How NOT to miss autoinflammatory diseases

A resource for medical professionals, including primary care physicians, pediatricians, internists, rheumatologists and immunologists

- Recognition of autoinflammatory diseases can be challenging given their variable organ involvement and often non-specific symptoms that can mimic other conditions[1-5]
- Early diagnosis is important: timely and targeted treatment of autoinflammatory disease can have a life-changing impact on patients[1,4,6]
- Patient history is key:
  - Recognizing characteristic patterns of clinical manifestations can support identification of an autoinflammatory disease[7]
  - Symptoms can be episodic and may be triggered by a variety of stressors (eg, cold) and so may not be present on the day of examination[1,8-9]

Characteristic clinical manifestations, key warning signs and considerations to support an identification-to-treat strategy are listed below.

A recurring episodic pattern[9-10] *of ⩾2 of:*



Fever

>38° C/100.4° F often accompanied by chills and/or night sweats, without obvious signs of infection, and lasting up to several days[1,11-16]



Unexplained musculoskeletal, abdominal and/or chest pain[2,4,12,17-18,16]

Causes include serositis (can present as abdominal, pleuritic or pericardial chest pain)[20-22] and fasciitis[23]



Swollen lymph nodes

May be painful in some cases[1,6]



Skin/mucosal features

Eg, urticaria-like rash, often without itch[1,12,17-18], maculopapular rash[1,6,12], migratory rash[6], oral ulcers[17,19] and swelling of extremities[15]



CNS features

Eg, headache, aseptic meningitis, seizures, hearing loss and cognitive impairment in some severe cases[1,8,23]



Renal impairment

Can be seen as a result of AA amyloidosis; early-stage AA amyloidosis is characterized by low-grade proteinuria and can progress to nephrotic syndrome and renal damage[20-21]

- Renal involvement is usually observed sometime after disease onset and is rarely the first disease manifestation[20,26]



GI features

Eg, nausea and vomiting, diarrhea, colitis[1-2,9], and swollen liver/spleen in some cases[1,17]



Ocular features

Eg, conjunctivitis[8,10,17,24], periorbital edema[6,18,25] and uveitis[24]



Positive family history for symptoms of autoinflammatory disease or AA amyloidosis[1,10-11,14,25]

General considerations

- Some patients may have childhood-onset symptoms with significant delays in diagnosis, whereas others have true adult-onset autoinflammatory disease[9]
- Non-specific symptoms, such as fatigue which is common in autoinflammatory diseases[1,4,6,17], may be mistakenly attributed to common viral illnesses[5] and can result in a prolonged diagnostic path[4]
- Clinical manifestations of autoinflammatory diseases often follow stereotypical patterns[14,27] and so patients and parents may recognize a typical episode or flare

Other disease-specific considerations:

- Pharyngitis (erythematous or exudative) and tonsilitis, are also commonly seen in patients with PFAPA and can be seen in MKD[11,28-29]
- Skeletal abnormalities, such as frontal bossing, and sensorineural hearing loss are both seen in CAPS but are not common in other autoinflammatory conditions[1,6]

See page 2 for more information on **'What to do if you suspect an autoinflammatory disease'** after performing a clinical history / physical examination

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Abbreviations: AA, amyloid A; CAPS, cryopyrin-associated periodic syndromes; CNS, central nervous system; FMF, familial Mediterranean fever; GI, gastrointestinal; MKD, mevalonate kinase deficiency; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

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What to consider if you suspect an autoinflammatory disease:

1



Perform blood tests to check for markers of inflammation, including peripheral neutrophil counts, hemoglobin levels, platelet counts, CRP and ESR (and SAA/S100 proteins if available). Repeated blood tests during and outside of symptomatic episodes are important to establish patterns of inflammatory activity[1-2,4,6,30]

Presence of inflammatory markers:

If elevated markers of inflammation are present* (either during episodes only or continuously):

Absence of inflammatory markers:

Consider referral to a specialist center[1]

2



Appropriate management of patients may require a multidisciplinary team† depending on the clinical presentation[1]

- Genetic testing, if available, can help to exclude other conditions and enable a definitive diagnosis of an autoinflammatory disease[1,10]
- Identification of the causative gene can be pivotal for determining the most appropriate targeted anti-inflammatory treatment[1]
- Patients with an autoinflammatory disease might not have definitive genetic test results[10,11,17]. Therefore, it is important to view genetic results in context of the clinical setting[10]

3



Following an autoinflammatory disease diagnosis, **clinical management** focussing on the severity of inflammatory attacks and evidence of disease-associated damage may be appropriate[1]

4



A **treat-to-target** approach, with the aim to normalize markers of systemic inflammation, control clinical signs and symptoms, and prevent or address disease-related damage may be appropriate[1,6]. Patient diaries of disease activity can be useful to monitor disease course and to evaluate treatment effect[31-32]

*Patients who have very mild disease or who maintain normal inflammatory markers in between episodes may not have elevated markers at the time of testing[1]
†Including (pediatric) rheumatologists, immunologists and other specialists such as neurologists, ophthalmologists, gastroenterologists and dermatologists

Abbreviations: CRP, C-reactive proteins; ESR, erythrocyte sedimentation rate; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; SAA, serum amyloid A.

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This material summarises key warning signs and steps to support an identification-to-treat strategy for autoinflammatory diseases, based on the cited references and the experts' input.
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