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ORIGINAL PAPER

PFAPA syndrome in siblings. Is there a genetic background?

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Abstract "PFAPA syndrome" is an autoinflammatory entity composed of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. There have been many reports of children with the disease, but only occasionally have been described in siblings, and no specific genetic mutation has been determined yet. Corticosteroids are the mainstay in the treatment of the acute attacks. The role of surgery in long-term follow-up (tonsillectomy with or without adenoidectomy) is controversial. We report two brothers affected with the syndrome, in whom corticosteroids as the only treatment led to an improvement. A genetic work-up was performed, making very unlikely other possible syndromes of recurrent fever. *Conclusion*: PFAPA syndrome is the most common recurrent periodic fever disorder described in childhood. Its genetic background has not been elucidated yet. Our contribution with two siblings affected with PFAPA syndrome further support the genetic basis for the entity.

Keywords PFAPA syndrome · Familial Mediterranean fever (FMF) · Mevalonate kinase deficiency syndrome (MKD) · Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) · Siblings

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Introduction

Autoinflammatory syndromes are diseases manifested by recurrent episodes of inflammation and fever with no production of autoantibodies but increase of interleukins and acute-phase reactants. There are several types of autoinflammatory syndromes, which are classified by the clinical findings and the genetic pattern. The most relevant ones are familial Mediterranean fever (FMF), mevalonate kinase deficiency syndrome (MKD), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) [12].

By far, the most common autoinflammatory syndrome is PFAPA, which acronym means periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. It is an idiopathic recurrent febrile syndrome characterized by episodes of periodic fever with a set of symptoms that recur at regular intervals in time. It was first described by Marshall [14] in 1987, and since then, there have been many reports of children with the disease [16, 20]. Clinically, these patients have recurrent episodes of high fever, mouth ulcers, prominent cervical lymph nodes, and pharyngitis with negative throat cultures.

Although the etiology is still unknown and no specific genetic mutation has been described, autoimmunity seems to play a role in the pathogenesis [17]. The fast resolution of the attacks by steroids supports this theory. Even though no familial relation has been established, some publications have reported cases in siblings during the past few years [1, 6, 18, 21]. The objective of this article is to describe the clinical findings, diagnostic work-up with genetic studies,

and treatment of two siblings diagnosed with PFAPA syndrome.

Case report

Patient 1 is an 11-year-old boy with no previous medical problems. He was a full-term baby with normal birth weight. He had no history of dietary or developmental issues, and he had received the routine vaccinations. Since 6 years of age, he has presented episodes of fever up to 39.5°C that recur with a regular periodicity every 3 weeks. The fever is accompanied by chills, occasional vomiting, headache, and continuous sore throat with inflamed cervical lymph nodes. He has no arthritis, mouth ulcers, or exudates in tonsils.

Antibiotics have been used several times with no improvement. The episodes have been difficult to control with antipyretics but have subsided spontaneously after a period of 3–4 days.

On physical examination, he appears healthy with normal weight and height for his age and without any remarkable findings. Laboratory results during a febrile episode showed normal hemoglobin (13.3 g/dl, normal 11.5–15), no leukocytosis (7,700 cells/mcl, normal 4,000–13,500), neutrophils (4,400 cells/mcl, normal 1,500–8,000) and mild C-reactive protein (CRP) elevation (42.1 mg/L, normal 0–6). Immunoglobulins were within normal limits: IgG 990 mg/dl (normal 700–1200), IgA 173 mg/dl (normal 70–200), and IgM 71.8 mg/dl (normal 40–120). We did not repeat these studies during follow-up. Throat culture for *Streptococcus pyogenes*, as well as *Toxoplasma gondii*, Epstein-Barr virus, and cytomegalovirus (CMV) serologies performed once during one of the febrile episodes were all negative. As complementary studies, we quantified immunoglobulin D (0.00 mg/dl, normal 1.00–5.00) and investigated *MEFV* gene for FMF, the *TNFRSF1A* gene for TRAPS, and the most common mutation (*V3771*) for MKD which were all negative. A single dose of oral prednisone at

Table 1 Clinical characteristics, laboratory results, treatment, and follow-up of both siblings

Cases	Patient 1	Patient 2
Age at onset	6 years	6 months
Current age	11 years	4 years
Lenght of fever episode	3–4 days	2–3 days
Periodicity of episodes	Every 3 weeks	Every 2–3 weeks
Fever (maximum)	39.5°C	40.5°C
Pharyngitis	+	+
Cervical adenitis	+	+
Aphthous stomatitis	−	+
Arthralgias/myalgias	−	+
Headache	+	+
Vomiting	+	−
Abdominal discomfort	−	−
Leucocyte count	7,700 cells/mcl	15,000 cells/mcl
Hemoglobin	14.3 g/dl	10.9 g/dl
C-reactive protein	42.1 mg/L	48.8 mg/L
Immunoglobulins		
IgG	990 mg/dl	846 mg/dl
IgA	173 mg/dl	112 mg/dl
IgM	71.8 mg/dl	79.6 mg/dl
Thorat culture for *S. pyogenes*	Negative	Negative
Serologies for *Toxoplasma*, Epstein-Barr virus, and cytomegalovirus	Negative	Negative
Immunoglobulin D quantification	0.00 mg/dl	11.5 mg/dl
FMF, *TNFR1*, and *MVK* mutations	Negative	Negative
Corticosteroids treatment	0.5 mg/kg at 1–2 doses	1 mg/kg at 1–2 doses
Present evaluation	Good response to steroids	Good response to steroids
	Shorter febrile episodes. They initially occurred more frequently but spaced during the years	Shorter febrile episodes. They occur more frequently

Table 2 Summary of reported familial cases

	Sampaio et al.	Valenzuela et al.		Adachi et al.	Present patients
Patient's background					
Type of patient/sex	Two siblings (boy/girl)	Two sisters	Two brothers	Monozygotic twin girls	Two brothers
Consanguinity	None	None	None	None	None
Age at diagnosis	(1) 10 years	(1) 9 years	(1) 7 years	(1) 2 years	(1) 11 years
	(2) 4 years	(2) 7 years	(2) 3 years	(2) 3 years	(2) 4 years
Age at onset	(1) 18 months	(1) 18 months	(1) 3 years	(1) 11 months	(1) 6 years
	(2) 3 years	(2) 2 years	(2) 2 years	(2) 12 months	(2) 6 months
Parents affectation	No	Both parents	No	Mother	Mother
					Grandmother
Race	Unknown	German–Italian–Chilean	Spanish	Japanese	Spanish
		Jewish Ashkenazi–Spanish–Chilean	Spanish	Japanese	Spanish
Growth and development	Normal	Normal	Normal	Normal	Normal
Clinical characteristics					
Maximum of fever	High, not exactly described	(1) 39.5	(1) 39.5	High, not exactly described	(1) 39.5
		(2) 39	(2) 40		(2) 40.5
Periodicity of fever	Monthly (both)	(1) 8 weeks	(1) 3 weeks	(1) 15–20 days	3 weeks
		(2) 4 weeks	(2)16–20 days	(2) 14–18 days	2–3 weeks
Length of fever	4–5 days	3–4 days	3–4 days	3–5 days	(1)3–4 days
	(Both)	(Both)	(Both)	(Both)	(2) 2–3 days
Aphthous stomatitis	+ (Both)	+ (Both)	+ (Both)	+ (Both)	(1) No
					(2) +
Pharyngitis	+ (Both)	+ (Both)	+ (Both)	+ (Both)	+ (Both)
Cervical adenitis	+ (Both)	+ (Both)	+ (Both)	+ (Both)	+ (Both)
GI problems	None	Vomit (Both)	(1) No	None	(1) Vomit
			(2) Vomit, diarrhea		(2) No
Artharlgia/myalgia	None	None	None	None	(1) No
					(2) +
Headache	Not described	Not described	Not described	No	+ (Both)
Rash	No	Not described	Not described	No	No
Laboratory findings					
Leukocytosis	+	+	+	+	+
Neutropenia	No	No	No	No	No
Elevated CRP/ESR	+	+	+	+	+
Immunoglobulins	Normal	Normal	Normal	Normal	Normal
Complement	Normal	Not described	Not described	Normal	Normal
Throat cultures	Negative	Negative	Negative	Negative	Negative
Serologies	Negative	Unknown	Unknown	Unknown	Negative
Immunoglobulin D quantification	Not described	Unknown	Unknown	Mildly elevated	Negative
FMF, *TNFR1*, and *MVK* mutations	Not described	Unknown	Unknown	Negative	Negative
Treatment					
Antibiotics	No response	No response	No response	No response	No response
Cimetidine	Unknown	Not described	Not described	Discontinued	Not prescribed
Corticosteroids	Response	Not prescribed	Not prescribed	Response	Response

Table 2 (continued)

	Sampaio et al.	Valenzuela et al.		Adachi et al.	Present patients
Tonsillectomy	Not done	Not done	Not done	Not done	Not done
Prognosis					
Age at last attack	Unknown	(1) 6 years (2) 6 years	(1) 7 years (2)Not described	Continued	Continued
Present status	No remission	Complete remission	Complete remission	No remission	(1) Previous increase of frequency. Currently decrease of frequency
	Decrease of frecuency.			Decrease of frecuency	(2) Increase of frequency

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate

Modified from Adachi et al.

0.5 mg/kg yielded a rapid response in all febrile episodes during the following years.

After corticosteroid treatment was initiated, the intervals initially occurred more frequently but spaced along the last 2 years. This change in the febrile pattern suggests an improvement of the syndrome (Table 1).

Patient 2 is his 4-year-old younger brother. He is a healthy boy with normal birth history. He had normal diet, development, and vaccinations without complications. Since the age of 6 months, he has had recurrent episodes of fever up to 40.5°C lasting for 2–3 days. The periodicity of the attacks was initially irregular, but during the past year and a half, he has been suffering an episode every 2–3 weeks. The fever is associated with persistent cervical lymphadenopathy but occasional pharyngitis, stomatitis, malaise, and headache. During one of the episodes, he had arthralgias on both legs causing him a limp that resolved spontaneously with the reduction of fever. A single dose of oral prednisone was prescribed because of the preceding diagnosis of his older brother. Although higher doses (1 mg/kg) were needed to achieve satisfactory responses, every episode was usually resolved within 24 hours and a higher periodicity of the intervals was noted.

On physical examination, he has no abnormalities. Laboratory findings during a febrile episode were hemoglobin (10.9 g/dl, normal 11.5–15), mild leukocytosis (15,000 cells/mcl, normal 4,000–13,500), neutrophils 8,400 cells/mcl (normal 1,500–8,000), and mild CRP elevation (48.8 mg/L, normal 0–6). Immunoglobulins were within normal limits: IgG 846 mg/dl (normal 700–1,200), IgA 112 mg/dl (normal 70–200), and IgM 79.6 mg/dl (normal 40–120). Throat culture for *S. pyogenes* and serologies for *T. gondii*, Epstein-Barr virus, and cytomegalovirus performed once during follow-up was also negative.

Immunoglobulin D quantification was mildly elevated (11.5 mg/dl, normal 1.00–5.00) and no mutations for FMF, MKD, and TRAPS were detected. At the last examination, he has shorter febrile episodes with a higher frequency of the intervals between them.

Family history has revealed a 40-year-old father and an 8-year-old brother with no previous recurrent pharyngitis or an unexplained fever. The 39-year-old mother and the grandmother suffered from periodic fever with tonsillitis during childhood. The mother had tonsillectomy at the age of 7 years. Parents are non-consanguineous. Genetic analysis was performed after a written informed consent. Genomic DNA was extracted from peripheral blood of the patients and studied at the immunology laboratory.

The most common genetic mutations were studied in *MEFV* gene (exons 2 and 10), *TNFRSF1A* gene (exons 2, 3, 4, 7, and intron 8), and the most frequent mutation (*V377I*) in *MVK* gene. No immunoassay of mevalonate kinase was performed in our patients. No molecular defects were found.

Discussion

"PFAPA syndrome" was first reported by Marshall in 1987 to describe an entity composed of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. The illness usually appears before 6 years of age, with episodes of abrupt onset (10–12 per year), every 3–4 weeks and lasting for 4–6 days. It has male predominance and race diversity. The fever is the main characteristic sign (97%). It increases up to 40.5°C, lasts for 3–5 days, and is resistant to antipyretics. In addition, it may be associated with solitary or scattered mouth ulcers, pharyngitis with negative culture, and reactive cervical adenitis. Other minor symptoms are headache, abdominal pain, nausea, vomiting, chills, malaise, myalgia, and arthralgia. Between the episodes, these children are healthy with normal growth and development [13]. Sometimes, parents describe a history of recurrent pharyngitis or unexplained fevers in their childhood. At present, the etiology of the syndrome remains unknown. There are several hypotheses.

The ability of steroids to resolve the attacks and the elevated levels of cytokines during each process suggest an inflammatory origin. We have not measured these cytokine levels in our patients. Primary dysregulation of the innate immune system has been suggested to be involved, even if it is postulated that this dysregulation could trigger other autoimmune disorders [2]. However, it does not seem to be related with the defects of immunity as none of these children are immunodeficient. Some articles have described an abnormal cytokine profile suggesting also an auto-inflamatory response [19]. A few authors have classified some hereditary autoinflammatory disorders by genetic analyses, but no mutation has been identified yet in this syndrome. Although no familial relation had been previously described, some publications have reported cases in siblings during the past few years [1, 6, 18, 21]. These descriptions further emphasize a thinkable genetic basis on its pathophysiology (Table 2). Moreover, some studies have performed diagnostic scores for molecular analysis to help pediatricians in the evaluation of children with periodic fever and optimize the positive results on genetic testing [11].

The diagnosis is usually straightforward based on clinical findings and the rapid response to corticosteroids. During follow-up, laboratory evaluation can be performed to rule out other common disorders. These tests include throat culture, chest radiography, complete blood counts, erythrocyte sedimentation rate (ESR), CRP, immunoglobulin (IgA, IgM, IgG, and IgD) quantification, C3, C4, CH50, Epstein-Barr virus, CMV, *Toxoplasma*, and adenovirus serology. These analyses are usually negative except for mild leukocytosis and an elevated CRP or ESR during febrile attacks [3, 8]. Procalcitonin concentrations are usually within normal limits [22]. As in one of our patients, IgD quantification may be slightly elevated but at lower levels than Hiper IgD syndrome (<14 mg/dl).

We think that these studies do not have to be repeated during follow-up if the clinical diagnoses are clear and other disorders have been ruled out. Some authors have postulated it may be necessary to detect the presence of some monogenic periodic fevers, as their clinical presentation can overlap PFAPA syndrome. These diseases, familial Mediterranean fever (FMF, *MEFV* gene), tumor necrosis factor (TNF) receptor-associated syndrome (TRAPS, *TNFRSF1A* gene), and mevalonate kinase deficiency (MKD, MVK gene) have well-known mutations [5, 10].

Even though these mutations have been described in genes located in different regions of the DNA, the study of the most frequently involved exons/introns makes very unlikely the diagnosis of these monogenic fevers, as we have performed with our patients.

Moreover, although the possible involvement of *MEFV* and *TNFRSF1A* gene mutations has been further described [7], we think MKD must be the most frequent one to be investigated because the age of presentation and duration of the episodes may be similar. We decided, with the consent of the parents, to investigate these three genes to clarify the origin. This genetic research in siblings was previously performed in a Japanese report with the same negative results [1].

Treatment is controversial. Corticosteroids (prednisone or prednisolone) at 1–2 mg/kg as 1–2 doses resolve the attacks in less than 24 hours. The lack of response makes PFAPA unlikely. There is no consensus on the correct dose of steroids because each patient may respond differently. We decided to begin with 0.5 mg/kg of oral prednisone with the older boy, but his younger brother needed a higher dose for a successful response. Several patterns in evolution have been described, the most common one being a decrease in the duration and frequency of the episodes; however, there are cases with an increase in the periodicity of the febrile intervals after treatment initiation. Some of them usually resolve with steroids. Antibiotics and antipyretics are not useful for the condition. For the long-term, tonsillectomy with or without adenoidectomy may be an option. Some studies have reported patients who are symptom-free at 12–18-month follow-up compared with no surgery. However, there is no long-term follow-up in patients who underwent tonsillectomy and adenotonsillectomy [4, 9]. The duration of the syndrome is variable and resolution without sequelae by the age of 9 to 11 years is the rule. The overall prognosis is excellent. The risk and benefit of performing surgery should be balanced on an individual basis [15]. We decided in agreement with parents not to undergo surgery due to the self-limited and benign condition.

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