

## REVIEW ARTICLE

# Review of autoinflammatory diseases, with a special focus on periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome

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## Keywords

Aphthous stomatitis, Autoinflammatory diseases, Disease mechanisms, Periodic fever, Pharyngitis and cervical adenitis

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## INTRODUCTION

When Michael McDermott and Daniel Kastner coined the concept of autoinflammatory diseases in 1999, it marked a paradigm shift as it depicted an entirely new group of immunological diseases in conceptual, clinical and mechanistic terms. Autoinflammatory diseases were defined as 'conditions characterised by seemingly unprovoked episodes of inflammation, without high-titre autoantibodies or antigen-specific T-cells' (1,2). The concept was suggested in the same paper that described the genetic background of the TNF receptor-associated periodic syndrome (TRAPS), but was also linked to the identification, two years earlier, of mutations that cause familial Mediterranean fever (FMF) (Table 1) (1,3). This review discusses the emerging field of autoinflammatory conditions, with a special emphasis on periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome. PFAPA is a relative common and important differential diagnosis for many infections occurring in preschool children, and every paediatrician

## Abbreviations

CAPS, Cryopyrin-associated periodic syndrome; CINCA, Chronic infantile neurological, cutaneous and articular syndromes; DIRA, Deficiency of IL-1 receptor antagonist; FCAS, Familial cold autoinflammatory syndrome; FMF, Familial Mediterranean fever; HIDS, Hyperimmunoglobulinaemia D with periodic fever syndrome; MKD, Mevalonate kinase deficiency; MWS, Muckle-Wells syndrome; PFAPA, Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis; TRAPS, Tumour necrosis factor receptor-associated periodic syndrome.

## ABSTRACT

There have been remarkable developments in the field of autoinflammatory diseases over the last 20 years. Research has led to definitions of new conditions, increased understanding of disease mechanisms and specific treatment. The polygenic autoinflammatory condition of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) is the most common autoinflammatory disorder among children in many parts of the world. The clinical features often include clockwork regularity of episodes, prompt responses to corticosteroids and therapeutic effects of tonsillectomy, but the disease mechanisms are largely unknown.

**Conclusion:** This review discusses the emerging understanding of autoinflammatory diseases, with special emphasis on PFAPA.

will encounter PFAPA several times during her or his career.

## CLINICAL FEATURES OF AUTOINFLAMMATORY DISEASES

Autoinflammatory diseases or periodic fever syndromes are clinically characterised by recurrent episodes of fever, systemic inflammation and symptoms such as skin rashes, abdominal pain, chest pain, lymphadenopathy or arthritis. Autoinflammatory diseases that have been more recently defined often have symptoms similar to those of the classical autoinflammatory diseases, but in a continuous manner rather than in episodes and, or, with milder systemic inflammation (4). Phenotypes of the different diseases are used to classify autoinflammatory diseases

## Key notes

- There have been remarkable developments in the field of autoinflammatory diseases over the last 20 years.
- This review discusses the emerging understanding of autoinflammatory diseases, with special emphasis on the polygenic autoinflammatory condition of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome.
- The clinical features of PFAPA often include clockwork regularity of episodes, prompt responses to corticosteroids and therapeutic effects of tonsillectomy, but the disease mechanisms are largely unknown.

**Table 1** Clinical characteristics of (some) monogenic autoinflammatory diseases and PFAPA

Clinical classification	Fever (length of episodes)	Main organs involved/symptoms	Skin rash	Gene (inheritance)	Protein	Suggested treatment
Periodic fever syndrome TRAPS	Yes (1–6 weeks)	Eyes: conjunctivitis, periorbital oedema, pleuritis, pericarditis CNS: headache Abdominal pain Splenomegaly Arthritis/arthralgia, myalgia Large joints: serositis, peritonitis, pleuritis and/or arthritis	Migrating erysipelas-like, painful	<i>TNFRSF1A</i> (AD)	TNF receptor 1 (TNFR1)	IL-1 blockade Corticosteroids Etanercept NSAID Colchicine
FMF	Yes (½–3 days)	Arthritis/arthralgia, myalgia Large joints: serositis, peritonitis, pleuritis and/or arthritis	Sometimes erysipelas-like erythema, most often in the ankle region	<i>MEFV</i> (AR)	Pyrin	Colchicine (IL-1 blockade in refractory cases or colchicine side-effects) IL-1 blockade
FCAS (CAPS)	Yes (12–24 hours) Triggered by cold exposure Yes (24–48 hours)	Eyes: conjunctivitis Joints: arthralgia	Urticaria-like rash	<i>NLRP3</i> (AD)	NLRP3	IL-1 blockade
MWS (CAPS)	Continuous with fever during flares	CNS: hearing loss, headache Eyes: conjunctivitis Joints: arthralgia/arthritis CNS: meningitis, hearing loss, headache Eyes: conjunctivitis, uveitis and papilloedema Bone: bony overgrowth Joints: arthralgia/arthritis	Urticaria-like rash Urticaria-like rash increase with flares	<i>NLRP3</i> (AD)	NLRP3	IL-1 blockade
HIDS/MKD	Yes (3–7 days) Flares triggered by vaccinations	Abdominal pain, diarrhoea, lymphadenopathy, splenomegaly Headache Oral and/or genital ulcers Arthritis/arthralgia	Exanthema (Maculopapular or purpuric)	<i>MVK</i> (AR)	Mevalonate kinase (MK)	IL-1 blockade NSAID Corticosteroids TNF blockade
FCAS2	Yes, flares triggered by cold	Arthritis/arthralgia Arthralgia, headaches, aphthous stomatitis, abdominal pain Hearing loss	Urticarial rash	<i>NLRP12</i> (AD)	NLRP12	NSAID Corticosteroids
PFAPA	Yes (3–7 days, most commonly 4–5 days)	Recurrent attacks of fever often regularly associated with the acronym PFAPA in the absence of upper respiratory tract infection	No, in our hands the diagnosis is questioned in patients with skin rash	N/A	N/A	NSAID Tonsillectomy Colchicine Corticosteroids
Diseases with pyogenic lesions DIRA	No	Multifocal osteomyelitis periarticular soft-tissue swelling	Pustular	<i>IL-1RN</i> (AR)	IL-1 receptor antagonist	IL-1 blockade
Diseases with granulomatous lesions BS/PGA				<i>NOD2</i> (AD)	CARD15	

**Table 1** (Continued)

Clinical classification	Fever (length of episodes)	Main organs involved/symptoms	Skin rash	Gene (inheritance)	Protein	Suggested treatment
Diseases with panniculitis-induced lipodystrophy CANDLE/PRAAS	Rarely, not a dominant feature Yes (often continuous)	Arthritis Uveitis Myositis, arthritis/arthralgia Joint contractures, muscle atrophy Hepatomegaly, splenomegaly Basal ganglia calcifications, Anaemia	Tan coloured rash. Ichthyosis-like exanthema Panniculitis, lipodystrophy Nodular exanthema	<i>PSMB8</i> (AR), <i>PSMA3</i> , <i>PSMB4</i> , <i>PSMB9</i> , <i>POMP</i>	PSB8, PSMA3, PSMA4, PSMB9 and POMP	TNF blockade Corticosteroids Methotrexate Corticosteroids? JAK inhibition?
Diseases with psoriatic lesions DITRA	Flares with fever	Arthritis, geographic tongue, cholangitis nail dystrophy	Generalised pustular psoriasis (often without psoriasis vulgaris)	<i>IL36RN</i> (AR)	IL-36Ra	IL-1 blockade? TNF blockade? Corticosteroids Methotrexate
CAMPS	Not a distinct feature	<i>Psoriatic arthritis</i>	Generalised pustular psoriasis (often with psoriasis vulgaris) Some cases of familial pityriasis rubra pilaris och psoriasis vulgaris Erythrodermic psoriasis	<i>CARD14</i> (AD)	CARD14	IL-12/23 blockade? or IL-17 blockade?
Diseases with neurologic and dermatologic manifestations AGS	Rarely	Progressive brain disease	Chilblains	Seven different genes (AD or AR)	Several different proteins	No established treatment
Diseases with IBD EO-IBD (IL-10 receptor deficiency, IL-10 deficiency)	Recurrent fever rare	Early-onset enterocolitis with haematochezia, colonic abscesses, perianal fistulas, oral ulcers and failure to thrive	Recurrent folliculitis	<i>IL-10</i> , <i>IL-10RA</i> and <i>IL-10RB</i>	IL-10, IL-10RA and IL-10RB	Beyond the scope of this review

TRAPS = Tumour necrosis factor receptor-associated periodic syndrome; FMF = Familial Mediterranean fever; FCAS = Familial cold autoinflammatory syndrome; MWS = Muckle-Wells syndrome; CINCA = Chronic infantile neurological, cutaneous and articular syndromes; CAPS = Cryopyrin-associated periodic syndrome; HIDS = Hypeimmunoglobulinaemia D with periodic fever syndrome; MKD = Mevalonate kinase deficiency; FCAS2 = Familial cold autoinflammatory syndrome 2; PFAPA = Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis; DIRA = Deficiency of IL-1 receptor antagonist; BS = Blau syndrome; PCA = Paediatric granulomatous arthritis; CANDLE = Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; PRAAS = Proteasome-associated autoinflammatory syndrome; DITRA = Deficiency of IL-36 receptor antagonist; CAMPS = CARD14-mediated psoriasis; AGS = Aicardi-Goutières syndrome; EO-IBD = Early-onset inflammatory bowel disease; AD = Autosomal dominant; AR = autosomal recessive.

(Table 1), with clinical signs and symptoms forming the basis of the differential diagnosis and guiding the genetic analysis (5).

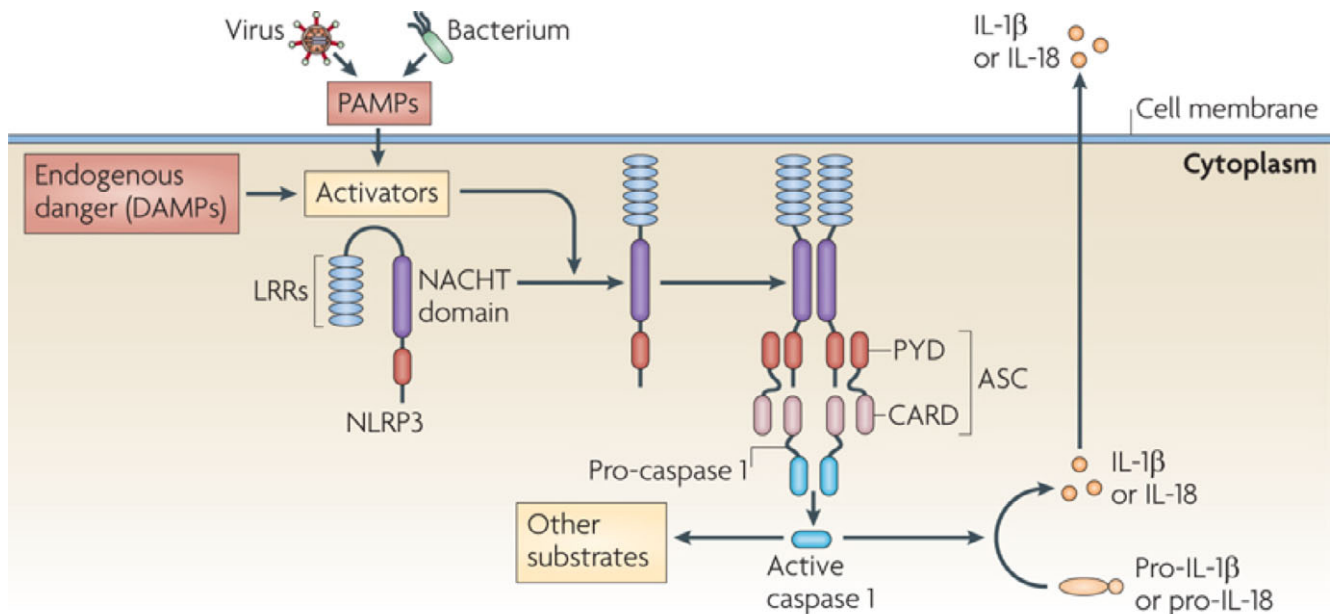
### AUTOINFLAMMATORY CONDITIONS ARE CAUSED BY DYSREGULATION OF INNATE IMMUNITY

It has become clear that autoinflammation is caused by dysregulation of innate immunity, as described by Kastner et al. (6), who proposed that autoinflammatory diseases are 'clinical disorders marked by abnormally increased inflammation, mediated predominantly by cells and molecules of the innate immune system, with a significant host predisposition'. This definition was closely related to the identification and pathophysiological understanding of mutations in the NOD-like receptor 3 gene (*NLRP3*) that causes cryopyrin-associated periodic syndromes (CAPS) (4,7). Under normal conditions, *NLRP3* recognises unique microbial and danger components and forms a *NLRP3* inflammasome that is essential for the defence against infections and the innate immune response. The formation of the *NLRP3* inflammasome leads to processing of procaspase-1 into caspase-1 that, in turn, cleaves to pro-IL-1 $\beta$  to IL-1 $\beta$  (Fig. 1). Mutations in *NLRP3* can result in three autoinflammatory phenotypes, which often are overlapping. In

order of increasing severity, these are familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological, cutaneous and arthritis (CINCA), also known as neonatal-onset multi-system inflammatory disease (NOMID) (Table 1) (3,4). Intriguingly, the same CAPS-associated mutation can give rise to more than one disease phenotype – FCAS, MWS or CINCA – and mutation negative patients often have a somatic mutation in some of the cells tested, which is known as somatic mosaicism (8).

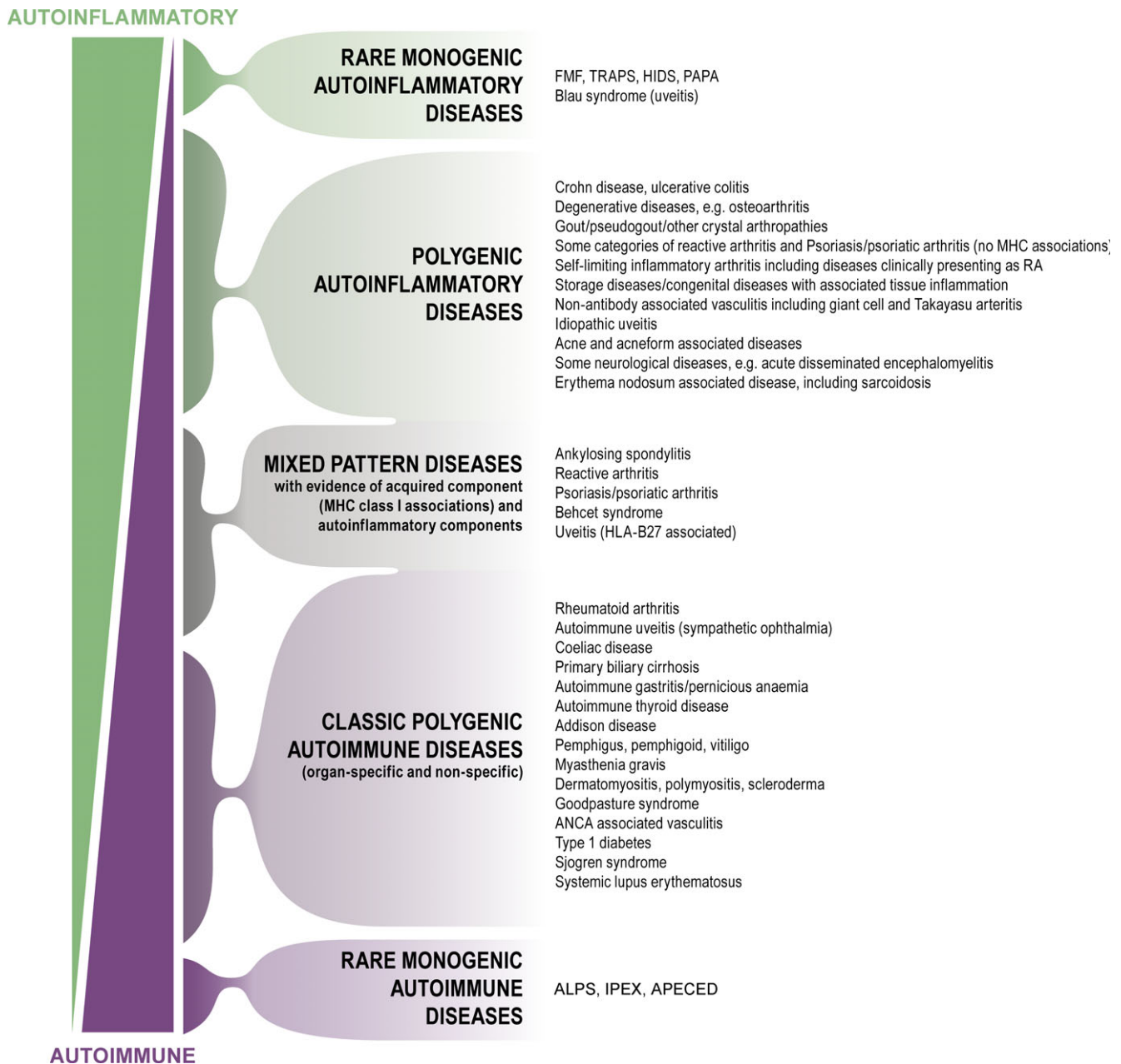
### The importance of the balance between IL-1 and its receptor antagonist IL-1Ra

IL-1 $\beta$  is a potent proinflammatory cytokine that initiates an inflammatory response, including secretion of IL-6 from the liver. Although IL-1 $\beta$  is necessary for the disease pathology in many autoinflammatory conditions, increased serum concentrations of IL-1 $\beta$  are rarely measurable. The common way to demonstrate the pathogenic role of IL-1 $\beta$  in a specific autoinflammatory disease *in vivo* is by a IL-1 blockade, exemplified by the treatment of CAPS. The effect of IL-1 $\beta$  is balanced by the presence of the IL-1 receptor antagonist (IL-1Ra). This is exemplified by the autosomal recessive disease deficiency of the IL-1 receptor antagonist (DIRA), where the lack of IL-1Ra leads to unopposed



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**Figure 1** NLRP3 inflammasome activation. Under healthy conditions, NOD-like receptor family, pyrin domain containing 3 (*NLRP3*) is auto-repressed through interaction between the NACHT domain and the leucine-rich repeat domain (LRR). Cellular activation by PAMPs and DAMPs removes this auto-repression. As a result, *NLRP3* unfolds itself and the NACHT domain is exposed. This leads to oligomerisation of *NLRP3* that recruits apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase 1, inducing activation of caspase 1, which in turn activates IL-1 and IL-18. Tschopp & Schroder K. *Nat Rev Immunol* 2010; 10:210–5. With permission (3802450071000). PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; LRRs, leucine-rich repeats; NACHT, NAIP (neuronal apoptosis inhibitory protein), CIITA (MHC class II transcription activator), HET-E (incompatibility locus protein from *Podospirina anserina*) and TP1 (telomerase-associated protein); ASC, apoptosis-associated speck-like protein containing a CARD; PYD, pyrin domain; CARD, caspase-recruitment domain.



**Figure 2** The immunological disease continuum. McGonagle and McDermott's continuum model moved the understanding of immunological diseases forward by integrating the concept of autoinflammation with that of autoimmunity and also applied the concept of autoinflammation to polygenic diseases and to diseases that may have both an autoinflammatory and an autoimmune component. McGonagle & McDermott (17). With permission. TRAPS, tumour necrosis factor receptor-associated periodic syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinaemia D with periodic fever syndrome; PAPA, pyogenic arthritis, pyoderma gangrenosum (PG) and acne syndrome; ANCA, antineutrophil cytoplasmic antibodies; APLS, autoimmune lymphoproliferative syndrome; IPEX, immunodysregulation polyendocrinopathy enteropathy x-linked syndrome; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.

normal levels of IL-1 $\alpha$  and IL-1 $\beta$ , in contrast to the hypersecretion of IL-1 $\beta$  in CAPS (9). This difference in disease mechanism may explain the different clinical features in DIRA and CAPS, with a pustular rash and sterile osteomyelitis in DIRA and urticaria-like rash and bony overgrowth in CAPS (Table 1). Just like CAPS, DIRA can be efficiently treated by an IL-1 blockade.

#### Current classification according to mechanisms in monogenic autoinflammatory conditions

Although much of the focus in the autoinflammatory field has been on the importance of IL-1 $\beta$ , a number of conditions with other defining cytokines, or pathways, have been described, including conditions mediated by NF- $\kappa$ B. The conditions include familial cold autoinflammatory



**Table 2** The main cytokines involved in major monogenic autoinflammatory diseases

Defining cytokine
IL-1 $\beta$
CAPS (FCAS, MWS, CINCA)
DIRA
HIDS/MKD
IL-1 $\beta$ and others
TRAPS
FMF
Multiple cytokines via NF- $\kappa$ B activation
FCAS 2
BS/PGA
CAMPS
INF type I
PRAAS/CANDLE
AGS 1/2/3/4/5/6/7
Deficiency of IL-10 signalling
EO-IBD (IL-10 receptor deficiency, IL-10 deficiency)
IL-36
DITRA

CAPS = Cryopyrin-associated periodic syndrome; FCAS = Familial cold autoinflammatory syndrome; MWS = Muckle–Wells syndrome; CINCA = Chronic infantile neurological, cutaneous and articular syndromes; DIRA = Deficiency of IL-1 receptor antagonist; HIDS = Hyperimmunoglobulinaemia D with periodic fever syndrome; MKD = Mevalonate kinase deficiency; TRAPS = Tumour necrosis factor receptor-associated periodic syndrome; FMF = Familial Mediterranean fever; FCAS2 = Familial cold autoinflammatory syndrome 2; BS = Blau syndrome; PGA = Paediatric granulomatous arthritis; CAMPS = CARD14-mediated psoriasis; CANDLE = Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; PRAAS = Proteasome-associated autoinflammatory syndrome; AGS = Aicardi–Goutières syndrome; EO-IBD = Early-onset inflammatory bowel disease; DITRA = Deficiency of IL-36 receptor antagonist.

syndrome 2 (FCAS2) (10), Blau syndrome or paediatric granulomatous arthritis (11,12) and CARD14-mediated psoriasis (CAMPS); diseases mediated by type I interferon, such as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) or proteasome-associated autoinflammatory syndrome (PRAAS) (13), Aicardi-Goutières syndrome (14); disorders mediated by IL-36, for example deficiency of the IL-36 receptor antagonist (DITRA) (15) and conditions due to decreased IL-10 activity such as early-onset enterocolitis (16), allowing for classification according to a defining cytokine as depicted in Table 2 (4). See Table 1 for the clinical classifications.

Monogenic autoinflammatory diseases have also been classified according to pathogenic mechanisms, in other words, in terms of how molecules of innate immunity are dysregulated. Such mechanisms include intracellular sensor function defects, accumulation of intracellular triggers, loss of a negative regulator of inflammation and effects on signalling molecules that upregulate innate immune cell function. A classification of autoinflammatory diseases according to their pathogenic mechanisms is shown in Table 3. Some conditions could be assigned to more than one category.

## THE CONTINUUM MODEL OF IMMUNOLOGICAL DISEASES

In the first definition of autoinflammatory diseases, McDermott made a clear distinction between autoinflammation and autoimmunity. Today, there is an emerging understanding that innate and adaptive immunity are closely linked and that autoinflammatory conditions may have an adaptive or autoimmune component (4). In 2006, McDermott and McGonagle proposed that immunological diseases should be conceived as a continuum with ‘pure monogenic autoinflammatory diseases’ at one end and ‘pure monogenic autoimmune diseases’ at the other, as illustrated in Figure 2 (17).

Since the continuum model was formulated, it has become clear that even ‘pure monogenic autoinflammatory diseases’ (17) activates the adaptive immune system. One such example is the Th17 differentiation of CD4<sup>+</sup> cells in CAPS, a response that diminishes in response to the IL-1 blockade (18,19). There are rare monogenic autoinflammatory conditions, which have clinical phenotypes that combine autoinflammation with immunodeficiency or autoimmunity, but these are beyond the scope of this review (4,6).

## The complex pathophysiology of polygenic or multifactorial autoinflammatory diseases

Examples of polygenic or multifactorial autoinflammatory diseases in addition to PFAPA are chronic nonbacterial osteomyelitis, systemic-onset juvenile idiopathic arthritis and adult onset Still’s disease. As illustrated above, the search for disease mechanisms in monogenic autoinflammatory diseases has been a success story, where the definition of disease-causing mutations has led to the identification of disease mechanisms and sometimes to specific treatment. In other cases, effective responses to specific treatment have led to the identification of candidate genes and disease-causing mutations (9). In polygenic diseases, genetic characterisation is complex because of the many genes involved. The defining cytokines in polygenic diseases are seldom known, if any, and specific treatment is rarely available. Therefore, the approaches used to define and understand monogenic conditions have been of limited value when applied to the study of polygenic autoinflammatory diseases. Researchers trying to define disease mechanisms in polygenic conditions often depend on sets of clues from cellular and cytokine studies.

## Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome

The most common autoinflammatory condition among children, outside regions with a high prevalence of FMF, is PFAPA, which is polygenic or multifactorial. The clinical phenotype of PFAPA has all the features of a classical periodic fever syndrome, with unprovoked febrile episodes and systemic as well as localised inflammation (20). Even though studies have shed new light on the pathophysiology of PFAPA, the disease mechanisms are largely unknown. Families, paediatricians and researchers are still intrigued by the often clockwork regularity with which typical

**Table 3** The mechanisms in monogenic autoinflammatory diseases

Innate mechanism	Component	Mechanism
Intracellular sensor function defects		
CAPS (FCAS, MWS, NOMID/CINCA)	NLRP3 (cryopyrin)	Activation of NLRP3 inflammasome (gain-of-function) leading to IL-1 $\beta$ production
FMF	Pyrin	Inflammasome activation, increased IL-1 $\beta$ production
BS/PGA	NOD2	NF- $\kappa$ B and RIP2K activation
CAMPS	Adaptor molecule C CARD14	Increased NF- $\kappa$ B
Accumulation of intracellular triggers		
TRAPS	Folding defect and accumulation of TNFR1	MAPK activation, Increased production of mROS, ER stress
CANDLE/PRAAS	Proteasome dysfunction	IFN response gene induction
HIDS/MKD	Mevalonate kinase	Lack of prenylation leads to cytoskeletal changes and inflammasome activation
Loss of a negative regulator of inflammation		
DIRA	Loss of IL-1 antagonism	Uncontrolled IL-1 signalling
DITRA	Loss of IL-36 antagonism	Uncontrolled IL-36 signalling
EO-IBD	Loss of IL-10 or IL-10 receptor antagonist	Decreased IL-10 signalling
Effects on signalling molecules that upregulate innate immune cell function		
AGS	Type I interferonopathy-related proteins	Increased INF type I production

CAPS = Cryopyrin-associated periodic syndrome; FCAS = Familial cold autoinflammatory syndrome; MWS = Muckle–Wells syndrome; CINCA = Chronic infantile neurological, cutaneous and articular syndromes; FMF = Familial Mediterranean fever; BS = Blau syndrome; PGA = Paediatric granulomatous arthritis; AGS = Aicardi–Goutières syndrome; CAMPS = CARD14-mediated psoriasis; TRAPS = Tumour necrosis factor receptor-associated periodic syndrome; CANDLE = Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; PRAAS = Proteasome-associated autoinflammatory syndrome; HIDS = Hyperimmunoglobulinaemia D with periodic fever syndrome; MKD = Mevalonate kinase deficiency; DIRA = Deficiency of IL-1 receptor antagonist; DITRA = Deficiency of IL-36 receptor antagonist; EO-IBD = Early-onset inflammatory bowel disease.

**Table 4** Classical diagnostic criteria for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) as defined by Thomas et al. (27)

## Diagnostic criteria for PFAPA

- Regularly recurring fevers with an early age of onset (<5 years of age)
- Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:
  - Aphthous stomatitis
  - Cervical lymphadenitis
  - Pharyngitis
- Exclusion of cyclic neutropenia
- Completely asymptomatic interval between episodes
- Normal growth and development

episodes appear, the prompt response to corticosteroids and the therapeutic effect of tonsillectomy.

### Epidemiology

In early studies, it was estimated that no more than one case of PFAPA would be diagnosed during an entire paediatric career. Today, PFAPA is diagnosed at a much higher frequency in children below the age of five years. However, the syndrome is also recognised in older children and even in adults (21–23). PFAPA has been described in many parts of the world, but the only estimate of annual incidence is from Norway, which was 2.3 per 10 000 children up to five years old (24). In western Sweden, approximately 300 children were given a definite or probable diagnosis of PFAPA during a 10-year period (Berg S and Wekell P, unpublished data). This corresponded to an annual

incidence of at least three per 10 000 children below the age of five years, which is similar to the data from Norway. A predominance of boys has been described in several PFAPA cohorts (24–26).

### Clinical manifestations

Patients who suffer from PFAPA have recurrent attacks of fever and symptoms associated with the core features of the disease – aphthous stomatitis, pharyngitis and adenitis – in the absence of upper respiratory tract infection. Between the episodes, children with PFAPA are healthy, with normal growth and development, as delineated in the classical diagnostic criteria (Table 4) (27).

The duration of the fever attacks is usually three to seven days most commonly four to five days, with an interval of two to eight weeks, most commonly three to six weeks (24,27–30). At some stage of the disease, the episodes characteristically occur with a regular interval, ‘sometimes to a point that the parents can predict the time for an episode and inform their employer’ according to Federici and Galtornò (31). The regularity may disappear over time, and the child then experiences longer intervals and shorter or milder episodes (or both) (22). In our clinical experience, children with PFAPA appear to have fewer upper respiratory infections than other children as long as their PFAPA is active, but the upper respiratory infections seem to re-emerge as the child grows out of the episodes (Wekell P, Berg S and Fasth A, unpublished observation).

In addition to the signs and symptoms included in the classical criteria, children with PFAPA often have mild abdominal pain, leg pain and nausea and vomiting during

episodes (27,30). The spectrum of additional symptoms was even more striking in a study by Hofer et al. (26) that rightly stressed the importance of establishing new disease criteria with better specificity. Even though children with PFAPA are, by definition, free of symptoms between episodes, aphthous stomatitis is not confined to the episodes and a few children with very frequent attacks do not recover completely between attacks (32).

### Diagnosis

The diagnosis of PFAPA is still largely based on recognition of the clinical features delineated in the classical PFAPA criteria (Table 4) (27). These criteria are not totally exclusive to other conditions, including hereditary periodic fever syndromes and need to be refined to improve specificity, in particular, but also sensitivity (20,28). Until a gold standard has been defined, for example in terms of genetic predisposition or disease mechanism, it is hard to see how the validity of different sets of clinical criteria can be accurately evaluated.

Recurrent infections also need to be considered as a differential diagnosis of PFAPA, namely repeated streptococcal infections, urinary tract infections and viral infections involving the throat and causing raised inflammatory markers, for example adenovirus. Over time, several characteristics of PFAPA will make an infectious aetiology less likely, as the often clockwork episodes, the presence of aphthous stomatitis, the lack of response to antibiotics, the distinct response to corticosteroids, the lack of infections among family members and negative cultures all point towards another diagnosis.

The exclusion of the very rare disease cyclic neutropenia, in which the blood neutrophils typically oscillate with a 21-day interval, is included in the classical criteria. On occasions, cyclic neutropenia cannot be excluded on clinical grounds as the nadir of the neutrophil count may occur before the onset of fever. In such cases, analysing the neutrophil elastase gene (*ELANE*) or repeated neutrophil counts three times a week for six weeks can confirm the diagnosis and thus differentiate it from PFAPA (33).

Gattorno et al. (21) proposed a diagnostic score with the aim of predicting the likelihood that a child with PFAPA-like symptoms could actually have a hereditary periodic fever syndrome instead. It is important to remember that the accuracy of such a prediction will always depend on the prevalence of relevant conditions in the population, for example the prevalence of PFAPA and FMF, respectively, in a specific context. In addition, it is not clear how somatic mosaicism of monogenic autoinflammatory disorders would influence the validity of the diagnostic score developed by Gattorno.

PFAPA also needs to be distinguished from monogenic periodic fever syndromes, such as FMF, MKD and TRAPS, and the diagnosis of PFAPA should be challenged in children who fulfil the criteria but show additional signs and symptoms suggestive of hereditary periodic fever syndromes. These include skin rashes, arthritis, severe abdominal pain, diarrhoea, chest pain and splenomegaly,

fever episodes longer than seven days, a history of hearing loss or symptoms secondary to cold exposure (21,34,35). The above-mentioned diagnostic score could be useful for this purpose (21).

The diagnostic workup for PFAPA can be particularly challenging in children who originate from a population with a high prevalence of FMF. Another hereditary periodic fever (HPF) to bear in mind is MKD, also called *hyperimmunoglobulinaemia D with periodic fever syndrome* (HIDS), that commonly has the same length of episodes, but is often associated with diarrhoea and exanthema as well as flares triggered by vaccinations. In the differential, it is important to note that hyper-IgD is not a specific indicator for HIDS, as increased IgD concentrations are also seen in other inflammatory conditions, including autoinflammatory diseases such as FMF, TRAPS and PFAPA (29,36). Increased excretion of mevalonate acid *during* an inflammatory episode is a valid screening test for MKD, provided that the laboratory can detect very low concentrations of the substance in urine. If indicated, MKD is diagnosed by the identification of mutations in the *MVK* gene.

### Innate immune dysregulation leads to activation of adaptive immunity in PFAPA

Dysregulation of innate immunity in PFAPA is indicated by the clinical phenotype, increase of proinflammatory cytokines, neutrophilia, prompt response to corticosteroids, lack of response to antibiotics and a possible response to the IL-1 blockade. The role of the fever-mediating cytokine IL-1 $\beta$  needs to be further examined (37). A study of whole blood gene expression on the messenger ribonucleic acid level showed increased expression of the IL-1-related genes *IL1B*, *IL1RN*, *CASP1* and *I18RAP* during PFAPA episodes (38). Studies of *ex vivo* LPS-stimulated peripheral blood mononuclear cells (PBMCs) and purified monocytes from febrile patients with PFAPA showed that the cells had an increased IL-1 $\beta$  secretion compared to cells from afebrile patients (39). One small case series suggested that PFAPA flares were responsive to IL1-blockade (38). The role of IL-1 $\beta$  is still not settled in PFAPA and a well-designed study of IL-1 blockade would be an important step forward to demonstrate whether IL-1 $\beta$  has any role in PFAPA.

A number of other proinflammatory cytokines in addition to IL-1 have been evaluated in PFAPA with the expectation that inflammatory mediators are increased during the febrile episode. IL-6 is indeed increased in serum during disease flares (24,37–40). One study also showed increased IL-18 levels during febrile episodes (38). In addition, IL-1 $\beta$  and the INF- $\gamma$ -related cytokine IP-10/CXCL10 were increased in PFAPA attacks compared to the afebrile phase (38–41), as were MIG/CXCL9 (38) and MIP-1/CCCL4 (38,41). In summary, this cytokine pattern supports an increased INF- $\gamma$  secretion somewhere during the PFAPA cycle, with an adjoining Th1 differentiation of CD4 $^{+}$  T cells. The Th1 differentiation in PFAPA may be due to IL-18, which, in the presence of IL-12, induces INF- $\gamma$  and promotes a Th1 response (37). These findings indicate that there is an activation of both the innate and the adaptive



immune system in PFAPA with a Th1 differentiation of CD4+ cells during febrile episodes.

Febrile attacks were associated with lymphopenia, and it is not clear whether this was a result of increased myelopoiesis paralleled by a decrease in lymphopoiesis as in acute inflammation or was a consequence of homing of lymphocytes to lymphatic tissue including cervical lymph nodes and tonsils (42). It has also been shown that neutrophil function was altered in PFAPA, including apoptosis, priming and generation of an intracellular oxidative burst during febrile attacks (43).

The role of the tonsils in PFAPA is unknown, but has been highlighted by the often positive response to tonsillectomy. One can speculate that the tonsils are either the primary centres for immune dysregulation or that they harbour a trigger of the immune dysregulation that is a trigger in individuals with a predisposition for PFAPA. One important limitation in studying the role of tonsils in PFAPA is that studies are limited to analyses of tonsils in the afebrile phase. None of the available studies have been able to delineate a plausible mechanism or probable trigger (44–47). One interesting study showed that the microbiota of the tonsils differed in patients with PFAPA and postulated that the microbiota may have played a role in triggering the inflammatory processes (48).

### Biomarkers in PFAPA

Inflammatory variables are significantly increased during PFAPA episodes, including the acute phase proteins CRP and serum amyloid A (SAA). SAA is a useful inflammatory indicator in the management of children with autoinflammatory conditions for three reasons: firstly to measure inflammation during attacks and low-grade inflammation between attacks, secondly to monitor effectiveness of anti-inflammatory treatment and thirdly to estimate the risk of developing amyloidosis (49). In PFAPA, both CRP and SAA should normalise between episodes, while in FMF SAA often remains elevated between fever episodes (49).

Several small studies have suggested that procalcitonin, a marker associated with infection, is not markedly elevated during febrile episodes of PFAPA (40,50). These results parallel the findings in FMF, in which a slight but significant increase in procalcitonin levels was observed during inflammatory episodes (51). Hence, procalcitonin is of limited use when it comes to distinguishing PFAPA from FMF. There is an increase of S100A8/A9 and S100A12 in febrile PFAPA that seems to normalise in the afebrile phase (39,43). High levels of S100 proteins are characteristic of active systemic juvenile idiopathic arthritis and FMF (52).

There is no indication that the immunomodulator galectin-3 is increased during febrile attacks of PFAPA or during the afebrile phase (43). This is in contrast to the increased serum levels of galectin-3 during attack-free periods in FMF (53). Furthermore, a study of plasma galectin-3 showed increased concentrations in septicaemia but not in viral infections or in attacks of nondetermined autoinflammatory syndromes, as compared to healthy controls (54). The increase of galectin-3 in several other inflammatory

conditions has been reported, including *systemic lupus erythematosus* (SLE) (55), *Behçet's disease* (56) and *juvenile idiopathic arthritis* (57), as well as in *Crohn's disease* and *ulcerative colitis* (58). If the findings of increased plasma levels of galectin-3 in other inflammatory diseases and low levels in PFAPA are verified, galectin-3 might be used as tool to distinguish these conditions from PFAPA, particularly with regard to young children who originate in regions with a high prevalence of FMF.

### Management

Non-steroidal anti-inflammatory drugs (NSAIDs) are more efficient than paracetamol in reducing fever during PFAPA episodes (32). Corticosteroids abort a PFAPA flare with such extreme efficiency, usually resolving fever within hours, that clinicians can question the PFAPA diagnosis if the effect fails to materialise (25,27,30,32,59). For unknown reasons, a significant proportion of children with PFAPA experience shortening of the intervals after treatment with corticosteroids (23,25,30).

In western Sweden, steroid treatment is primarily used to postpone a febrile episode that occurs at an unsuitable time for the child or the family, whereas in some parts of the world the chosen approach is to treat each episode with corticosteroids (60). Tonsillectomy has turned out to be the most attractive treatment alternative, resolving 80–90% of episodes in cases in an initial case series (61). The effectiveness of tonsillectomy in PFAPA has been supported in two small randomised control trials (62) and in meta-analyses (63). Treatment by tonsillectomy is based on clinical experience, and so far, no pathophysiological ground has been found. That is why it is important to carefully evaluate, in discussion with the parents, the balance of risks and benefits for each child, bearing in mind the age of the child as well as the length, intensity and frequency of the episodes and the likely time to resolution without treatment (63).

Cimetidine, a histamine type 2 receptor antagonist, has previously been reported to induce remission of PFAPA (27), but a recent report found it to be ineffective in the majority of patients (60). Colchicine, which is the first choice of treatment for FMF, has been evaluated in a few patients with PFAPA, resulting in an increased interval between the episodes, but not in resolution of the disease. The role of colchicine needs to be further investigated (64). We tend to use colchicine in children with atypical PFAPA, namely children who have additional symptoms but are not suffering from a hereditary periodic fever syndrome, or in children who did not improve following tonsillectomy. Another role for colchicine might be treating children with a predominance of aphthous stomatitis, although this still has to be evaluated. A small case series indicated that PFAPA flares were responsive to an IL-1 blockade, as discussed above (38).

### Prognosis

Children with PFAPA are usually healthy between flares, and the symptoms disappear within three to five years after disease onset or in adolescence (6,27–29,32,59). It is

important to note that relapses are well described in PFAPA (30), and we have seen late relapses in our clinic that occurred after several years (Wekell P and Berg S, unpublished observation). Despite the good prognosis, our clinical experience and preliminary data from parental interviews indicate that the disease considerably influences the quality of life of the child and the family as a whole, as long as the episodes persist (Sparud Lundin C and Wekell P, manuscript in preparation).

## DISCUSSION

For a long time, innate immunity was just seen as a basic, noncomplex way for the body to defend itself against microbes, by eliciting an inflammatory reaction. The more complex immune mechanisms involved in long-term immunity, immune deficiency and autoimmunity were all attributed entirely to the adaptive immune system. Charles Janeway first foresaw the existence and function of innate immunity in a classic paper in 1989 called *Approaching the asymptote? Evolution and revolution in immunology* (65). In this study, he proposed the idea of pattern recognition, a general principle of innate immune recognition, and his work provided a conceptual framework for the integration of innate and acquired immunity (66).

The innate immune response is a first line of defence, which is rapid and short-lived and recognises exogenous and endogenous danger, by a limited number of germline-encoded evolutionarily conserved receptors. As for all biological systems, dysfunction or dysregulation may lead to disease. In innate immunity, the field of autoinflammatory diseases has been defined as conditions associated with increased inflammation due to a significant host predisposition.

Over the last 20 years, an increasing number of monogenic autoinflammatory conditions have been characterised: their genetic background has been defined in 36 clinical conditions to date and a large proportion of these are represented in Table 1 (4). Although there are still substantial clinical and mechanistic knowledge gaps, these conditions are more accurately diagnosed, treated and their disease mechanism is better understood today. Even though, there are some clues as to which genes and molecular mechanisms are involved in polygenic or multifactorial diseases, over time it has been shown that it is more difficult to delineate the mechanisms of innate dysregulation in polygenic or multifactorial diseases. This is exemplified by PFAPA, the most common autoinflammatory condition among children outside regions with very high prevalence of FMF.

During two decades of remarkable developments in the field, research on autoinflammatory diseases has not only led to an increased understanding of disease mechanisms *per se*, but it has also been indispensable for the understanding of innate immunity as a whole, as well as shedding light on the importance of these mechanisms in other disease conditions. Today, researchers at one end of the autoinflammatory disease spectrum discuss rare monogenic

conditions, while discussions at the other end of the spectrum concern the role of inflammatory pathways in common diseases such as mellitus type 2, Alzheimer's disease and atherosclerosis (3,4). This is a development that no one could have foreseen 17 years ago, when the concept of autoinflammation was coined.

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