

INSTRUCTIVE CASE

A riddle for paediatricians: Two siblings with recurrent urticaria and fever

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Case Histories**Patient 1**

Patient 1 is the first son of non-consanguineous parents of Caucasian origin. At 12 weeks of age, after the first vaccination, he developed fever, erythematous rash on the trunk and lower limbs, and diarrhea, which lasted for 5 days, with spontaneous resolution. Since then, he had experienced recurrent and self-limited febrile attacks accompanied by a diffuse pruritic maculopapular rash (Fig. 1), abdominal pain, watery stools, cervical lymphadenopathy, headache with significant elevation in the acute-phase reactants. Attacks occurred every 4–6 weeks, lasting for 4–7 days, and were interrupted by asymptomatic intervals.

At the age of 5 years, he was referred to our Unit with ongoing episodes of periodic fever associated with abdominal pain, vomiting and a macular pruritic rash. Extensive investigations revealed erythrocyte sedimentation rate 90 mm/h (Westergreen, normal value (n.v.) < 16 mmh), C-Reactive protein 60 mg/L (n.v. 5 mg/L), white blood cells $15.00 \times 10^9/L$ with 82% of neutrophils, haemoglobin 10.9 g/dL, platelet count $546 \times 10^9/L$, Serum Amyloid A (SAA) 90 mg/L (n.v. 0–10) at the time of fever. Serum immunoglobulins, including immunoglobulin D (IgD) and immunoglobulin A (IgA), were in the normal range for age: IgD 25 IU/mL (n.v. 0–40), IgA 152 mg/dL (n.v. 14–159). Additional investigations were non-contributory.

An autoinflammatory syndrome was suspected. DNA analysis of genes associated with TNF receptor associated periodic syndrome (TNFRSF1A), cryopyrin associated periodic syndrome (CIAS1) and familial Mediterranean fever were normal. The



Fig. 1 Urticarial rash that appeared on the trunk and arms of brother 1 during periods of fever in December 2007.

patient was confirmed to have hyper-immunoglobulin D syndrome (HIDS) with mutation of the mevalonate kinase (MVK) gene (compound heterozygote I268D, 3137W). Colchicine was commenced, resulting initially in the reduction of the duration of attacks. Whilst on colchicine, the child has not had any further attacks for the last 2 years and SAA has normalised.

Patient 2

The brother has experienced, after the first vaccination, recurrent and self-limited febrile attacks accompanied by maculopapular eruption, abdominal pain, headache, throat pain and lymphadenopathy, occurring every month and lasting 3–7 days. When he was referred to our Unit, he was 4 years old, febrile and suffered from abdominal pain and vomiting. He presented with a pruritic rash on the trunk and the limbs. His SAA (110 mg/L) and leukocyte count ($18.50 \times 10^9/L$) were significantly elevated. Other investigations were non-contributory. IgA and IgD levels were within the normal range. Genetic analysis confirmed the brother to have HIDS, carrying the same mutations as his sibling. Colchicine was started with sustained improvement. There was a marked reduction in the number of attack days and the severity of each attack was noted to be decreased. Ten months after commencing colchicine, no febrile attacks were reported.

Key Points

- 1 Periodic urticarial rash and systemic symptoms with spontaneous resolution could suggest an autoinflammatory disease.
- 2 Normal serum levels of immunoglobulin D and immunoglobulin A do not exclude the presence of Hyperimmunoglobulinemia D with periodic fever syndrome.
- 3 A family history and a clinical examination during the 'periodic' episode are crucial elements for the correct and early diagnosis of periodic fevers

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Table 1 Hereditary periodic fever syndromes

	HIDS	FMF	TRAPS	CAPS (FCAS, MWS, NOMID/CINCA)
Races	Dutch, French and Northern European	Armenians, Arabs, Jewish, Turkish and Italian	Not restricted	Not restricted
Attack				
Duration (days)	2–7	1–3	7–21	1–3, but it is possible continuous
Fever	+	+	+	+
Abdominal pain	+	+	+	Rare
Chest pain	–	+	+	Rare
Arthralgia	+	+	+	+
Myalgia	–	–	+	+
Lymphadenopathy	+	–	–	Rare
Conjunctivitis and/or periorbital edema	–	–	+	+
Neurologic findings	Headaches with flares of symptoms	Acute aseptic meningitis is rare	Sometimes headaches with flares of symptoms	Headaches with flares of symptoms or after cold exposure Possible sensorineural deafness CINCA/NOMID: Possible chronic aseptic meningitis, high CNS pressure
Eruption				
Gross finding	Small erythematous macules, papules and nodules at the extremities	Erysipelas-like erythema at the lower legs	Generalised large erythematous migratory patches and plaques	Urticaria-like rash with increased neutrophils at the eccrine coils
AA amyloidosis	–	+	+	+
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant
Gene and protein	MVK	MEFV	TNFRSF1A	CIAS1/NLRP3/NALP3/ PYPAF1

CAPS, Cryopyrin-Associated Periodic Syndromes; CINCA, Chronic Infantile Neurologic Cutaneous Articular Syndrome; FCAS, Familial Cold Auto-inflammatory Syndrome; FMF, Familial Mediterranean Fever; HIDS, Hyperimmunoglobulinemia D With Periodic Fever Syndrome; MEFV, Mediterranean fever; MVK, mevalonate kinase; MWS, Muckle-Wells Syndrome; NOMID, Neonatal-Onset Multisystem Inflammatory Disease; TRAPS, TNF Receptor-Associated Periodic Syndrome.

The serum IgD and IgA levels remained within the normal range in both patients. No proteinuria was detected.

Discussion

Many conditions can present with cutaneous symptoms in childhood. These two case reports underline how a genetic autoinflammatory disease can be misdiagnosed.¹

HIDS is a rare autosomal-recessive autoinflammatory disease with recurrent febrile episodes that start in early childhood. These attacks are frequently preceded by chills and accompanied by headaches, bilateral cervical lymphadenopathy and sometimes by abdominal pain, diarrhea, articular and skin manifestations. The attacks last for 3–7 days, and are interrupted by asymptomatic intervals. They persist during the entire life although frequency and severity tend to diminish with age.^{2,3} The diagnosis of HIDS is based on clinical criteria and elevated serum IgD levels (>100 IU/mL).

Other than HIDS, many hereditary periodic fevers have been described. They can be distinguished based on mode of inheritance, genetic basis and clinical symptoms (Table 1). HIDS is caused by specific mutations in the gene encoding MVK resulting in depressed enzymatic activity. This is an enzyme in the isoprenoid pathway in which cholesterol is produced, in addition to a number of nonsterol isoprenoids. Isoprenoids are essential compounds in diverse cellular functions. MVK activity in HIDS is reduced leading to a slightly increased urinary excretion of mevalonic acid (<20 mmol/mol of creatinine) during febrile episodes. In contrast, in the case of a near-complete MVK deficiency, patients present with the clinical phenotype of mevalonic aciduria (MVA), and renal excretion of mevalonic acid is continually much higher (from ~3000 mmol/mol of creatinine up to >56 000 mmol/mol of creatinine). In addition to the typical clinical picture of HIDS, MVA patients present with psychomotor retardation, facial dysmorphism, cataract, failure to thrive and ataxia.⁴ The febrile episodes are commonly accompanied by hepatosplenomegaly, lymphadenopathy,

abdominal symptoms, arthralgia and skin rashes. Life expectancy is often compromised. Thus, MK deficiency comprises a continuous spectrum of loss of enzymatic activity, with the severe phenotype of MVA at the most pathologic extreme, occurring in <1% of MVK-deficient patients, and with HIDS as the milder variant.

In MVA, the diagnosis is established by detection of highly elevated levels of mevalonic acid excreted in urine. Increased levels of IgD and, in most patients of IgA, in combination with enhanced excretion of mevalonic acid during febrile attacks provide strong suspicion for HIDS. The diagnosis is confirmed by demonstration of deficient MVK enzyme activity or by demonstration of disease-causing mutations.⁴

We present herein the case of two siblings who developed a periodic fever with pruritic rash during childhood. A diagnosis of HIDS seemed unlikely because of repeatedly normal levels of IgD and IgA in these patients. Although high serum IgD concentrations constitute a unique hallmark of this syndrome, 22% of patients' IgD values are normal.³ In particular, IgD may be normal in patients under 3 years of age.⁵ In addition, an elevated serum IgD is not a specific marker for HIDS. Moreover, the level of serum IgD in HIDS does not correlate with disease severity or frequency of attacks. This suggests that IgD should not be a requirement for diagnosis, especially during the infancy, but can assist in making the diagnosis. The alterations of the immunoglobulin pattern in HIDS are not exclusively limited to IgD. Elevated immunoglobulin G and immunoglobulin M values have been found, and specially high IgA levels are found in the large majority of patients.⁶

There is no consensus for specific treatment for HIDS; some studies use drugs such as colchicine, steroids, simvastatin, anakinra, thalidomide and etanercept.^{3,7} In these cases, colchicine reduced the severity and frequency of both febrile attacks and episodes of generalised urticaria.

Despite having taken a thorough family history and performed a careful clinical examination and despite the knowledge that normal levels of IgD do not exclude the presence of HIDS, the diagnosis of HIDS in this family might have been missed. A better awareness of periodic fevers among paediatricians

is required at present, because HIDS syndrome, as other autoinflammatory syndromes and chronic diseases, adversely influences several aspects of quality of life³

In conclusion, HIDS is a challenging diagnosis to make, moreover when patients do not completely meet the criteria for the disease.

Although genetic testing has been available since the end of the last millennium, there continued to be a median delay to diagnosis of 9.9 years after onset of symptoms. Remarkably, skin symptoms could be the first to appear, in the form of an urticarial rash, with exacerbations coinciding with episodes of fever, abdominal pain, enlarged lymph nodes and raised parameters of inflammation. An exhaustive evaluation of blood and urine biochemical data, a clinical examination during the attack and a close follow-up could suggest the correct diagnosis early and prevent unnecessary hospitalisations.

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