Review article

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CPD

The systemic autoinflammatory disorders for dermatologists. Part 2: disease examples

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Summary

The systemic autoinflammatory disorders (SAIDS) or periodic fever syndromes are disorders of innate immunity, which can be inherited or acquired. They are almost all very rare and easily overlooked; typically, patients will have seen multiple specialities prior to diagnosis, so a high level of clinical suspicion is key. It is important to note that these are 'high-value' diagnoses as the majority of these syndromes can be very effectively controlled, dramatically improving quality of life and providing protection against the development of irreversible complications such as AA amyloidosis. In Part 1 of this review, we took an overview of SAIDS and described the common features; in this article, we take a more in-depth look at the better recognized or more dermatologically relevant conditions.

Introduction

The systemic autoinflammatory disorders (SAIDS) were introduced in Part 1 of this article. Some of the more common examples presenting to a dermatologist will be explored further below.

Cryopyrin-associated periodic syndromes

Cryopyrin-associated periodic syndromes (CAPS) was first described as a form of cold-induced rash in 1945, and the group is now recognized as a spectrum of clinical conditions ranging from mild familial cold urticaria to severe neonatal-onset multisystem inflammatory disease or chronic infantile neurological, cutaneous and articular syndrome. The common underlying pathology is a gain of function mutation in a key component of the interleukin (IL)-1 inflammasome.[1] CAPS are inherited in an autosomal dominant fashion, although a substantial proportion of patients have somatic mutations.[2]

CAPS affect an estimated one to three per million in the UK with no ethnic predisposition. Dysregulated production of IL-1 results in constitutional upset with febrile symptoms of myalgia, chills and night sweats, as well as severe fatigue, headache, ocular inflammation (resulting in red eyes) and a characteristic urticarial rash.[3] Many patients have daily symptoms in a diurnal pattern, with symptoms worsening over the course of the day.[2] This rash is distributed equally over arms, trunk or legs. The lesions present as erythematous macules or slightly raised papules/plaques. They are neither oedematous nor annular in nature, although they may have a peripheral halo of vasoconstriction. Individual lesions resolve within 24 h (Fig. 1).[4] If not treated, irreversible damage may occur, which can include sensorineural hearing loss, vision loss, skeletal deformities, cognitive disability and systemic AA amyloidosis.[5]

Treatment has been revolutionized by drugs providing long-term IL-1 blockade.[5] Anakinra, canakinumab and rilonacept are all given subcutaneously, and have been shown to alleviate symptoms with dramatic

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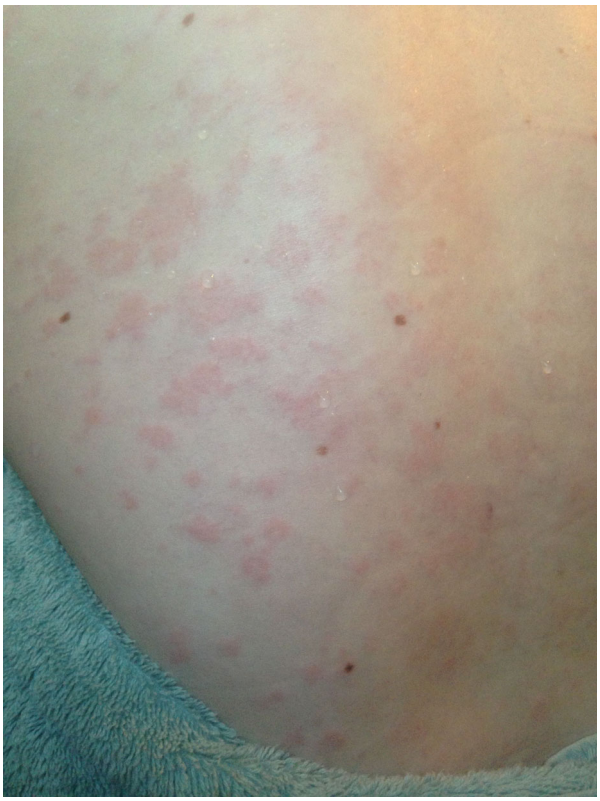

Figure 1 Typical presentation of cryopyrin-associated periodic syndromes. Courtesy of Helen Lachmann, National Amyloidosis Centre.

improvements.[6-8] There is now excellent safety data for over 15 years, with the only reported adverse effects being a modest increase in infections and development of mild neutropenia.[6]

Familial Mediterranean fever

Familial Mediterranean fever (FMF) is associated with mutations in the Mediterranean fever gene (*MEFV*), which encodes pyrin.[9] In the majority of patients, this is inherited in an autosomal recessive manner, although up to 20% have only one identified variant, and a few mutations are recognized to cause dominant inheritance.[10] Mutations appear to result in decreased phosphorylation of pyrin and gain of function, resulting in increased activation of the pyrin inflammasome and release of IL-1β.[11]

Familial Mediterranean fever is the most common of the inherited autoinflammatory diseases by far; it occurs worldwide but is most frequent in Eastern Mediterranean populations. Typical onset is early in life, with 50% having their first attack prior to 10 years of age and 90% prior to 20 years. Symptoms include recurring attacks of fever and extremely painful serositis lasting 12–72 h. Peritonitic abdominal pains occur in 80% of attacks (40% of patients undergo laparoscopy prior to diagnosis), and other common symptoms are pleuritic chest pain and nonerosive arthritis. The skin manifestation is an erysipelas-like erythema, usually between the knee and the dorsum of the foot, which is commoner in children and associated with the commonest and most severe mutation, M694V (Fig. 2).[12] Childhood polyarteritis nodosa and Henoch–Schonlein purpura are also recognized associations.[13] Between attacks there is often evidence of subclinical inflammation (raised inflammatory markers on blood tests).[12] Untreated FMF was historically associated with a very poor outcome, and 60% developed end stage renal failure due to AA amyloidosis.[14]

Most patients find that nonsteroidal anti-inflammatory drugs (NSAIDs) provide better symptom relief than other analgesics in acute attacks but the aim of treatment is to prioritize prophylaxis with lifelong colchicine, and long-term follow-up studies have provided reassuring safety data, including in pregnancy and breastfeeding.[15] With appropriate treatment, most patients will be symptom-free and the risk of amyloidosis disappears. In resistant cases, IL-1 inhibitors have been shown to be effective.[16] The European League Against Rheumatism published guidelines in 2015 with detailed recommendations on the management of FMF.[15]

Tumour necrosis factor receptor-associated periodic syndrome

Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal dominant

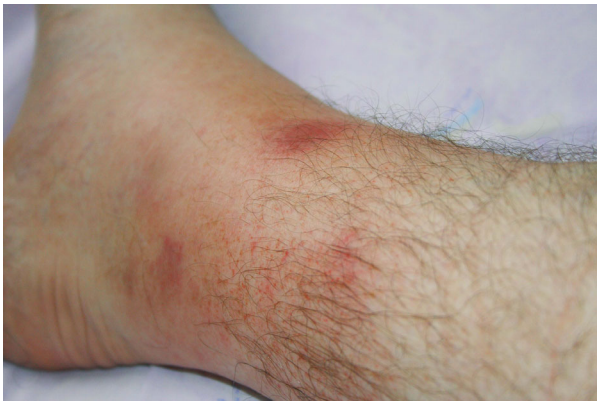

Figure 2 Typical presentation of familial Mediterranean fever. Courtesy of Helen Lachmann, National Amyloidosis Centre.

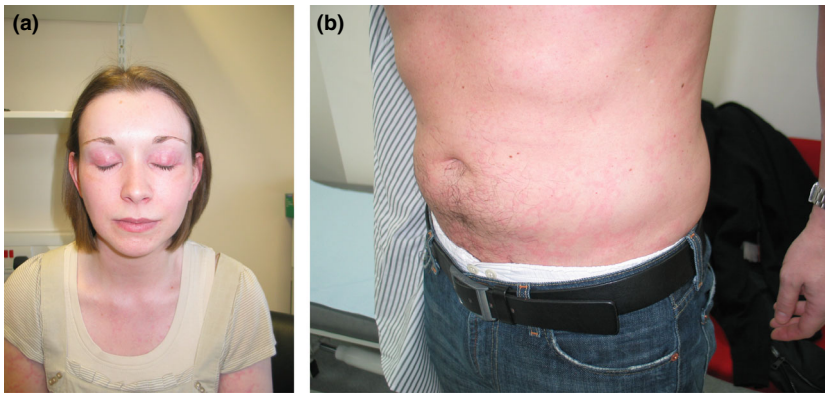

Figure 3 (a, b) Typical presentation of tumour necrosis factor receptor-associated periodic syndrome. Courtesy of Helen Lachmann, National Amyloidosis Centre.

disease caused by mutations in the gene for TNF receptor 1. The exact pathogenesis remains unclear, although it seems the variant protein does not reach the cell membrane.[17]

TRAPS has an estimated prevalence of 1מ per million in the UK. Median age at presentation is 7 years, with initially episodic attacks.[18] These attacks can be discrete or become near-continuous, and are often prolonged, lasting several weeks. They are accompanied by fever (88%), abdominal pain (74%), rash (63%), eye manifestations (43%), pleuritic pain (32%), headache (28%) and lymphadenopathy (14%).[18] The disease-associated rashes can be nonspecific and pleomorphic. Periorbital rash (Fig. 3) and oedema and migratory erythematous plaques overlying sites of myalgia are most commonly described, but serpiginous and urticarial rashes can also occur (Fig. 4). There is an acute phase response (which can be very elevated) and leucocytosis on blood tests. Untreated, TRAPS has a 25% risk of AA amyloidosis.[19]

An acute attack can be helped by NSAIDs (for symptoms) or steroids at 0.5–1 mg/kg for 5–10 days (ro shorten attack). In more severe disease, IL-1 blockade is highly effective.[20,21]

Mevalonate kinase deficiency

Mevalonate kinase deficiency (MKD) is a very rare autosomal recessive disease caused by a hypomorphic mutation in the mevalonate kinase gene (*MVK*). The MVK protein plays a role in the biosynthetic pathway that produces cholesterol and nonsterol isoprenoids. A proposed mechanism is reduced synthesis of isoprenoids, which in turn reduces prenylation of RoRetGTPases and disrupts their role in cytoskeletal regulation and vesicle trafficking, leading to

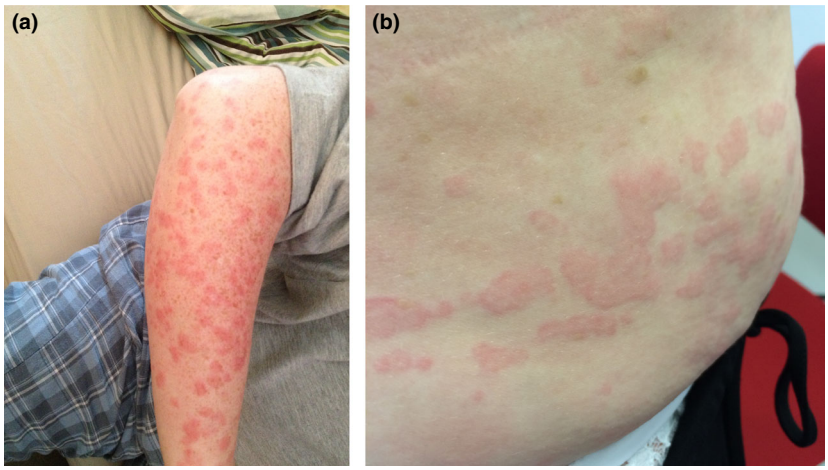

Figure 4 Typical presentations of (a) mevalonate kinase deficiency and (b) Schnitzler syndrome. Courtesy of Helen Lachmann, National Amyloidosis Centre.

Table 1 Summary of the key difference between the autoinflammatory conditions discussed

Autoinflammatory Disease	Ethnicity	Typical presentation	Typical dermatology findings	Normal treatment
CAPS	No predisposition		Myalgia, chills, night sweats, ocular inflammation. diurnal symptoms worsening over day	Urticarial rash affecting trunk and limbs
IL-1 blockade				
FMF	Eastern Mediterranean		Fever, extremely painful serositis	Erysipelas-like erythema between knee and foot
NSAIDs as acute treatment; lifelong colchicine				
TRAPS	Possibly Scottish/ Irish	Discrete or continuous. Abdominal pain, fevers, ocular inflammation, pleuritic pain	Pleomorphic. Periorbital rash and oedema. Erythematous plaques overlying myalgia.	Acute attack: NSAIDs/ steroids. May benefit from IL-1 blockade
MKD	Northwestern European	GI upset, lymphadenopathy, arthralgia, headache, ocular inflammation	Maculopapular Rash	IL-1 blockade
SS	No predisposition		Acquired: onset in 50s. Fever, arthralgia, bone pain, lymphadenopathy	Urticarial rash
IL-1 blockade				
DIRA	No predisposition		Neonatal onset. Osteitis	Pustular rash
IL-1 blockade				
DITRA	No predisposition		Childhood to 60s. Fever	Pustular rash
IL-1 blockade				

CAPS, Cryopyrin-associated periodic syndromes; DIRA, deficiency of the interleukin-1 receptor antagonist; DITRA, deficiency of the interleukin-36 receptor antagonist; FMF, familial Mediterranean fever; GI, gastroinestinal; IL, interleukin; MKD, mevalonate kinase deficiency; NSAID, nonsteroidal anti-inflammatory drug; SS, Schnitzler syndrome; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

overactivation of the pyrin inflammosome with consequent production of IL-1β.[22,23]

Mevalonate kinase deficiency has two clinical phenotypes. Total enzyme deficiency results in the metabolic disorder mevalonic aciduria, which is lethal unless early bone marrow transplantation is performed. Currently there are around 300 reported patients with the milder periodic fever syndrome variant, mostly from northwestern Europe, although the disease occurs worldwide.

Onset of MKD characteristically occurs in the first 6 months of life with recurrent episodes of fever lasting 3–7 days. Typical symptoms are gastrointestinal upset (98%), lymphadenopathy (90%), arthralgia (71%), oral aphthae (60%), maculopapular rash (39%) (Fig 4a), headache (38%) and eye inflammation (15%).[24] Long-term complications include AA amyloidosis, severe or recurrent infections, abdominal adhesions and joint contractures.

Treatment is difficult, but IL-1 blockade appears promising.[20] Patients who are resistant to this treatment sometimes respond to IL-6 blockade.[25]

Schnitzler syndrome

Schnitzler syndrome (SS) was first reported in 1974. The disease process appears to be mediated by a monoclonal immunoglobulin (IgM), although the mechanism is unclear.

The median age of onset of SS is 51 years. There is no associated family history and the condition is slightly more prevalent in men. Diagnosis is based on the the Strasbourg Diagnostic Criteria and typical features include fever, a chronic urticarial-like rash similar to CAPS, arthralgia, bone pain, and lymphadenopathy or hepatosplenomegaly (Fig. 4b).[26,27] Around 20% of patients eventually progress to overt plasma cell malignancy.[28] Treatment with IL-1 blockage seems to have excellent long-term response.[29-31]

Deficiency of the interleukin-1 and interleukin-36 receptor antagonists

Deficiency of the IL-1 receptor antagonist (DIRA) is a rare autosomal recessive disease caused by a mutation

of the *IL1RN* gene, resulting in absences or dysfunction of the IL-1 receptor antagonist and thus unopposed action at the IL-1 receptors. DIRA is characterized by a neonatal onset pustular rash, multifocal osteitis and periarticular soft-tissue swelling. It can be treated successfully with anakinra, which replaces the genetic deficiency.[32,33]

Another condition, deficiency of the IL-36 receptor antagonist (DITRA) is also an autosomal recessive disease. DITRA is caused by a mutation on the *IL36RN* gene resulting in loss of the IL-36 receptor antagonist.[34] Onset of DITRA is typically from childhood to the sixth decade of life, and may be precipitated by stress, pregnancy or drugs. It is characterized by a recurrent generalized sterile pustular rash accompanied by neutrophilia and fever. There are case reports indicating that patients with DITRA also benefit from anakinra.[35-37]

Undifferentiated syndromes

As previously mentioned many patients with suspected SAIDS do not fit into one of the aforementioned or other known syndromes (Table 1 summarizes these key features). They are considered to have undifferentiated disease and ruling out other differentials is included in Part 1. In addition, many do not have any identified autoinflammatory genetic abnormality. However, these patients may still have a long-term risk of amyloidosis. Treatment with colchicine, corticosteroids or biologics may therefore be considered if there is evidence of persistent inflammation and can be guided by a specialist.

Conclusion

The SAIDs are a collection of diseases that, although rare, are high-value diagnoses with the potential for highly effective, life-changing treatment. Most have some form of skin manifestation as a primary clinical feature, and therefore are important diseases for a dermatologist to bear in mind. Newer drugs have the potential for life-changing therapy.

Learning points

- SAIDS are disorders of innate immunity that can by inherited or aquired.
- Key features are recurrent, generalized inflammation.
- Many have dermatological features.
- If untreated, some of the conditions can progress to more severe conditions, including AA amyloidosis.
- Treatments include NSAIDs, colchichine, steroids and biologics.
- Diseases resulting from mutations in IL-associated genes can benefit from IL inhibitors.

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CPD questions

Learning objective

To demonstrate an understanding of the features and treatment of the commonest SAIDs

Question 1

Which of the following statements regarding treatment of cryopyrin-associated periodic syndromes is true?

(a) There is no effective treatment.
(b) The only treatment on offer is symptomatic relief.
(c) Treatment consists of long-term oral steroids.
(d) Treatment consists of topical steroids.
(e) Treatment consists of interleukin-1 blockade.

Question 2

Which of the following is known to typically exacerbate the rash of cryopyrin-associated periodic syndromes (CAPS)?

(a) Warmth.
(b) Viral infection.
(c) Cold.
(d) Lack of sleep.
(e) Pressure.

Question 3

What is the typical skin manifestation of familial Mediterranean fever (FMF)?

(a) Maculopapular rash localizing to the limbs.
(b) Erysipelas-like erythema between the knee and foot.
(c) Large scaly plaques predominantly on the trunk.
(d) Bullous eruption localizing to sun-exposed sites.
(e) Urticarial lesions over the forearms.

Question 4

Which of the following is associated with untreated familial Mediterranean fever (FMF)?

(a) AA amyloidosis.
(b) Bowel perforation.
(c) Sensorineural hearing loss.
(d) Skeletal deformity.
(e) Malignancy.

Question 5

Which of the following is strongly associated with Schnitzler syndrome (SS)?

(a) Hyperthyroidism.
(b) Gastrointestinal malignancy.
(c) Underlying Tuberculosis.
(d) Plasma cell malignancy.
(e) Lymphoma.

Instructions for answering questions

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- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
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