DR SPUR'S MYSTERY CASE

Monthly fevers
Can you AID me with this family's grievances?

Welcome to Dr Spur's Immunology Clinic
Referral letter:

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Dear Dr SPUR

I am managing a family in my practice who came with a long list of complaints. The mother is of Italian descent and the father is South African. Their ten-year-old daughter first came to medical attention at age four years, when she started to experience regular febrile illnesses with temperatures of up to 39 °C, with no apparent source of infection. These episodes recur at least twice a month. Over time, the episodes evolved into more complex presentations that also included acute peritonitis, pleuritic chest pain, arthritis and an erythematous skin rash.

Laboratory investigations failed repeatedly to reveal a pathogen. The symptoms do not respond to antibiotics and non-steroidal anti-inflammatory drugs; and the patient is usually severely ill until day three or four, when the symptoms and signs disappear. She has been worked up by several specialist disciplines over the years, including surgery, gastroenterology, rheumatology and cardiology. An appendectomy was performed at age eight when she presented with an acute abdominal pain. Acute rheumatic fever was excluded on several occasions when she had chest pain and arthralgia. An autoimmune workup revealed no autoantibodies. Her three-year-old brother has been experiencing frequent fevers of 39–41 °C since infancy, and has received numerous courses of antibiotics for unspecified infections.

The recurring illness and the lack of a definite diagnosis is taking a toll on the parents. I suspect an inborn error of immunity and need advice on where to start testing.

Regards
Dr Sikonathi Mabasa

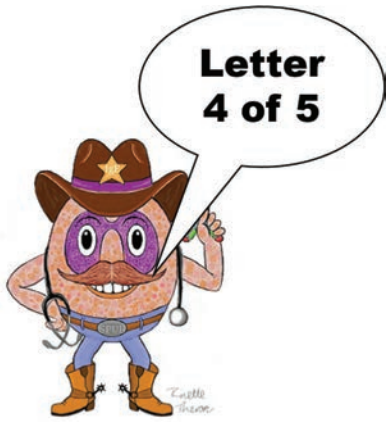
Dear Dr Mabasa

Inborn errors of immunity (IEI) can present with a variety of manifestations that include severe or unusual infections, allergic disease, autoimmunity or autoinflammation, lymphoproliferation and malignancy.[1] The multisystem symptoms and signs you describe suggest autoinflammation.

Inflammation is a very important protective immune response that may cause persistent infection if it is inadequate, and chronic inflammatory disease if it is excessive. Autoinflammation refers to a category of monogenic systemic inflammatory disorders with periodic fever as a central feature, disorders that are distinct from autoimmunity.[2] Autoimmunity results from errors in adaptive immunity and is associated with autoantibody production and specific HLA II alleles.

Autoinflammation results from errors in non-specific innate immunity and is not associated with autoantibody production or HLA II alleles.[3] Innate immunity relies on pattern-recognition receptors that detect pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). The activation of pattern-recognition receptors induces the secretion of pro-inflammatory cytokines and type I interferons by cells of the innate immune system, such as neutrophils. The activation of pro-inflammatory signalling in the absence of a pathogen causes sterile inflammation.[4] The adaptive and innate arms of the immune system also collaborate to amplify the immune effector response, and lymphocytic infiltration is common in the tissues of patients with autoinflammation.

The autoinflammatory disorders (AID) are classified as disorders of inflammasomes or IL-1 signalling, disorders of



interferon signalling and disorders of NFKB or tumour necrosis-factor signalling.[3] Many pathways are involved in the regulation of inflammation and diverse mutations have been described.

About 60% of AID cases are diagnosed before age ten years and 90% before age 20, but some patients may come to attention only in adulthood. AID episodes may take the form of regular high fevers or of fever combined with attacks of acute serositis (peritonitis, pleuritis, pericarditis, meningitis) or synovitis (arthralgia, acute arthritis). Skin manifestations may include angioedema, urticaria, vasculitis or an erysipelas-like erythematous rash. Lymphadenopathy and splenomegaly may be present due to lymphocyte proliferation.[3,5]

It is important to exclude chronic infections, acute rheumatic fever, cyclic neutropaenia, malignancy, autoimmune disease, inflammatory bowel disease, idiopathic juvenile arthritis, Still's disease and other IEIs.[3] Episodes may cause significant disability and prompt additional invasive investigations – and even emergency surgical interventions.

The most useful clinical sign is stereotypical fevers that don't behave like typical infections. For example, they recur at regular intervals, resolve spontaneously after a certain period, show no response to antipyretics or antibiotics, and they occur without other signs of infection.

Infants and young children <2 years may initially be misdiagnosed as having late neonatal sepsis or occult bacteraemia.[5] Episodes may occur from once a week to once every 3–4 months.[6] A family history of recurrent fever from an early age is a useful finding, but autoinflammatory disorders may also arise de novo. Genetic testing is central to the diagnosis and should be considered if the stereotypical symptoms persist beyond six months. Next-generation sequencing enables genetic testing for hundreds of IEIs in a single test at relatively low cost. Patients should first be classified clinically into one of the major groups of AIDs (see Table I) followed by classification by genotype (see Table II). An AID may be diagnosed with 80–100% sensitivity and specificity if the criteria are met.

Based on the clinical symptoms and signs you described, I suspect the children may have Familial Mediterranean Fever (FMF). FMF and PFAPA are the commonest AIDs and the most likely to be encountered in practice.[3] While FMF has historically been described in North African, Mediterranean and Middle Eastern populations, the disorder is not confined to these regions and cases have been diagnosed worldwide. The most common presenting features are fever, acute peritonitis and acute arthritis affecting 1–2 joints. A history of surgical intervention is common. Fever of unknown origin may be the only symptom, especially in young children.[6,7]

TABLE I: CLINICAL CRITERIA OF THE MAJOR AUTOINFLAMMATORY DISORDERS (AID)[3]

PFAPA[a]	CAPS[b]	FMF[c]	TRAPS[d]	MKD[e]
At least 7 of 8:	***At least 2 of 5:***	***At least 6 of 9:***	***Score ≥5 points:***	***At least 3 of 6:***
Present:	Urticarial rash	***Present:***	***Present:***	Age at onset <1 year
Pharyngotonsillitis	Cold- or stress-triggered episodes	Mediterranean ethnicity	Fever ≥7 days (2)	Gastrointestinal symptoms
Duration 3–6 days	Sensorineural hearing loss	Duration 1–3 days	Fever 5–6 days (1)	Painful lymph nodes
Cervical lymphadenitis	Chronic aseptic meningitis	Chest pain	Migratory rash (1)	Aphthous stomatitis
Periodicity	Skeletal anomalies (epiphyseal overgrowth, frontal bossing)	Abdominal pain	Periorbital oedema (1)	Triggers
		Arthritis	Myalgia (1)	Maculopapular rash
			Positive family history (1)	
Absent:		***Absent:***	***Absent:***	
Diarrhoea		Aphthous stomatitis	Aphthous stomatitis (1)	
Chest pain		Urticarial rash	Pharyngotonsillitis (1)	
Skin rash		Maculopapular rash		
Arthritis		Lymphadenopathy		

[a] PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, adenitis
[b] CAPS: Cryopyrin-associated periodic syndrome
[c] FMF: Familial Mediterranean Fever
[d] TRAPS: TNF receptor-associated periodic syndrome
[e] MKD: Mevalonate kinase deficiency

TABLE II: CLASSIFICATION OF AID ACCORDING TO GENOTYPE[3]

CAPS[f] (NLRP3 gene)	FMF[g] (MEFV gene)	TRAPS[h] (TNFRSF1A gene)	MKD[i] (MVK gene)
Confirmatory genotype	**Confirmatory genotype**	**Confirmatory genotype**	**Confirmatory genotype**
PLUS at least one:	*PLUS at least one:*	*PLUS at least one:*	*PLUS at least one:*
Urticarial rash	Duration 1–3 days	Duration ≥7 days	Gastrointestinal symptoms
Red eye (conjunctivitis, episcleritis, uveitis)	Arthritis	Myalgia	Cervical lymphadenitis
Sensorineural hearing loss	Chest pain	Migratory rash	Aphthous stomatitis
	Abdominal pain	Periorbital oedema	
		Relatives affected	
Non-confirmatory genotype	**Non-confirmatory genotype**	**Non-confirmatory genotype**	
PLUS at least one:	*PLUS at least one:*	*PLUS at least one:*	
Urticarial rash	Duration 1–3 day s	Duration ≥7 days	
Red eye (conjunctivitis, episcleritis, uveitis)	Arthritis	Myalgia	
Sensorineural hearing loss	Chest pain	Migratory rash	
	Abdominal pain	Periorbital oedema	
		Relatives affected	

[f] CAPS: Cryopyrin-associated periodic syndrome
[g] FMF: Familial Mediterranean Fever
[h] TRAPS: TNF receptor-associated periodic syndrome
[i] MKD: Mevalonate kinase deficiency

FMF arises from a gain-of-function mutation in MEFV, the gene that encodes the protein pyrin.[6,8] Pyrin is expressed in neutrophils, monocytes, dendritic cells, and serosal and synovial fibroblasts. It acts both as a danger sensor and as a scaffold protein for the assembly of inflammasomes, which are intracellular protein complexes that induce inflammation in response to PAMPs and DAMPs. Hyperactive pyrin promotes inflammasome assembly in the absence of an infectious trigger and drives uncontrolled secretion of IL-1, IL-18 and other mediators that precipitate an acute attack of autoinflammation.

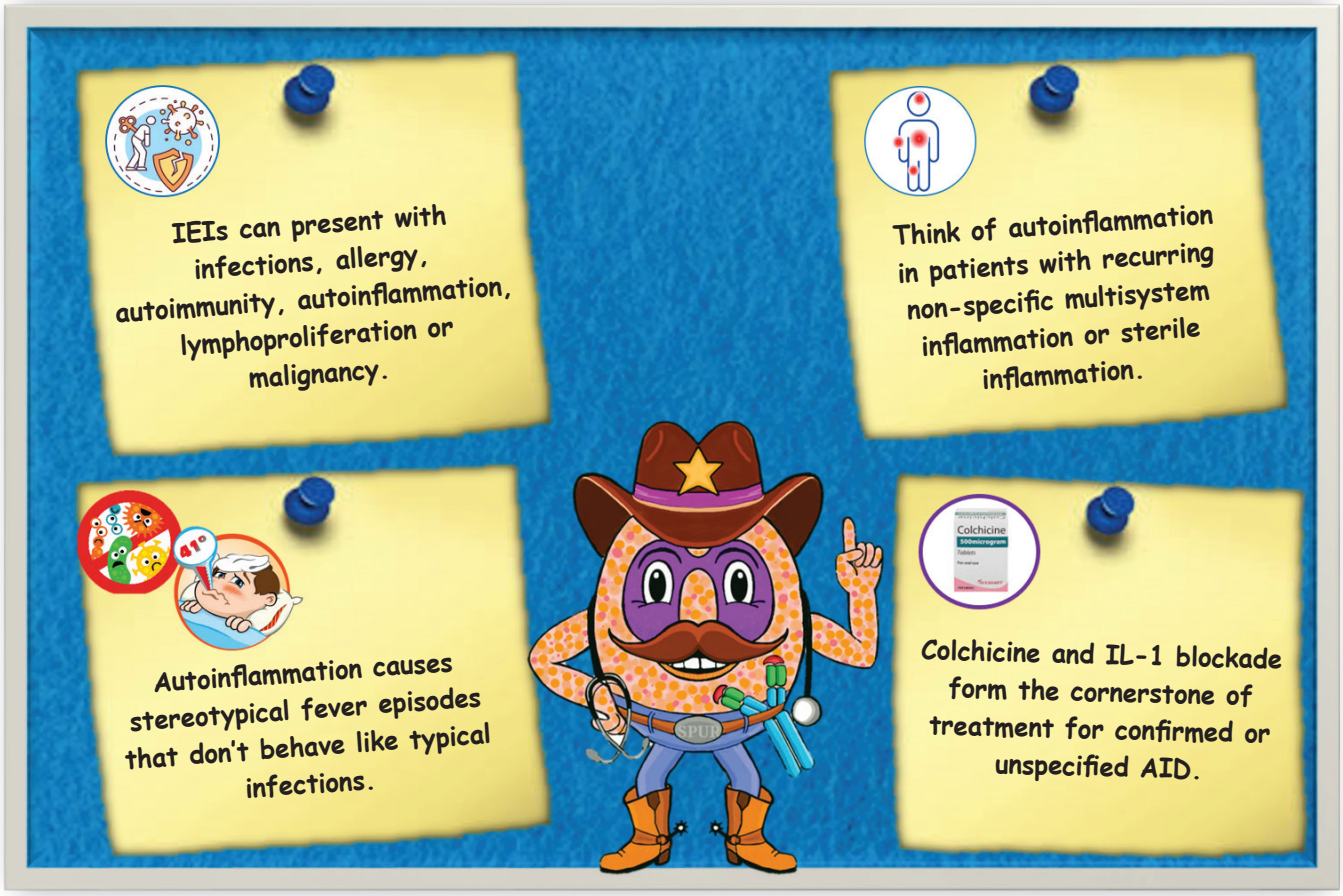
Arthritis in FMF resembles septic arthritis, but the joint fluid is sterile and neutrophil-dominant. Triggers of acute attacks in FMF include strenuous physical activity, cold exposure, travel, emotional stress, nutritional changes, menstruation and the use of contraceptives.[7] Inflammation markers such as CRP and ESR are elevated during and between episodes. While initially regarded as autosomal recessive, it has been recognised that patients with significant illness harbour pathogenic MEFV variants on one or both alleles, and that disease modifiers play a role in clinical expression. The disorder is therefore now more commonly regarded as autosomal dominant with limited penetrance.[3]

Colchicine and/or IL-1 blockade is used to manage and prevent FMF attacks.[9] It also prevents secondary renal amyloidosis due to chronic serum amyloid A deposition.[10] Colchicine is a microtubule inhibitor that disrupts neutrophil chemotaxis and superoxide production, inflammasome assembly and pro-inflammatory TNF-α and NF-kB signalling.[6] Immunomodulation with anakinra may be considered in colchicine-resistant FMF (>1 attack in three months), in patients with secondary renal amyloidosis, or if inflammatory markers are persistently elevated on colchicine.[9]

Definite diagnosis and treatment are essential to improve quality of life. AID can now be treated effectively with targeted cytokine inhibition therapy. Genetic counselling is also required to respond to reproductive concerns and health risks to other family members.[7]

The AID spectrum is expanding, and atypical presentations are increasingly being reported related to somatic mosaicism, low-penetrance variants or novel variants. It is still challenging to make a diagnosis in patients with AID symptoms and negative genetic testing, and there are also no treatment recommendations for such patients. Preliminary evidence suggests that colchicine can be used effectively as an empiric therapy in AID patients with no demonstrable pathogenic variants.[11]

Dr Spur's take-home message:



Dr Spur's mystery SOLVED:

You needed aid. This is a case of AID.

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