



CPD

The systemic autoinflammatory disorders for dermatologists. Part 1: overview

J. Oldham¹ and H. J. Lachmann¹

¹Portsmouth Hospitals NHS Trust, National Amyloidosis Centre, UCL Division of Medicine and Royal Free London NHS Foundation Trust, Portsmouth, Hampshire, UK

doi:10.1111/ced.14250

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 this article, we take an overview of SAIDs and look at the common features; in Part 2, we take a more in-depth look at the better recognized or more dermatologically relevant conditions.

Introduction

The systemic autoinflammatory disorders (SAIDs) or periodic fever syndromes are disorders of innate immunity, which can be inherited or acquired and can be monogenic or polygenic. They are almost all very rare and easily overlooked; typically patients will have been under the care of multiple specialities prior to diagnosis, so a high level of clinical suspicion is key.¹ 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 this article, we discuss common features of SAIDs before going into more depth for the better-recognized or more dermatologically relevant conditions.

SAIDs are a collection of diseases characterized by recurrent, generalized inflammation where no infectious or autoimmune cause can be detected. They are mediated predominantly by the innate immune system, particularly macrophages and neutrophils, with resultant production of inflammatory cytokines.² These diseases have led to a remarkable expansion in the understanding of the molecular biology of innate immunity and the role of the inflammasomes in the activation of interleukin (IL)-1 β , among other mechanisms. Since the concept of SAIDs was first coined in 1999, it has expanded to include recognition of a continuum between autoinflammatory and autoimmune disorders, and now includes > 20 implicated genes along with an increasing number of polygenic and multifactorial syndromes such as Behçet syndrome (Fig. 1).^{2,3}

The best recognized and understood inherited SAIDs include cryopyrin-associated periodic syndrome (CAPS), familial Mediterranean fever (FMF), tumour necrosis factor (TNF) receptor-associated periodic syndrome and mevalonate kinase deficiency. Diagnosis is based mainly on clinical features with support from genetic testing and/or functional testing where available.

Correspondence: Dr Helen J. Lachmann, Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital, Southwick Hill Road, Portsmouth, PO6 3LY, Hampshire, UK
Email: h.lachmann@ucl.ac.uk

Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 11 March 2020

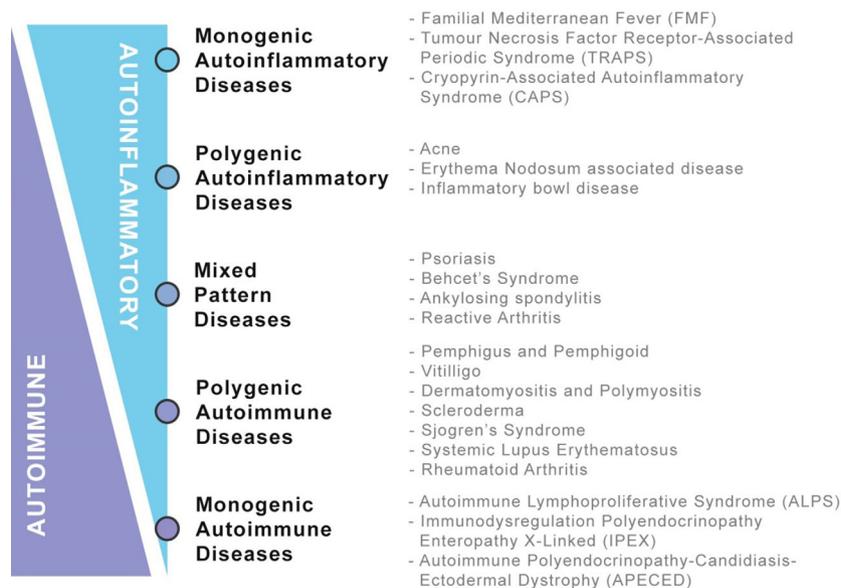


Figure 1 Continuum of immunological disease (adapted from McGonagle *et al.*, 2006²).

Common presenting features

Symptom onset in the genetic syndromes is typically early, from the neonatal period to childhood or adolescence. Adults are still picked up more frequently than children, mostly as previously 'missed' diagnoses, but 10% genuinely do not develop symptoms until well into adulthood. Meanwhile, the acquired diseases can affect both children [such as systemic onset juvenile inflammatory arthritis (sJIA)] and adults. Some adult disease such as Schnitzler syndrome or CAPS caused by somatic mosaicism may present very late, well beyond the eighth decade of life.⁴

The typical presentation is of unexplained fluctuating or recurrent febrile symptoms (varying from > 38 °C to > 41 °C) usually accompanied by inflammation affecting some or all of the skin, eyes, joints or other serosal surfaces. Between attacks, patients are usually symptom free but may have ongoing subclinical inflammation (i.e. raised inflammatory markers on blood tests).⁵ The clinical picture may give diagnostic clues, but there is considerable clinical overlap between conditions. Additionally, at least 25% of cases with probable autoinflammatory disease do not fit any described condition, and are currently defined as 'undifferentiated'.

The skin lesions can be highly variable with a wide spectrum of manifestations both in type of lesion,

severity and extent. Typical skin findings for some specific disease examples will be covered in Part 2 of this review.

Differential diseases to consider depend strongly on the patient's age and the clinical context. In general, in children occult or recurrent infections, immunodeficiency and sJIA are important considerations, whereas malignancy or atypical autoimmune diseases are more typical in adults. Important clues lie largely in the patient's history, including ethnicity (e.g. populations from the Middle East are at increased risk of FMF), family history and symptom precipitants.

Common signs and investigations

Signs of chronic inflammation may include organomegaly and growth retardation in children and chronic anaemia at any age. During attacks, the patient almost always has an elevated white cell count and raised biochemical markers of inflammation such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid A protein or ferritin (which can be over 2000 ng/mL in Still disease; normal range 50–500 ng/mL in men). With attacks, the acute phase response proteins should be very elevated, typically CRP levels > 30 mg/L and sometimes well above 100 mg/L (normal < 10 mg/L). Between attacks, the

acute phase response may be normal or elevated, and interpretation of results is highly dependent on the timing of blood sampling. Ideally, serial blood tests should be taken including during symptomatic and asymptomatic periods.

Very high levels of ferritin are seen in haemophagocytic lymphohistiocytosis (HLH), a syndrome of uncontrolled, life-threatening, systemic hyperinflammation. HLH is characterized by a proliferation of morphologically benign lymphocytes and macrophages that secrete high levels of inflammatory cytokines, and it is classified as a cytokine storm syndrome. HLH may present as a secondary phenomenon to a wide variety of underlying disorders, including inherited and acquired SAIDs.⁶

Genetic testing for the SAIDs is available as either single gene testing if only one disease is suspected, or panels covering the currently recognized genetic syndromes (<https://www.ucl.ac.uk/amyloidosis/national-amyloidosis-centre/molecular-genetic-testing>).

The most feared complication of SAIDs is AA amyloidosis. Historically, in untreated diseases, the lifetime risk was as high as 60%, although the incidence has fallen dramatically over the past 25 years, reflecting improvements in disease recognition and treatment. AA amyloidosis is predominantly a renal disease and is extremely unlikely if renal function is normal and there is no proteinuria. If there is concern about the possibility of AA amyloidosis, further testing can be done with a renal or screening biopsy, typically gastrointestinal tract or fat aspirate, or an iodine-123-labelled serum amyloid P scan (highly sensitive nuclear medicine means of screening for systemic amyloidosis).

Histological findings

There is no one typical histological appearance found for autoinflammatory disease, and findings can vary depending on the underlying disease. For example in FMF, erysipelas-like lesions will appear as oedema of the superficial dermis and sparse perivascular infiltrates, while immunofluorescence can show deposits of IgM, C3 and fibrinogen in capillary walls of the papillary dermis.⁷ In CAPS, the histology appears as a neutrophilic urticarial dermatosis where the neutrophils typically cluster around or within the eccrine ducts or inside the epidermis.⁸ Typical histological appearances have been described for a number of different autoinflammatory conditions, so biopsy may be useful in diagnosis.

Differential diagnosis

The differential diagnoses of SAIDs are very wide and depend heavily on clinical context. There is no single 'shopping list' of investigations that effectively excludes all possible causes of recurrent inflammation of uncertain cause. Investigations should be tailored to the individual and directed by careful medical history-taking and examination. In general, initial investigations tend to be more focused on excluding immunodeficiency, infection and rare genetic diseases in children, whereas in adults acquired disorders such as autoimmunity, vasculitis, sarcoidosis and malignancy become more prominent.

Conclusion

The SAIDs are a collection of diseases that, although rare, are high-value diagnoses with the potential for highly effective, life-changing treatment. The SAIDs are a prime example of success in reverse translational medicine, and have helped to hugely develop our understanding of the innate immune system. For a dermatologist, they are important to bear in mind, as most have some form of skin manifestation as a primary clinical feature. In considering the diagnosis, important tests to perform are CRP and ESR, which are inexpensive and informative, and will both be raised in an acute attack. In addition, skin biopsy findings have been characterized for a number of these diseases. As the field expands, evidence for the role of autoinflammation in commoner conditions such as psoriasis is becoming more convincing.⁹ It is undoubtedly an area to watch closely with the promise of exciting potential.

Learning points

- SAIDs are a collection of rare but high-value diagnoses.
- They are disorders of innate immunity that can be inherited or acquired.
- Key features are recurrent, generalized inflammation.
- During attacks, acute phase markers such as CRP and ferritin should be high.
- There is effective treatment for a number of these disorders.
- With treatment, many long-term sequelae can be avoided.

References

- 1 Hausmann JS, Lomax KG, Shapiro A, Durrant K. The patient journey to diagnosis and treatment of autoinflammatory diseases. *Orphanet J Rare Dis* 2018; **13**: 156.
- 2 McGonagle D, McDermott MF. A proposed classification of the immunological diseases. *PLoS Med* 2006; **3**: e297.
- 3 McDermott MF, Aksentijevich I, Galon J *et al*. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999; **97**: 133–44.
- 4 Simon A, Asli B, Braun-Falco M *et al*. Schnitzler's syndrome: diagnosis, treatment, and follow-up. *Allergy* 2013; **68**: 562–8.
- 5 Kallinich T, Gattorno M, Grattan CE *et al*. Unexplained recurrent fever: when is autoinflammation the explanation? *Allergy* 2013; **68**: 285–96.
- 6 Hutchinson M, Tattersall RS, Manson JJ. Haemophagocytic lymphohistiocytosis—an underrecognized hyperinflammatory syndrome. *Rheumatology (Oxford)* 2019; **58**: vi23–30.
- 7 Barzilai A, Langevitz P, Goldberg I *et al*. Erysipelas-like erythema of familial Mediterranean fever: clinicopathologic correlation. *J Am Acad Dermatol* 2000; **42**: 791–5.
- 8 Broekaert SMC, Böer-Auer A, Kerl K *et al*. Neutrophilic epitheliotropism is a histopathological clue to neutrophilic urticarial dermatosis. *Am J Dermatopathol* 2016; **38**: 39–49.
- 9 Fanoni D, Venegoni L, Vergani B *et al*. Evidence for a role of autoinflammation in early-phase psoriasis. *Clin Exp Immunol* 2019; **198**: 283–91.

CPD questions

Learning objective

To demonstrate an understanding of the systemic autoinflammatory disorders, the initial investigations for them, and their treatment and management.

Question 1

Which of the following statements regarding systemic autoinflammatory disorders is true?

- (a) They are mediated predominantly by the adaptive immune system.
- (b) They are a result of a response to recurrent infection.
- (c) They are a result of amyloid protein.
- (d) They are a result of immunodeficiency.
- (e) They are mediated predominantly by the innate immune system.

Question 2

What blood test should be done during an acute flare of a suspected systemic autoinflammatory disorder?

- (a) Urgent genetic profiling.
- (b) C-reactive protein.
- (c) Lactate dehydrogenase.
- (d) Zinc.
- (e) Urea and electrolytes.

Question 3

What is the most effective symptomatic treatment during a flare of a systemic autoinflammatory disorder?

- (a) Paracetamol.
- (b) Nonsteroidal anti-inflammatory drugs.
- (c) Oral steroids.
- (d) Topical emollients.
- (e) Topical steroids.

Question 4

What is haemophagocytic lymphohistiocytosis?

- (a) A specific type of systemic autoinflammatory disorder.
- (b) A subtype of haematological malignancy.
- (c) A description of the blood film appearance in a flare of systemic autoinflammatory disorder.
- (d) A syndrome of uncontrolled, life-threatening, systemic hyperinflammation.
- (e) A syndrome caused by excessive iron replacement.

Question 5

What is the typical histology finding in a skin biopsy from a lesion caused by a systemic autoinflammatory disorder?

- (a) Dermal oedema.
- (b) Neutrophilic infiltration of the epidermis.
- (c) Positive immunofluorescence at the dermal–epidermal junction.
- (d) Perivascular inflammatory infiltrate.
- (e) There is no typical appearance.

Instructions for answering questions

This learning activity is freely available online at <http://www.wileyhealthlearning.com/ced>

Users are encouraged to

- 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
- Register or login online at <http://www.wileyhealthlearning.com/ced> and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.