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Clinical and genetic features of Spanish patients with Mevalonate kinase deficiency

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Introduction

Mevalonate kinase deficiency (MKD) is a recessively-inherited autoinflammatory condition caused by *loss-of-functionMVK* mutations. This gene encodes for the enzyme mevalonate kinase (MVK), which catalyzes a crucial step of the biosynthetic pathway of cholesterol and isoprenoids. The partial deficiency of enzymatic activity causes the Hyper-IgD and periodic fever syndrome (HIDS), whereas it complete deficiency provokes the Mevalonic Aciduria (MA).

Objectives

The aim of this study was to describe the clinical and genetic features of Spanish patients with MKD diagnosed during the past 15 years.

Methods

The patients' data as well as the outcome of the administered treatments were collected from charts reviews. *MVK* analysis was performed by Sanger-based sequencing.

Results

Forty-one patients from different Spanish hospitals were included. Thirty-eight patients (92.7%) suffered from HIDS and three patients (7.3%) from MA. The MKD diagnosis was established in all of them by the detection of biallelic *MVK* mutations. Eighteen different *MVK* mutations were detected, with the p.[(V377I)] and p.[(I268T)] mutations as the most prevalent, accounting for 54.9% and 26.8% of mutated alleles, respectively. The majority of these mutations (96.4%) were missense mutations. The remainder mutations included premature stop (1.2%), frameshift (1.2%), and splice site mutations (1.2%). In the group of patients with HIDS (n: 38), twelve patients (31.6%) carried homozygous genotypes and twenty-six patients (68.4%) compound heterozygous genotypes. In the group of HIDS patients with homozygous genotypes (n= 12), ten patients (83.3%) carried the p.[(V377I)];[(V377I)] genotype. By contrast, in the group of patients with MA only one patient (33.3%) carried a homozygous genotype (the p.[(I268T)];[(I268T)]).

From a clinical point of view, the median age at the disease onset was 6 months (range 0-408), and the median duration of flares was 4.8 days (range 2-17.5). Mandatory vaccinations were identified as triggering factors for acute episodes in eleven patients (26.8%). The most prevalent manifestations during inflammatory episodes were fever (80.5%), lymphadenopathies (70.7%), abdominal pain (63.4%), diarrhea (58.5%), aphthous ulcers (53.7%) and arthralgia (51.2%). AA amyloidosis was only detected in one patient (2.4%), but had a severe course.

Conclusion

We herein provide a detailed description of the clinical and genetic features of a Spanish cohort of MKD patients carrying biallelic *MVK* mutations. Most of patients suffered from the mild MKD phenotype, the HIDS syndrome. Two prevalent *MVK* mutations, p.[(V377I)] and p.[(I268T)], were found in our cohort, and fever and lymphadenopathies were the most common features in enrolled patients.

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