CASE REPORT

Recurrent fevers in children: TRAPS for young players

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SUMMARY

We present the case of an 11-month-old girl who presented with recurrent febrile episodes and was found to have tumour necrosis factor receptor-associated periodic syndrome due to a novel mutation in the TNFRSF1A gene. The concept of autoinflammatory diseases is discussed and the management of this condition reviewed.

BACKGROUND

Fever is a common presentation in children and in most cases is due to self-limited viral infections. Recurrent fever in the paediatric population has a variety of differential diagnoses, including recurrent viral infections and primary immunodeficiency. Less common but important causes of recurrent fever include malignancy, autoimmune disease such as systemic lupus erythematosus and systemic inflammation such as inflammatory bowel disease.

The last two decades have brought increasing awareness and understanding of another category of illness characterised by attacks of unprovoked inflammation without autoantibodies or autoreactive T cells typical of autoimmune diseases.¹ These have been termed autoinflammatory diseases, the most well known of which are the hereditary periodic fever syndromes. Typically, these have their onset in childhood and present with stereotypical bouts of fever, often in association with other clinical features. A lack of awareness of these syndromes may result in a prolonged period of unnecessary and invasive investigations and worry over diagnostic uncertainty for affected families. We present the case of a toddler with recurrent fevers who was eventually diagnosed with tumour necrosis factor receptor-associated periodic syndrome (TRAPS).

CASE PRESENTATION

A previously well 11-month-old girl presented with a 12-day history of daily fevers $>38.5^{\circ}\text{C}$ with no obvious focus. Associated features included intermittent periorbital oedema, mild conjunctival erythema early in the illness, transient rash and cervical lymphadenopathy. There was no tongue erythema and her cardiac and abdominal examinations were normal. Initial investigations included a raised white cell count 29.5 (normal $6.0\text{--}18.0\times 10^6/\text{L}$), neutrophilia 16.8 (normal $1.0\text{--}8.5\times 10^6/\text{L}$) and thrombocytosis (platelets 982 ; normal $150\text{--}450\times 10^6/\text{L}$). Inflammatory markers were also raised (C reactive protein (CRP) 171 (normal $<8\text{ mg/L}$)). Covering the possibility of a bacterial infection, the patient was

treated with intravenous benzylpenicillin and gentamicin; however, multiple blood cultures were negative. Given the prolonged fever, transient rash, cervical lymphadenopathy and history of intermittent conjunctivitis, a diagnosis of incomplete Kawasaki disease was suspected and a single dose (2 g/kg) of intravenous normal human immunoglobulin administered. The patient defervesced over 36 h , following a total of 14 days of fever. An inpatient echocardiogram showed a structurally normal heart with no coronary artery dilation. She was subsequently discharged on low-dose aspirin with a plan for a follow-up echocardiogram in 6 weeks.

Post-discharge the patient was well for 1 month before re-presenting with fever without focus. On examination, she again had an intermittent blanching truncal rash and periorbital oedema, with no arthritis. Haematological investigations again revealed a neutrophilia 19.9 (normal $1.0\text{--}8.5\times 10^6/\text{L}$) and raised inflammatory markers (CRP 206 ; erythrocyte sedimentation rate 120 mg/L , normal $0\text{--}6\text{ mg/L}$). Ferritin was mildly elevated ($337\text{ }\mu\text{g/L}$, normal $8\text{--}135\text{ }\mu\text{g/L}$). Urine and blood cultures were negative. An abdominal ultrasound and urinary catecholamine screen were both normal. PCR for Epstein-Barr virus and cytomegalovirus was negative, as was streptococcal serology. She was started on empiric antibiotics, which were ceased after 5 days as the cultures returned negative. Over this time her fevers eventually settled following a total of 15 days of fever. On review in the outpatient clinic 2 weeks later, she was afebrile, with normal inflammatory markers and only mildly raised platelets of 524 (normal $150\text{--}450\times 10^6/\text{L}$).

In the course of her second admission, the patient's family history was clarified. The patient was of Caucasian background. Her father, now aged 29 years, described suffering recurrent episodes of high fever associated with an intermittent blanching rash and myalgia, beginning at age three and persisting into adulthood. He did not have a history of arthritis, nor any ocular symptoms or sensorineural hearing loss. His two younger siblings were well. Since adulthood, febrile episodes had occurred once in every $2\text{--}3$ years and had been treated successfully with corticosteroids. On the basis of this history and the stereotypical nature of the episodes experienced by our patient, a diagnosis of TRAPS was suspected and genetic testing requested. This revealed a novel $\text{A}\rightarrow\text{C}$ nucleotide substitution in exon 3 of the TNFRSF1A gene resulting in replacement of histidine by proline at amino acid position 95 (H95P). This was considered to be deleterious and consistent with a clinical diagnosis of TRAPS.

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OUTCOME AND FOLLOW-UP

In the 12 months following diagnosis, the patient has had approximately 6-weekly exacerbations of fever managed with short courses (5–7 days) of steroids. This has generally produced rapid improvement in fever and clinical status. Occasionally, prolonged fever episodes up to 16 days, as evidenced by recurrence of fever with steroid tapering, have still occurred. Although effective in controlling the symptoms of flares, steroid therapy has been associated with significant irritability. The patient also had a fever flare temporally associated with the routine live attenuated measles-mumps-rubella (MMR) vaccine at age 12 months. This was associated with symptoms typical of her fever episodes, which occurred 7 days after MMR administration and required management with a brief course of corticosteroids.

DISCUSSION

Hereditary periodic fever syndromes are characterised by spontaneous, recurrent, episodic and generalised inflammation. They include familial Mediterranean fever (FMF), TRAPS, Muckle-Wells syndrome, familial cold autoinflammatory syndrome, hyperimmunoglobulin D syndrome (HIDS) and periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome. All are examples of 'autoinflammatory disease', a term used to describe conditions in which inflammation is the central underlying pathology and for which no infectious or autoimmune cause can be identified.²

With the exception of FMF, hereditary periodic fever syndromes are very rare, with an estimated prevalence of less than two per million.³ TRAPS has an estimated prevalence of one per million. Reports are more frequent in patients of Caucasian origin, but it is uncertain whether this is a true increased incidence or due to ascertainment bias.⁴ Recent advances have enabled identification of the underlying molecular basis for many of these syndromes, specifically within the pyrin, death domain and tumour necrosis factor receptor superfamilies.⁵ In contrast to most autoimmune conditions, where the adaptive immune system plays a key role, these diseases are mediated primarily as a result of abnormal activation of the innate immune system.

Clinical features suggestive of a diagnosis of a hereditary periodic fever syndrome include a long-standing history of recurrent febrile episodes, often of similar length, a stereotypical constellation of symptoms and signs with each episode and a history of similar problems in other family members. Routine clinical investigations are usually unhelpful in differentiating between various forms of autoinflammatory syndromes but are important in excluding other differentials early in the disease course.⁶ Characteristic clinical findings in TRAPS include recurrent prolonged fevers (5 days–3 weeks' duration), abdominal pain, migratory skin rash, myalgia, arthralgia and periorbital swelling.⁷ The median age of symptom onset is around 4 years (range 0.2–63 years); however, there is often a long delay before TRAPS diagnosis.⁴ Renal AA amyloidosis represents the most serious long-term disease complication, with a prevalence ranging from 14% to 25%.⁸

Our patient's clinical history of TRAPS is notable for the apparent triggering of an episode following immunisation with the MMR vaccine. Vaccination is a recognised trigger of febrile episodes in patients with HIDS⁹ however, to the best of our knowledge, this is the first description of this phenomenon in a patient with TRAPS. While fever can occur in the 5–14 days post MMR vaccine, in this case it was prolonged, associated with a similar constellation of symptoms to the patient's other TRAPS episodes and responded to corticosteroid therapy.

TRAPS results from mutations in the gene encoding the tumour necrosis factor (TNF) receptor superfamily, member 1A (TNFRSF1A) on chromosome 12 and is autosomal dominantly inherited.^{1–10} There is significant phenotype heterogeneity between patients with different mutations as well as between those with the same mutation.⁶ Disease-associated mutations in the TNFRSF1A are exclusively clustered in the extracellular domain of the receptor, encoded by exons 2, 3, 4 and 6.¹¹ The R92Q mutation is the most frequently observed variant of the TNFRSF1A gene, with allele frequency ranging from 1.2% to 4%.⁷ This mutation correlates with a milder phenotype, higher rate of spontaneous resolution and lower prevalence of amyloidosis.⁷ Our patient was found to have a deleterious mutation involving substitution of H95P in exon 3 of the TNFRSF1A gene. While this particular substitution is novel, other missense changes at this position are recognised in association with TRAPS.^{12–13}

Treatment options for TRAPS depend on the course of the disease and its complications. Fever episodes usually respond to systemic corticosteroids, though these may be associated with troublesome short-term side effects, as with our patient, and longer-term side effects if required frequently.⁶ Colchicine, effective in some other periodic fever syndromes—most notably FMF, does not prevent recurrences of TRAPS symptoms.⁷ Identification of the genetic basis of TRAPS has led to trials of biological therapies for disease treatment. The rationale is based on evidence that the inflammatory response in TRAPS depends on the interaction between TNF- α and TNFR1. In a recent prospective, open-label, dose-escalation study of etanercept, a TNF- α antagonist, in 15 patients with TRAPS, treatment significantly attenuated the total symptom score and reduced the frequency of symptoms. Etanercept did not, however, completely normalise symptoms or acute phase reactant levels and long-term compliance was poor.¹⁴ Anakinra, an interleukin-1 (IL-1) receptor antagonist, which blocks the activity of IL-1 α and IL-1 β preventing signal transduction, has been used in small numbers of patients with promising results.¹⁵ Anakinra appears to be less effective in patients carrying R92Q mutations than in those with mutations affecting cysteine residues. The anti-IL-1 monoclonal antibody canakinumab has also shown positive results in early trials and is a potential future therapy for patients with frequent relapses, chronic symptoms or unresponsive to corticosteroids.¹⁶

Hereditary periodic fever syndromes are an important differential diagnosis in children with recurrent fevers in whom other causes have been excluded. Our case highlights the importance of examining febrile episodes for stereotypical features and obtaining a family history for clues to the presence of these conditions. Genetic tests are now available for the majority of the

Learning points

- ▶ Hereditary periodic fever syndromes are a rare but important differential diagnosis in the child with recurrent fevers once infectious, malignant and systemic inflammatory conditions have been ruled out.
- ▶ Clues to the diagnosis of an autoinflammatory syndrome include family history, the apparent unprovoked nature of febrile episodes and stereotypical symptoms and signs.
- ▶ Corticosteroids can be effective in management of tumour necrosis factor receptor-associated syndrome.

periodic fever syndromes and treatment options are expanding as knowledge of their underlying pathogenesis increases. For some, such as TRAPS, early diagnosis and treatment can be important in preventing long-term disease complications.

Contributors KAH drafted and revised the case report. NWC and JDA reviewed the case report.

Competing interests None.

Patient consent Obtained.

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