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Lesson of the month 1: Autoinflammatory syndromes – an unusual cause of pyrexia of unknown origin

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ABSTRACT

Autoinflammatory diseases are disorders of innate immunity and are characterised by recurring and unprovoked episodes of inflammation. We present a case of episodic pyrexia, associated with a significant inflammatory response, in a young man in whom the cause had remained unexplained since infancy. He was eventually diagnosed with hyperimmunoglobulinaemia D syndrome (HIDS); one of the autoinflammatory syndromes.

KEYWORDS: autoinflammatory syndrome, hyperimmunoglobulinaemia D syndrome, periodic fever syndrome, pyrexia of unknown origin

Case history

A 29-year-old man was referred to the outpatient renal clinic with non-visible haematuria and proteinuria. He had been feeling unwell for the previous 2 months, with recurring episodes of high temperature. Over the previous week he had developed a red, itchy and scaly rash affecting the arms, buttocks and feet. His GP had empirically commenced prednisolone 3 days earlier.

Further enquiry, and a review of medical records, revealed that he had been assessed by several medical practitioners since early childhood. He had suffered recurring episodes of pyrexia since infancy, which had been treated as upper respiratory tract infections. He subsequently underwent a tonsillectomy and adenoidectomy at the age of 5. The episodes of pyrexia persisted into adulthood and he estimated that he had missed approximately one third of his school education through illness. They occurred once or twice per month during his school and university years and typically lasted for a week, with recorded temperatures up to 40°C. Episodes had been variably associated with diarrhoea, abdominal pain, mouth ulcers and joint pains. He had been investigated as an inpatient for pyrexia of unknown origin (PUO) 5 years earlier.

On examination, he appeared well. He had erythematous scaly patches and plaques over the extensor surfaces of his arms, feet and knees. His systemic examination was otherwise unremarkable. His urinalysis showed +3 blood.

Table 1 summarises the initial laboratory investigations. His C-reactive protein and erythrocyte sedimentation rate were high, with a normal white cell count and a mild anaemia. His recurrent pyrexia raised a clinical suspicion of primary immunodeficiency and an immunoglobulin assay was requested. The serum IgA was elevated at 11.3 g/L (normal range 0.80–2.80 g/L) and serum IgM reduced at 0.53 g/L (normal range 0.60–2.10 g/L). Serum IgG was normal at 12.0 g/L (normal range 4.9–16.1 g/L).

He was referred to dermatology and a biopsy, performed 1 week later, reported lymphoid interface dermatitis. Immunostains for IgG, IgM, IgA and complement were negative.

The prednisolone commenced by his GP was prescribed for a total of 5 days. His symptoms resolved 2 weeks after presentation to the renal clinic. However, he developed recurrent fever, rash and malaise 6 weeks after resolution of his initial symptoms.

At this point, the patient was referred to a clinical immunologist. A diagnosis of periodic fever syndrome was considered and a test for serum IgD was requested. This was elevated at 1600 iU/L (normal <100 iU/L) and a diagnosis of hyperimmunoglobulinaemia D syndrome (HIDS) was made. Simvastatin was commenced at 20 mg once daily and increased to 40 mg once daily over 2 months. The patient noticed an immediate and dramatic improvement in the frequency and severity of episodes of illness. He has been relatively symptom free and functioning well over the past 2 years. A mutation analysis for the mevalonate kinase (MVK) gene was performed. This returned positive for the V377I variant; a mutation that is well-recognised in HIDS.[1]

Discussion

This case highlights an unusual cause of PUO that may present to practitioners in several specialties. The considerable length of time taken to make the diagnosis and the dramatic response to statin therapy were also noteworthy.

HIDS was first reported in the Netherlands and is more commonly described in north-western Europe.[2,3] This case was

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Table 1. Blood test results from initial outpatient appointment (abnormal or out-of-range results in bold)

Test	Result	Reference range
Haemoglobin	**9.7 g/L**	13.5–18.0 g/L
White blood cells	4.1 × 10^9/L	4.0–11.0 × 10^9/L
Neutrophils	3.14×10^9/L	2.00–7.50 × 10^9/L
Lymphocytes	**0.75 × 10^9/L**	1.10–3.50 × 10^9/L
Platelets	**124 × 10^9/L**	150–400 × 10^9/L
C-reactive protein	**320 mg/L**	0–10 mg/L
Erythrocyte sedimentation rate	**80 mm/hour**	0–22 mm/hour
Creatinine	80 µmol/L	55–125 µmol/L
Total bilirubin	**25 µmol/L**	0–22 µmol/L
Albumin	40 g/L	35–50 g/L
Alanine aminotransferase	20 U/L	0–50 U/L
Calcium	2.35 mmol/L	2.1–2.6 mmol/L
Phosphate	0.89 mmol/L	0.8–1.45 mmol/L
Globulin	**42 g/L**	21–35 g/L
Immunoglobulin G	12.0 g/L	4.9–16.1 g/L
Immunoglobulin M	**0.53 g/L**	0.60–2.10 g/L
Immunoglobulin A	**11.3 g/L**	0.80–2.80 g/L
Complement C3	1.26 g/L	0.75–1.65 g/L
Complement C4	0.27 g/L	0.14- 0.54 g/L
Antinuclear antibody	0.2	<0.7
Anti dsDNA	1.7 IU/mL	<10 IU/mL
ANCA PR3	0.50 u/mL	<6 u/mL
ANCA MPO	2.20 u/mL	<6 u/mL
Rheumatoid factor	**29 IU/mL**	<20 IU/mL

Anti dsDNA = Anti-double stranded DNA; ANCA PR3 = Anti-neutrophil cytoplasmic antibody proteinase 3; ANCA MPO: Anti-neutrophil cytoplasmic antibody myeloperoxidase

Table 2. Autoinflammatory syndromes

Syndrome	Gene defect	Clinical features
Familial mediterranean fever	MEFV	Abdominal pain, large joint arthritis. Mean length of fever is 1–3 days
Hyperimmunoglobulinaemia D syndrome	MVK	Cervical lymphadenopathy, rash, abdominal pain. Mean length of fever is 3–7 days
Tumour necrosis factor receptor-associated periodic syndrome	TNFRSF1A	Abdominal pain, myalgia, arthralgia. Mean length of fever is 14 days
Muckle-Wells syndrome	NLRP3	Urticarial rash, arthritis, conjunctivitis, hearing loss
Familial cold auto-inflammatory syndrome	NLRP3	Fever triggered by cold exposure, urticarial rash, polyarthralgia
Neonatal-onset multisystem inflammatory disease	NLRP3	Aseptic meningitis, urticarial rash, neonatal onset

MEFV = Mediterranean fever; MVK = Mevalonate kinase; NLRP3 = NLR family, pyrin domain containing 3; NLR = Nucleotide-binding domain and leucine-rich repeat containing; TNFRSF1A = Tumour necrosis factor receptor superfamily, member 1A.

of a young man in the UK. A definite ancestral history was not available.

The periodic fever syndromes describe a group of rare and hereditary autoinflammatory diseases whose clinical characteristics and molecular pathogenesis are well-recognised. They are characterised by recurring episodes of fever and systemic inflammation affecting the skin, mucosa, serosa, eyes and joints. The diseases have overlapping clinical manifestations but unique gene mutations and different patterns of inheritance.[1,4] Table 2 summarises the various syndromes.

HIDS is an autosomal recessive disorder and is caused by a mutation in the gene for MVK.[5,6] It is reported that deficiency of MVK results in overproduction of the inflammatory cytokine interleukin-1β secondary to a reduced synthesis of isoprenoids.[6] The level of MVK deficiency determines the clinical phenotype and HIDS results from a partial deficiency.[6]

Episodes of HIDS typically last for 3–7 days and recur every 4–6 weeks. They can start in the first year of life and continue into adulthood. Flares are associated with cervical lymphadenopathy (94% of patients), abdominal pain (72%), diarrhoea (82%), polyarthralgia (80%), skin lesions (82%) and serositis (6%). Fever and elevated acute phase reactants (erythrocyte sedimentation rate, C-reactive protein and white blood cell count) accompany the symptoms. Immunisation, trauma or stress can trigger the flares.[1,3]

HIDS was originally defined by a high level of serum immunoglobulin D.[2,7] The identification of mutations in the MVK gene has changed our understanding of its molecular pathogenesis.[3,5] Elevated serum IgD is frequently observed but is not essential for diagnosis.[7] It may be associated with an elevated serum IgA.[1,7] Our patient presented with haematuria, which may be explained by IgA deposition in the kidneys. A renal biopsy was not performed to confirm the diagnosis as he had normal excretory function and no proteinuria.

Current treatment is aimed at suppressing inflammation through anti-IL1β therapy. Anakinra and canakinumab have been shown to be effective at reducing the frequency and severity of attacks.[4] Statins have been tried in some patients; they inhibit the enzyme hydroxyl-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which precedes MVK in the isoprenoid pathway.[8] However, variable response to statin therapy has been reported.[1] Other suggested treatments, which are generally not effective, have included non-steroidal anti-inflammatory drugs and corticosteroids.[1]

Our patient had a favourable response to simvastatin and the frequency of his flares reduced from bi-monthly to bi-annual.

Lesson

Autoinflammatory syndromes should be considered in the differential diagnosis of recurrent pyrexia of unknown origin. ■

Conflicts of interest

The authors have no conflicts of interest to declare.

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