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ORIGINAL ARTICLE

Clinical and genetic features of hereditary periodic fever syndromes in Hispanic patients: the Chilean experience

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Abstract Hereditary periodic fever syndromes (HPFS) are rare genetic diseases characterized by recurrent episodes of inflammation. Little information is available concerning HPFS in Latin American Hispanic population. The purpose of this study was to determine the clinical and genetic features of HPFS in Chilean population. A multicenter retrospective study of Hispanic Chilean patients with genetically confirmed HPFS was performed. We included 13 patients, 8 with familial Mediterranean fever (FMF) and 5 with TNF receptor-associated periodic syndrome (TRAPS), evaluated at rheumatology or pediatric rheumatology clinics between January 2007 and December 2010. Median age of symptoms onset was 8 years (range 1–35) and 8 years (range 0.3–21) for FMF and TRAPS, respectively. Median duration of fever was 3 days (range 2.5–15) for FMF and 21 days (range 9.5–30) for TRAPS. Genotyping of the *MEFV* gene in FMF patients revealed a homozygous M694V missense mutation in one patient, and heterozygous missense mutations in seven patients: M694V (n=3), E148Q, R717H, A744S, and A511V. Sequencing of the *TNFRSF1A* gene in TRAPS patients revealed heterozygous missense mutations in four patients: T50M, C30R, R92Q, and IVS3+30:G→A, and a two-base pair deletion (IVS2-17_18del2bpCT) in one patient. Mutation in *MEFV* R717H and mutations in *TNFRSF1A* IVS2-17_18del2bpCT and IVS3+30:G→A are novel and have not been described previously. This study reports the largest series of genetically confirmed HPFS in Latin America, and adds evidence regarding the clinical and genetic characteristics of patients with FMF and TRAPS in Hispanic population. Mutations

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identified in *MEFV* and *TNFRSF1A* genes include defects reported in other ethnicities and novel mutations.

Keywords Autoinflammatory syndromes · Familial Mediterranean fever · Hispanics · Periodic fevers · Tumor necrosis factor receptor-associated periodic syndrome

Introduction

Hereditary periodic fever syndromes (HPFS) are rare diseases characterized by recurrent, self-limited episodes of fever and localized inflammation, which arise from monogenic defects involving innate immunity and inflammation [1]. The pathogenesis of these disorders differ from autoimmune diseases, such as systemic lupus erythematosus or rheumatoid arthritis, because they are not mediated by antigen-specific T cells or autoantibodies, and thus have also been labeled as autoinflammatory syndromes (AIS). Current classifications of AIS group HPFS together with several other chronic autoinflammatory disorders, enlarging the spectrum of diseases characterized by recurrent spontaneous inflammation. These include some monogenic disorders (e.g., NFκB activation disorders like Blau syndrome) and other diseases with more complex inheritance patterns such as systemic onset juvenile idiopathic arthritis and chronic gout [2–4]. Several different HPFS with a known specific gene defect have been described to date, including familial Mediterranean fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), and the cryopyrin-associated periodic syndromes (CAPS).

FMF is the most prevalent among all of these diseases, with an estimated prevalence of 1:400–1:1,000 in countries of the eastern Mediterranean basin, such as Turkey, Armenia, and Israel [5]. This probably reflects the high frequency of the disease among individuals from Turkish, Sephardic Jew, Armenian, and Arab populations, with lower rates reported in people from other ethnicities or locations. FMF patients develop periodic, short (1 to 3 days) febrile episodes often associated with abdominal pain, arthritis, pleuritis, skin rash, and a marked acute phase response. If untreated, some FMF patients can develop reactive AA-type amyloidosis as a late complication, which potentially can provoke chronic renal failure and death [6]. FMF is caused by mutations in the *MEFV* gene, which encodes a protein called pyrin. The pathogenesis of FMF has been shown to be driven by gain-of-function mutations in pyrin that extrinsically activate the inflammasome driving IL-1β production and clinical symptoms [7]. FMF generally has an autosomal recessive inheritance. However, this concept is currently under investigation due to the presence of a high number of FMF patients (up to 30%) with only a single mutated *MEFV* allele [8]. On the contrary, TRAPS is a clear autosomal dominantly inherited disease due to mutations in the *TNFRSF1A* gene, which encodes the TNF receptor 1. Mutations in this gene cause protein misfolding and abnormal trafficking, leading to intracellular retention of mutant receptors that potentiate inflammation through activation of mitogen-activated protein kinases [9]. Although originally described in an Irish-Scottish family and consequently named familial Hibernian fever, the TRAPS syndrome has been described in people from a wide range of ethnical backgrounds, with no predilection for any particular ethnicity. Patients with TRAPS suffer from long (more than 7 days), recurrent febrile episodes, associated with mygratory myalgias, painful erythematous skin rash, abdominal pain, conjunctivitis, and periorbital edema [10, 11].

Most clinical studies of HPFS like FMF and TRAPS have been done in developed countries or in populations with a high FMF prevalence. There is growing evidence that these diseases also exist in other parts of the world with different ethnic composition. However, there is very little clinical and genetic information of patients from these places, such as the Latin American Hispanic population. The purpose of this study is to determine the main clinical and genetic characteristics of Hispanic patients with HPFS from Chile.

Patients and methods

In the present multicenter retrospective study, we included 13 HPFS patients with a confirmed genetic diagnosis evaluated at rheumatology or pediatric rheumatology clinics between January of 2007 and December of 2010. Participating centers were Hospital Clínico Universidad Católica (n=4), Hospital Salvador (n=2), Hospital FACH (n=2), Hospital Gustavo Fricke (n=1), Hospital Militar de Santiago (n=1), and Hospital Naval Almirante Nef (n=3). All patients were Chilean and had Hispanic Latin American ethnicity with no other known ethnic origin up to the third generation (Chilean grandparents). This study did not include patients with autoinflammatory syndromes other than HPFS.

Inclusion criteria for FMF were the presence of the characteristic clinical features associated with at least one mutated *MEFV* allele, whereas the TRAPS inclusion criteria were the presence of long inflammatory episodes associated with *TNFRSF1A* mutations. Clinical and laboratory data were obtained through direct interviews and chart reviews. Data collection included the patient's age, age at diagnosis, sex, clinical presentation, laboratory data, late complications, and responses to treatments. Genetic HPFS analyses were performed by direct sequencing at Hospital Clínic, Barcelona, Spain as previously described [12]. Written

informed consent from each studied individual was obtained prior to genetic studies. The ethics committee at Pontificia Universidad Catolica de Chile School of Medicine approved the study.

Results

Thirty-seven patients were screened for HPFS in the study period: 21 suspected of having FMF, 15 of TRAPS, and 1 of CAPS. Thirteen patients with a genetically confirmed HPFS were included in the study, 8 with FMF diagnosis and 5 with TRAPS. Two patients with TRAPS (patients 1 and 4) have been previously reported by our group [13]. No patients with other genetically proven HPFS, like HIDS or CAPS syndromes, were seen in the study period. Median age at disease onset was 8 years (range 1–35) for FMF patients and 8 years (range 0.3–21) for TRAPS patients. Three out of eight FMF patients (37%) were female, and three out of five (60%) in the TRAPS group. Family history of the disease was present in only two FMF patients (patient 5 and 8), and none of the TRAPS patients.

Clinical characteristics of FMF patients are shown in Table 1. All FMF patients suffered from periodic febrile episodes lasting 1 to 4 days, which typically recurred every 1 to 3 weeks. Only one FMF patient displayed an atypical presentation, with long febrile episodes (around 15 days) accompanied by myalgias and rash, which recurred every 6 months. In the FMF group, the fever was often associated with abdominal pain (six out of eight), myalgias (five out of eight), arthritis (four out of eight), and rash (three out of eight). One patient (patient 2), who also had paroxysmal nocturnal hemoglobinuria, developed portal vein thrombosis and Budd–Chiari syndrome. All FMF patients had at least a partial response to colchicine therapy, with two patients with fully resolving episodes of recurrent fevers. Fortunately, reactive AA-type amyloidosis was not observed among this group of FMF patients.

The clinical characteristics of TRAPS patients are shown in Table 2. All TRAPS patients were diagnosed in adulthood, despite disease onset widely varied between 3 months to 21 years of age. The observed febrile episodes were long, lasting at least 10 days, and preceded by malaise and periorbital edema in two patients. The most common detected symptoms other than fever were migratory myalgias (four out of five), rash (three out of five), arthralgias/arthritis (three out of five), and abdominal pain (three out of five). Two patients underwent surgery for acute abdomen. One of them had a blank laparotomy (patient 1), and the other had intestinal obstruction by adhesions, probably a consequence of recurrent inflammatory episodes (patient 4). All TRAPS patients were responsive to high-dose corticosteroids during febrile episodes, with the only exception of patient 3 whose inflammatory disease mimicked the adult-onset Still's disease, was also refractory to multiple different treatments (thalidomide, chlorambucil, etanercept, adalimumab, infliximab, and rituximab), and could finally be controlled with abatacept, which provoked the complete resolution of inflammatory episodes.

Mutation analysis

Mutational analyses of *MEFV* (exons 1 to 10) and *TNFRSF1A* (exon 2 to 7) were performed in all included patients by bidirectional direct sequencing. *MEFV* gene mutational analyses in the FMF patients revealed one patient with a homozygous p.M694V/p.M694V genotype, and seven patients with only one mutated MEFV allele [p.M694V (n=3), p.E148Q, p.A511V, p.R717H, and p.A744S]. Mutation p.R717H was novel, and mutation p.A511V has only been reported previously in a Chilean patient [14]. *TNFRSF1A* mutational analyses in the TRAPS group revealed three different missense mutations (p.C30R, p.T50M, p.R92Q) and two novel heterozygous intronic variants (IVS2-17_18del2bpCT and IVS3+30:G→A). FMF patients had no mutations on the *TNFRSF1A* gene, and no TRAPS patients carried mutations in the *MEFV* gene. In the case of FMF patient 3, mutational analyses of *MVK* and *NLRP3* genes did not detect disease-associated mutations. The phenotype/genotype correlations for each patient with FMF and TRAPS are shown in Tables 1 and 2, respectively.

Discussion

The present study reports the largest series of genetically confirmed HPFS, mainly FMF and TRAPS, in Latin America. Previous reports from this continent have been published as case reports or series without genetic confirmation [15–17]. Matos et al. described three Brazilian patients with different HPFS (CAPS, FMF, and TRAPS). Although they stated that patients with TRAPS and CAPS had genetic confirmation, details about specific mutations were not provided [15]. A larger series of 52 patients with a clinical diagnosis of FMF from Mexico City, 13 of which were Syrian born, showed typical clinical characteristics and no patients with reactive AA-type amyloidosis. However, inclusion criteria were rather loose and no genetic studies were performed [17]. Our study shows that Chilean patients with FMF and TRAPS have a similar clinical presentation to patients in other regions. However, some of our patients also showed atypical manifestations, and family history of periodic fever was negative in all but two patients. In addition in our series, the disease begun during adult age in 37% of FMF patients, in contrast to literature data where the majority of patients showed a disease onset before 20 years

Table 1 Genetic and clinical characteristics of Chilean patients with familial Mediterranean fever

Patient	1	2	3	4	5	6	7	8
MEFV genotype	M694V/M694V	R717H/-	A744S/-	E148Q/-	M694V/-	A511V/-	M694V/-	M694V/-
Exon/intron	10	10	10	2	10	5	10	10
Sex	F	M	M	M	M	F	F	M
Disease onset (years)	1	35	1	2	30	20	10	6
Delay in diagnosis (years)	20	15	7	16	15	38	21	19
Duration of attacks (days)	2.5	3	3	15	3	3	4	2.5
Recurrence rate (months)	1	1	1	6	1	2	4	2
Fever	+	+	+	+	+	+	+	+
Abdominal pain	+	−	+	−	+	+	+	+
Arthritis	+	+	−	−	+	−	+	−
Skin manifestations	+	+	−	+	+	−	−	−
Myalgias	+	+	−	+	+	−	+	−
Ocular manifestations	−	−	−	−	+	−	−	−
Oral ulcers	−	−	−	−	−	+	+	−
Pericarditis	−	−	−	−	−	+	−	−
Pleuritis	−	−	−	−	+	−	+	−
Response to colchicine	+/−	+/−	+/−	+/−	+	+	+	+

[18–20]. In our series, age distribution at disease onset in TRAPS patients was similar to previously reported literature [21]. Due to the low frequency and therefore low index of suspicion of these diseases in our country, the delay in diagnosis of an HPFS was 18.5±9 years. However all patients had a diagnosis of undefined inflammatory syndrome except TRAPS patient 3 who carried the diagnosis of adult-onset Still's disease.

Most FMF patients in our series carried only one mutated *MEFV* allele, which differs from other populations with high prevalence of FMF, where over 80% of patients have mutations in both alleles [22]. It has been suggested that in those countries where FMF has a low prevalence, patients usually have negative family history and the disease-causing mutations may lead to an atypical presentation or milder disease [5]. In this setting, genetic testing plays a much more crucial

Table 2 Genetic and clinical characteristics of Chilean patients with TNF receptor-associated periodic syndrome

Patient	1	2	3	4	5
TNFRSF1A genotype	p.T50M	IVS2-17_18del2bpCT	IVS3+30: G→A	p.C30R	p.R92Q
Exon/intron	3	Intron 2	Intron 3	2	4
Sex	F	F	M	M	F
Disease onset (years)	0.25	21	18	0.3	8
Delay in diagnosis (years)	23	10	32	18	6
Duration of attacks (days)	14	30	25	10	21
Recurrence rate (months)	3–6	24	1	3–6	12
Fever	+	+	+	+	+
Abdominal pain	+	+	−	+	−
Arthralgias/arthritis	+	+	+	−	−
Skin manifestations	+	−	+	+	−
Myalgias	+	+	+	+	−
Ocular manifestations	+	−	−	+	−
Lymphadenopathy	+	+	−	−	−
Orchitis	−	−	−	+	−
Response to corticosteroids	+	+	+/−	+	+

role in identifying FMF patients, and single *MEFV* mutations gain more relevance. Several authors have suggested that a single heterozygous mutation in patients with typical characteristics of FMF is enough to establish both a diagnosis of FMF and a therapeutical trial with colchicine [8, 23].

It has been reported that FMF is an inflammatory disease generally restricted to Turks, Armenians, Arabs, and non-Ashkenazi Jews, with a relative genetic homogeneity because five different mutations that have a founder effect (p.M680I, p.M694V, p.M694I, p.V726A, and p.E148Q) can explain up to 85% of cases in these ethnic groups [24]. Most cases described outside the Mediterranean basin have been associated to migratory movements [5]. Chilean population is a blend of European, mainly Spanish, and American Indian ethnicities. During the nineteenth and twentieth centuries, large groups of immigrants from Western Europe and the Middle East (mainly Palestinians, Syrians, and Lebanese) came to Chile. It is currently estimated that approximately 0.5% of the Chilean population descends from Middle Eastern immigrants [25]. In this scenario, it is plausible to hypothesize that those *MEFV* mutations typically detected in Middle Eastern population were brought to Chile by immigrants that blended into the population. Thus, in our series 67% of FMF patients were carriers of the p.M694V (patients 1, 5, 7, and 8) or p.E148Q (patient 4) mutations. The other three FMF patients in our series had nonfounder mutations A744S, A511V, and R717H, being the latter a novel MEFV mutation. A missense mutation leading to replacement of arginine in position 717 to serine has been described to cause symptomatic FMF with atypical presentation. This suggests that the R717H mutation in our patient is likely to be pathogenic as well. Interestingly, mutation A511V has only been reported in a patient from Chile as mentioned previously, suggesting this variant may be specific to our population.

Of special note is the patient who developed portal vein thrombosis and Budd–Chiari syndrome. FMF has been previously suggested as a risk factor for Budd–Chiari syndrome [26]. Our patient also had paroxysmal nocturnal hemoglobinuria, a well recognized cause of Budd–Chiari syndrome [27]. It is possible that the combination of two risk factors in our patient led to this complication.

Worldwide, TRAPS is much less frequent than FMF, and although the disease was originally described in an Irish-Scottish family, it is accepted that it does not have any ethnic predilection [28]. In our series, we describe five Chilean patients with TRAPS, two of them with novel heterozygous intronic variants (IVS3+30:G→A and IVS2-17_18del2bpCT). The pathogenic role of these variants is unclear. However, both patients had a recurrent autoinflammatory disease with other manifestations typical of TRAPS. The only patient in our series with the debated p.R92Q variant had recurrent fevers without any other clinical manifestations. The p.R92Q variant is considered as a low-penetrance mutation found in 1–6% of the general population [29, 30]. As in our patient, it has been usually related to atypical presentations with a milder phenotype than other disease-associated mutations.

In our TRAPS series, the patients suffered from recurrent febrile episodes responsive to systemic corticosteroids, as has been reported previously [31]. Only one TRAPS patient (patient 3) was treated with TNF-α inhibition for putative adult-onset Still's diseases prior to genetic confirmation of TRAPS. Interestingly, he had persistent inflammation refractory to several different TNF-α blockers, and only responded to abatacept, a CTLA4 soluble fusion protein that blocks T-cell costimulation. It has been shown that in TRAPS during febrile attacks, there is an expansion of effector T cells and a predominantly Th1 response [32]. Another report showed that tacrolimus, a suppressor of activated T cells via calcineurin inhibition, was effective at controlling inflammation in a TRAPS patient [33]. It is possible that the blockade of the T-cell activation decreases the soluble TNF-α secretion and consequently the acute inflammatory episodes can be, at least partially, controlled. Further studies are warranted to elucidate the role of T cells in the pathogenesis of TRAPS as well as the potential therapeutical efficacy of inhibition of T cell activation.

In conclusion, we report the clinical and genetic characteristics of Chilean patients with FMF and TRAPS, which represent, to our knowledge, the largest series of genetically confirmed HPFS in a Latin American Hispanic population. The prevalence of these diseases in our continent must be low, but is still unknown, and HPFS are probably underdiagnosed due to lack of clinical recognition and limited availability of genetic studies to obtain a definitive diagnosis. Our study also supports the clinical utility of genetic studies in populations where these diseases are uncommon, which enabled us to detect both novel and previously described *MEFV* and *TNFRSF1A* mutations. Further collaborative studies are needed to expand the knowledge about clinical diversity as well as genetic characteristics of HPFS in Latin America.

Disclosures None.

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