

Mevalonate Kinase Deficiency (Hyper-IgD Syndrome) Overlap Mutation Familial Mediterranean Fever[☆]



Deficiencia de mevalonato quinasa (síndrome de hiper-IgD) y solapamiento con mutación de fiebre mediterránea familiar

Dear Editor,

We report the case of a 10-year-old patient who was diagnosed with mevalonate kinase deficiency or hyper-IgD syndrome (p.V377I) and overlap with p.E148Q mutation for familial Mediterranean fever (FMF) with a clinical response to canakinumab after refractoriness with other treatments.

Mevalonate kinase deficiency (hyper-IgD syndrome) is an autosomal recessive autoinflammatory disease that pertains to the group of monogenic periodic fever syndromes, and is characterized by recurrent fever episodes associated with abdominal pain, lymphadenopathy, aphthous stomatitis and, sometimes, an increase in immunoglobulin D. To date, 63 mutations have been identified.^{1,2}

Familial Mediterranean fever is another monogenic periodic fever syndrome with periodic fever episodes and serositis, frequently reported in Ashkenazi Jews and Turkish and Armenian populations.³ The simultaneous development in the same patient of 2 mutations of different periodic fever syndromes is unusual.

The patient is a 10-year-old boy born in Santander, in northern Spain, of consanguineous parents (cousins). Since he was four months old, he develops, every 2–8 weeks, episodes of fever lasting 3 days, accompanied by oral aphthae, abdominal pain and emesis, leukocytosis ($15,000\text{ mm}^3$), increased erythrocyte sedimentation rate and C-reactive protein (values between 50 and 100 mg/L); the remaining variables are normal. Chest radiography was normal and abdominal ultrasound revealed mesenteric lymphadenopathy and splenomegaly. A genetic study disclosed 2 mutations; one was homozygous p.V377I (mevalonate kinase deficiency) and the second was homozygous p.E148Q (FMF). Immunoglobulin D levels were normal (37 mg/dL) and serum amyloid A was elevated (initially 50 mg/L and presently 5 mg/L). Given the genetic confirmation of mevalonate kinase deficiency, we prescribed 1 mg/day colchicine, which was ineffective, and he began to take anakinra at 2 mg/kg, with no response 3 months later. He then received etanercept 0.8 mg/kg with a partial clinical response, but it was interrupted 4 months later because of eczema. He did not respond to methotrexate, which was interrupted after 3 months due to recurrent stomatitis. Given the important impact on his life, we started canakinumab (2 mg/kg/4 weeks), with clinical response 2 months after initiating it, and complete and maintained remission of the symptoms 12 months later, although he sometimes develops aphthae, as an isolated event.

The coexistence of mutations of different autoinflammatory syndromes in the same patient has been reported very rarely, and its implications are not clear, but they include atypical clinical manifestations with a variable response to treatment.⁴

To date, the simultaneous finding of the same mutations, p.V377I (hyper-IgD) and p.E148Q (FMF), was reported in an Arab brother and sister; however, they were both heterozygote for p.E148Q, whereas, our patient was homozygote.⁵ Individuals with the latter mutation represent 85% of the clinical cases of FMF.⁶ In

another similar case, a patient with episodes of fever and abdominal pain demonstrated the coexistence of p.1268T/p.V377I (hyper-IgD) and p.E230K (FMF).⁶ Overlapping of autoinflammatory syndromes has been reported, with FMF being the syndrome most frequently involved.⁵

There are few publications on the treatment of mevalonate kinase deficiency with canakinumab. In the largest series, with 50 patients, 3 were treated with canakinumab, one with a partial response and 2 with a complete response.⁷ Another series describes 6 patients treated with canakinumab, with a complete response in 3 of them.⁸ Remission with canakinumab was documented in an 8-year-old patient.⁹

The present case is the first reported in the literature involving the association of a homozygote p.V377I (hyper-IgD) and a homozygote p.E148Q mutation. Studies would be needed to conclude whether the coexistence of 2 mutations in the same patient confers resistance to therapy, although, in cases of hyper-IgD that are difficult to manage, canakinumab seems to be a satisfactory approach.¹⁰

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