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Clinical note

Comparative analysis of rare periodic fever syndromes including the first Korean case of hyperimmunoglobulinemia D and periodic fever syndrome

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Periodic fever syndromes (PFS) are characterized by recurrent episodes of unexplained fever occurring at least 7 days apart in 6 months.[1] Beyond recurrent fever, PFS presents with lymphadenopathy and/or oral, gastrointestinal, articular, and cutaneous symptoms during each febrile episode. Most patients with PFS lack identifiable genetic abnormalities and are diagnosed with periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome after exclusion of infection, autoimmune diseases, and malignancy. Meanwhile, hereditary forms linked to monogenic variants responsible for inborn errors of innate immunity are rarely reported. This report details the first documented case of hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) in a Korean patient comparing it with PFAPA syndrome and other hereditary PFS in Korea.

A 12-year-old boy presented with a history of recurrent fevers since infancy, beginning at 3 months of age. These episodes typically lasted 3–5 days and recurred every 2–4 weeks. Interestingly, the intervals between attacks appeared to shorten following vaccinations. Each febrile episode was accompanied by symptoms, including exudative tonsillitis, cervical lymphadenopathy, severe abdominal pain, and diarrhea, accelerating the use of antibiotics. Additionally, the patient experienced oral ulcers, chills, general weakness, conjunctivitis, arthralgia, and a maculopapular rash on the trunk and extremities. Notably, the patient was asymptomatic during the afebrile periods. The symptoms in the patient persisted despite a tonsillectomy performed at the age of 10. A physical examination revealed only splenomegaly (14.5 cm in length) as an abnormality. Laboratory profiles were largely unremarkable except for elevated C-reactive protein, erythrocyte sedimentation rate, and amyloid A levels during febrile episode. Additionally, serum levels of immunoglobulin (Ig) D and IgA were consistently elevated (Fig. 1A). Targeted gene panel sequencing revealed 2 novel variants in the MVK gene: NM_000431.4: c.119G>A (p.Arg40Gln) and c.992T>C (p.Leu331Pro). Both parents were confirmed as heterozygous carriers of these variants (father: heterozygous carrier for c.119G>A; mother: heterozygous carrier for c.992T>C), suggesting a transconfiguration of the variants in the patient (Fig. 1B). Mevalonate kinase (MVK) deficiency is an autosomal-recessive autoinflammatory disorder caused by mutations in the MVK gene.[2] While mevalonic aciduria is the most severe spectrum of MVK deficiency characterized by near-absent MVK enzyme activity, HIDS is a less severe form associated with partial enzyme activity. The Eurofever score for MVK deficiency in this patient was 90 (cutoff >42).[3] While the specific variants identified in this patient have not been previously reported in MVK deficiency,[4] characteristic pattern of recurrent fevers beginning in early infancy strongly suggests a pathogenic role for these variants.

Written informed consent-to-disclose was obtained from the parent of the patient and this study was approved by the Institutional Review Board of Korea University Guro Hospital (IRB No. 2023GR0582).

Q: Can PFS be differentiated before genetic testing?

Fig. 2 presents 4 cases: 3 rare hereditary PFS cases and a typical case of PFAPA syndrome. The familial Mediterranean fever (FMF) deviated from others with onset at an older age and atypical periodicity.[5] The patient presented with a total of 2 febrile episodes, with a significant gap between them. While the first episode lasted 7 days, the second episode, which started 5 months later, continued for 23 days without associated symptoms. Intense acute-phase responses and negative findings of infections, autoimmunity and malignancy led to a colchicine trial that successfully resolved the fever within 4 days. Abdominal pain is a common and often severe symptom in FMF and

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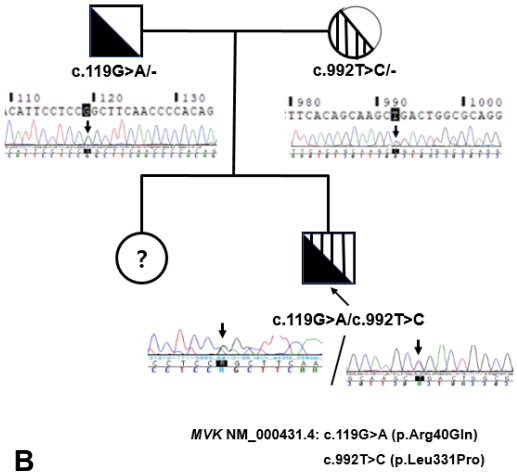
	April 17	April 24	May 3	July 13	Nov 16	Dec 2
Fever	+	-	±	+	-	+
WBC (x 10^3/μL)	11.3	7.7		9.8	9.7	13.9
ANC (/μL)	8837	4743		7154	6295	12051
CRP (mg/L)	209	<5		123	<5	128
ESR (mm/hr)	82	46		62	14	54
Amyloid A (mg/L)				199	1.9	142
IgD (mg/dL)					96	92
IgA (mg/dL)					301	298
Ferritin (ng/mL)				101		58
Fecal calprotectin (mg/kg)	35		3165	244		1204
Urine mevalonolactone (mmol/mol of creatinine)						1

A



B

Fig. 1. (A) Laboratory findings according to the presence versus absence of fever during 2023. Normal references: amyloid A ≤10 mg/L; immunoglobulin [Ig] D ≤14 mg/dL; fecal calprotectin ≤50 mg/kg; urine mevalonolactone, 0 mmol/mol of creatinine. (B) Pedigree of the proband. The patient had inherited variant c.119G>A (p.Arg40Gln) from his father and c.992T>C (p.Leu331Pro) from his mother. WBC, white blood cell; ANC, absolute neutrophil counts; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

	12-year-old boy	17-year-old boy	9-year-old girl	5-year-old boy
Recurrent fever Age of onset Interval of periodicity Duration of episode	3 months old 2-4 weeks 3-5 days	17 years old 5 month 7 and 27 days	1-2 months old 1-2 → 3-4 months 4-5 days	1 year old 1-2 months 3-5 days
Pharyngitis Cervical lymphadenitis Oral ulcer Anal/Genital ulcer Rash Arthralgia Abdominal pain Diarrhea	(+) (+) (+) (-) (+) (+) (+) (+)	(-) (-) (-) (-) (-) (-) (-) (-)	(+) (+) (+) (+) (+) (?) (+) (+)	(+) (+) (+) (-) (-) (+) (+) (+)
ANA	(-)	(-)	(+), 1:640	(-)
Presumptive diagnosis	PFAPA	FUO	PFAPA	PFAPA
Colchicine-responsive fever	(-)	(+)	(-)	(-)
Gene study	*MVK* : Arg40Gln/ Leu331Pro	*MEFV* : Glu148Gln, Arg202Gln	*TNFAIP3* : Trp164Ter	*C9* : Arg116Ter
Final diagnosis	HIDS	FMF[4]	HA20[6]	PFAPA

Fig. 2. Three rare hereditary periodic fever syndrome cases and a typical case of PFAPA. Patterns of fever, associated symptoms, characteristic findings, and genetic study results are presented. ANA, antinuclear antibody; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and adenitis; HIDS, hyperimmunoglobulinemia D and periodic fever syndrome; FUO, fever of unknown origin; FMF, familial Mediterranean fever; HA20, haploinsufficiency A20.

HIDS, potentially leading to misdiagnosis as acute abdomen or inflammatory bowel disease. In fact, our case of HIDS received a prior diagnosis of Crohn disease at another hospital, although an endoscopic biopsy revealed no evidence of chronic inflammation to support the lifelong history of abdominal pain and diarrhea. Consistent with the known association of haploinsufficiency A20 (HA20) with early-onset Behcet's disease and autoimmune conditions,[6] the HA20 case presented distinguishable features such as anal/genital ulcers and high titers of antinuclear antibody.[7]

Currently, no universally accepted classification criteria for PFAPA have been established. Diarrhea, chest pain, skin rash, and arthritis have been proposed as negative components of PFAPA[8]; however, these have also been documented in a minority of cases. While atypical periodicity and rare symptoms do not necessarily preclude a PFAPA diagnosis, the absence of symptom-free intervals with normalized acute-phase responses between febrile episodes and normal growth and development argues against it. Polygenic involvement or variants in noncoding regions

of genes associated with Behcet spectrum disorder have been suggested for the pathogenesis of PFAPA.[9] Genetic analysis of PFAPA cases often showed heterozygous pathogenic variants of immune-related genes such as *C9* (Fig. 2) and *MEFV*.[10] Further research is necessary to determine the potential role of autosomal-recessive gene variants in PFAPA. Clinical manifestations of the same PFS may differ not only according to the region but also even within families harboring the same genetic variants, suggesting a possible role of environmental factors in pathogenesis. Advancements in genetic technology have improved accessibility, making genetic analysis a valuable tool for the workup of PFS. Integration of genetic studies can facilitate accurate diagnosis of PFS and further dissect the pathogenesis of PFAPA.

In conclusion, the manifestations of PFS were variable and overlapping. Early and comprehensive evaluations, including genetic analyses, can effectively differentiate diseases and thereby, enable the most effective management while avoiding unnecessary investigations and lowering the risk of amyloidosis.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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