¹⁴ in patients with PFAPA from populations with a high frequency of carriers (ie, patients of Jewish or Arabic ancestry). But in the latter study, as the molecular study focused on the search for three *MEFV* mutations (ie, the M694V, V726A, and M680I mutations), the possibility that *MEFV* mutations remained undetected could not be ruled out. In the current study, although the entire coding region and all flanking intronic sequences were screened for mutations, no other mutation was identified in the remaining 11 alleles. Such an exhaustive molecular analysis allowed us to conclude that those 11 alleles do not carry any *MEFV* mutation with a degree of confidence higher than that of an analysis focused on the search for a limited number of common mutations. In addition, numerous intragenic single nucleotide polymorphisms (SNPs) were identified, revealing the existence of several *MEFV* haplotypes among the six patients; because no particular *MEFV* haplotype was over-represented, we excluded the existence of a unique and rare *MEFV* mutation, resulting in PFAPA, which could have escaped our mutation analysis. This study, based on the complete screening of the *MEFV* gene in patients presenting with PFAPA, therefore strongly argues against the involvement of *MEFV* in the PFAPA syndrome.

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Outcome of hematopoietic stem cell transplantation in hyper-IgM syndrome caused by CD40 deficiency

To the Editor:

We reported in *The Journal of Pediatrics* the case of an infant with severe respiratory infections, chronic diarrhea, failure to thrive, and disseminated *Cryptosporidium parvum* infection. Laboratory investigations had disclosed the diagnosis of hyper-IgM syndrome caused by CD40 deficiency (hyper-IgM syndrome type 3 [HIGM3]). She was the fourth case reported in literature.

In this letter, we report her outcome, because she was the first case with HIGM3 who received a hematopoietic stem cell transplantation (HSCT). The first three cases of HIGM3 had lower respiratory tract infections, but regular administration of intravenous immunoglobulins, and prophylactic administration of trimethoprim-sulfamethoxazole prevented them from severe infections and they did not need HSCT.¹

Before receiving matched-sibling stem cell transplantation, our patient showed growth failure, chronic lung disease with bronchiectasis, and respiratory distress (that required tracheostomy), tracheal colonization by *Pseudomonas aeruginosa*, hepatomegaly, and sclerosing cholangitis associated with *Cryptosporidium parvum* infection.

The patient's 11-year-old human leukocyte antigen-matched brother served as the donor for HSCT. Peripheral blood stem cells (PBSC) were mobilized with granulocyte colony-stimulating factor (G-CSF), that was administered subcutaneously to the donor at the dosage of 5 µg/kg for 5 consecutive days. PBSC were then collected by leukopheresis on the fifth day of G-CSF administration. The patient received a nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m²×5 (days -7 to -3), melphelan 100 mg/m² (day -2) and antithymocyte globulin 2.5 mg/kg×5 (day -6 to 2), followed by the infusion of PBSC, containing 14.6×10⁸/kg mononuclear cells and 17.5×10⁶/kg CD34 (+) cells. Standard-dose cyclosporin A was used for prophylaxis of graft-versus-host disease. Subcutaneous low-molecular-weight heparin (100 U/kg/day) was used for prophylaxis of veno-occlusive disease (day -6 to +12). G-CSF (10 µg/kg/day) was started on day +7 until engraftment.

Intravenous immunoglobulin 0.5 g/kg per week, and prophylactic co-trimoxazole, ceftazidime, acyclovir, and fluconazole were used to prevent infections. In addition, the patient received paromomycin (30 mg/kg/day orally), azithromycin (10 mg/kg/day orally), and nitoxamide (200 mg/day orally) with the aim of preventing disseminated *Cryptosporidium parvum* infection. Inhaled tobramycin (3 mg/kg/day) was also used because of intratracheal *Pseudomonas* colonization.

The posttransplant course was complicated by high fever of undefined origin on day +5, which responded to broad-spectrum antibiotics and amphotericin B. Neutrophil engraftment (>1×10⁹/L) was achieved on day +10. However, at day +15, the patient developed severe pulmonary infection and respiratory distress, leading to hypoxia and generalized seizures. She died at day +16, after cardiorespiratory arrest. Molecular investigations with highly polymorphic DNA markers failed to reveal engraftment of donor-derived lymphocytes.

Bone marrow transplantation has been proposed and successfully used in HIGM1 (CD40 ligand deficiency), because of the severity of long-term outcome.² However, optimal treatment of HIGM3 is debated, because the potential benefit of such approach in HIGM3 is less obvious, because it would not correct lack of CD40 expression by endothelial and epithelial cells, which may play a role in the decreased resistance to opportunistic intracellular pathogens in HIGM3.^{3,4} Although assessment of the efficacy of HSCT in HIGM3 will require broader experience, our case supports the observation in HIGM1 that the presence of *Cryptosporidium* infection and chronic lung disease represent high-risk factors.

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