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REVIEW ARTICLE

Auto-inflammatory syndromes and oral health

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Auto-inflammatory diseases (periodic syndromes) are rare childhood-onset disorders which are characterized by fluctuating or recurrent episodes of fever and inflammation affecting serosal surfaces, joints, eyes and/or skin without significant autoantibody production or an identifiable underlying infection. They are disorders of innate immunity and the underlying genetic defect has been identified in most of the syndromes. Diagnosis relies on clinical symptoms and evidence of an elevated acute phase response during attacks, supported by finding mutations in the relevant genes. Several syndromes can lead to systemic AA amyloidosis. Aphthous-like oral ulceration has been reported as one manifestation in several of the syndromes, including periodic fever, aphthous-stomatitis, pharyngitis, adenitis (PFAPA) familial Mediterranean fever (FMF), hyperimmunoglobulinaemia D and periodic fever syndrome, tumour necrosis factor receptor associated periodic syndrome and pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA). Chronic jaw recurrent osteomyelitis has been recorded in chronic recurrent multifocal osteomyelitis. Advances in the molecular pathogenesis of these syndromes and the regulation of innate immunity have enhanced diagnosis, and rationalized therapies. This article reviews the periodic fever syndromes relevant to oral health and the suggested association of FMF with Behçet's disease.

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Introduction

The inflammatory process once initiated and maintained, typically resolves subsequent to achieving its purpose. Failure to so resolve may lead to disease. Disorders of this innate immunity can result in auto-inflammatory diseases (periodic syndromes) – rare disorders which usually appear in childhood characterized by fluctuating or recurrent episodes of fever and inflammation affecting serosal surfaces, joints, eyes and/or skin without significant autoantibody production or an identifiable underlying infection. An underlying genetic defect has been identified in many of the syndromes. Aphthous-like oral ulceration has been reported as one manifestation in several of the syndromes and some of the syndromes can lead to systemic AA amyloidosis.

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Innate immunity and inflammation

Innate immunity includes the basic mechanisms that facilitate resistance to infection. These include the epithelial anatomical barriers of the skin and mucous membranes and, in the respiratory tract, cilia, secretions such as saliva and tears, and the inflammatory response characterized by increased localized blood flow and capillary permeability releasing soluble factors from the bloodstream and an influx of phagocytes such as neutrophils and macrophages.

The inflammatory process is initiated and maintained by a range of chemical mediators, especially cytokines such as tumour necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and IL-6. Phagocytes such as neutrophils and macrophages, which restrict the penetration and dissemination of micro-organisms, are also recruited. Cytokines are small proteins released by cells that have a specific effect on cell communication or behaviour. Cytokines including the ILs, lymphokines and cell signal molecules, such as TNF and the interferons, regulate the intensity or duration of the immune responses by stimulating or inhibiting proliferation of various cells, or by modulating their secretion of antibodies or other cytokines. A major cytokine involved in inflammation is TNF-α, which is produced by a range of cells, but predominantly monocytes and activated macrophages. TNF-α is a non-glycosylated polypeptide that exists largely as a soluble protein, which can bind to specific cell surface receptors such as TNF receptor (TNFR1), triggering

inflammation, the immune response and cell differentiation through the regulation of multiple target genes (Warren, 1990).

Soluble TNF-α can initiate and perpetuate the inflammatory response through up-regulation of adhesion molecules on microvascular endothelial cells and the enhanced expression of major histocompatibility complex class I and II antigens, but also of co-stimulatory molecules on dendritic cells and macrophages. TNF-induced production of matrix metalloproteinases by stromal cells may lead to tissue remodelling and the enhanced TNF-mediated secretion of keratinocyte growth factor.

Soluble TNF-α is also a member of the death domain (DD) superfamily. Its binding to TNFR1 results in receptor trimerization and clustering of intracellular DDs, allowing binding of an intracellular adapter molecule called TRADD (TNFR-associated DD). TRADD has the ability to recruit a number of different proteins to the activated TNF receptor: recruitment of TRAF2 (TNF-associated factor 2) can lead to activation of nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1) inducing the Jun-n-terminal kinase (JNK) pathway and a wide range of genes, leading to inflammation. TRADD can also associate with FADD, which leads recruitment and cleavage of pro-caspase 8 and the induction of apoptosis (Figure 1).

Tumour necrosis factor-α can also induce fever, either directly via stimulation of prostaglandin PGE2 synthesis by the vascular endothelium of the hypothalamus, or indirectly by inducing release of IL-1 and can stimulate the production of collagenase and PGE2. It also shares an important inflammatory property with IL-6 and IL-1, i.e. the induction of hepatic acute phase reactant protein production. Liver-derived acute phase proteins including C-reactive protein (CRP) and serum amyloid A protein (SAA) are released into the circulation. These two proteins are clearly critical in the innate immune response and they are highly conserved with no known protein polymorphisms but their exact functions remain obscure. CRP can bind to some bacteria and fungi, activating complement and inflammation, as can SAA, which can stimulate macrophages to phagocytose debris.

Tumour necrosis factor-α and IL-1 further exert secondary inflammatory effects by stimulating IL-6 synthesis in several cell types. IL-6 then mediates its own effects, perpetuating inflammatory responses via a cascade of cytokines (Beutler and Cerami, 1988; Warren, 1990; Vilcek and Lee, 1991; Aggarwal, 1992).

Auto-inflammatory syndromes

The auto-inflammatory (or periodic fever) syndromes are diseases caused by primary dysfunction of the innate immune system – they are essentially inborn errors of inflammation (Medzhitov and Janeway, 2000a,b), without evidence of dysregulation in adaptive immunity, and they are related to mutations in proteins involved in the modulation of inflammation and apoptosis (Galeazzi *et al*, 2006). Many of the conditions are hereditary, either autosomal dominant or recessive (McDermott *et al*, 1999; Galon *et al*, 2004).

Mutations responsible for auto-inflammatory syndromes are in proteins involved in the modulation of inflammation and apoptosis. The terminology involved is complex and is outlined in Table 1.

The auto-inflammatory diseases are rare; some have one or more acronym, and they are summarized in Table 2. The majority are hereditary and due to mutations in the DD superfamily of proteins. In patients with auto-inflammatory syndrome the mechanisms that perpetuate and amplify inflammatory processes seem to involve an ongoing imbalance between pro-and anti-inflammatory factors, central to which are cytokines.

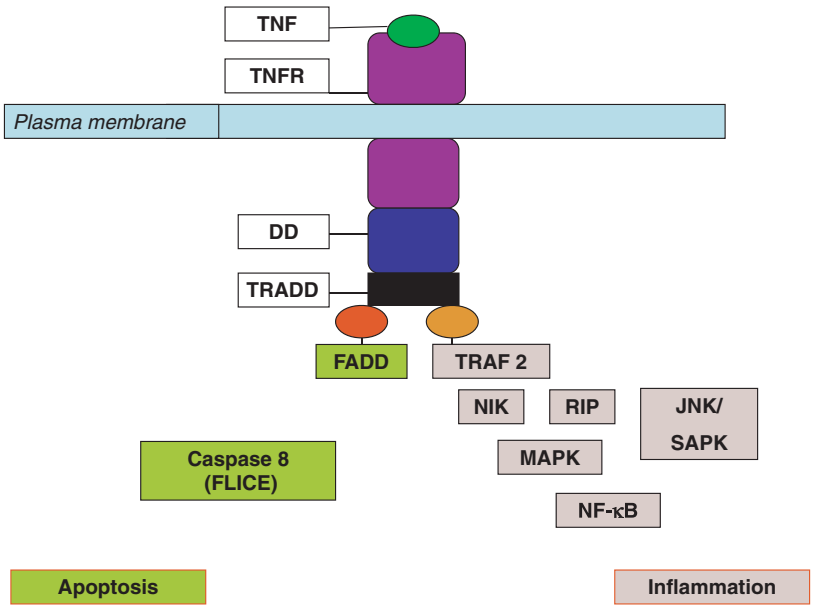

Figure 1 A simplified diagrammatic representation of the major factors involved in inflammation and apoptosis (acronyms explained in tables)

Table 1 Terms related to inflammation, and auto-inflammatory syndromes

Acronym	*Full meaning*
AP-1	Activator protein 1
AA	Arachidonic acid (or Amyloid A)
CAPS	Cyropyrin-associated auto-inflammatory diseases/periodic syndromes
CARD15	Caspase recruitment domain family, member 15 (also known as NOD2)
CD2BP1	CD2-binding protein 1
CINCA	Chronic infantile neurological cutaneous and articular syndrome
CRMO	Chronic recurrent multifocal osteomyelitis
CRP	C-reactive protein
DD	Death domain
DSOM	Diffuse sclerosing osteomyelitis of the mandible
ESR	Erythrocyte sedimentation rate
Fas	Fas antigen [also termed APO-1, APT1 and CD95, and now known as tumour necrosis factor receptor superfamily 6 (TNFRSF6)]
FADD	Fas-associated death domain
Fas L	Fas ligand
FCAS	Familial cold auto-inflammatory syndrome
FLICE	Caspase-8
FMF	Familial Mediterranean fever
FRA	Familial reactive arthritis
HIDS	Hyperimmunoglobulinaemia D and periodic fever syndrome
IFN	Interferon-γ
IL	Interleukin
JNK	Jun-n-terminal kinase
LPS	Lipopolysaccharide
MADD	MAP-kinase activating death domain
MAPK	Mitogen-activated protein kinase
MEFV	Familial Mediterranean fever gene encoding pyrin
MVK	Gene encoding mevalonate kinase
MWS	Muckle-Wells syndrome
NFκB	Nuclear factor-κB
NIK	Nuclear factor-κB inducing kinase
NOD2	Nucleotide-binding oligomerization domain containing 2 (also known as the caspase recruitment domain family, member 15; CARD15)
NOMID	Neonatal onset multisystem inflammatory disease
NSAID	Non-steroidal anti-inflammatory drugs
PAMP	Pathogen-associated molecular pattern
PAPA	Pyogenic sterile arthritis, pyoderma gangrenosum, acne
PFAPA	Periodic fever, aphthous-stomatitis, pharyngitis, adenitis
PG	Prostaglandin
PSTPIP1	Proline-serine-threonine phosphatase interacting protein
RIP	Myosin phosphatase-Rho interacting protein
PL-A2	Phospholipase-A2
PSTPIP1	Proline-serine-threonine phosphatase-interacting protein 1
SAPHO	Synovitis (inflammatory arthritis), acne (pustulosa), pustulosis (psoriasis, palmoplantar pustulosis), hyperostosis (acquired) and osteitis (osteomyelitis) syndrome
SAPK	Stress-activated protein kinase
TNF	Tumour necrosis factor-α
TNFR	TNF receptor
TNFRI	TNF receptor type I (also termed p55 or CD120a)
TNFRII	TNF receptor type II
TNFRSF	TNF receptor super families
TNFSF1A	The gene encoding TNF receptor type I
TRADD	TNF receptor type 1-associated DEATH domain protein
TRAF	TNF receptor-associated factor
TRAPS	TNF receptor-associated periodic syndrome

Innate immune response abnormalities seen in the auto-inflammatory syndromes include aberrant responses to pathogen-associated molecular patterns (PAMPs) including lipopolysaccharide (LPS) and peptidoglycan, neutrophilia, and dysregulation of the pro-inflammatory cytokines IL-1β, and/or TNF-α, or the receptors for these cytokines. For example, cyropyrin, the variant protein in cyropyrin-associated periodic syndrome (CAPS) is a component of the inflammasone, the activation platform for caspase 1 which processes pro IL-1 to mature IL-1α and Il-1β; and mutations in TNF1 Receptor protein are implicated in TNF receptor-associated periodic syndrome (TRAPS) (Table 2). The variant protein in familial Mediterranean fever (FMF), pyrin, is also a member of the DD superfamily, although its precise biological actions are not yet clearly understood.

DNA analysis has greatly enhanced the clinical characterization of these conditions, and elucidation of their molecular aetiopathogenesis has suggested that therapies may be aimed at specific targets within the immune cascade (Centola *et al*, 1998).

The auto-inflammatory syndromes include:

A. Periodic fever, aphthous-stomatitis, pharyngitis, adenitis (PFAPA) syndrome – not known to be inherited.
B. Hereditary conditions, which include:

1. Familial Mediterranean fever
2. Mevalonate kinase deficiencies [these include hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS) and mevalonate aciduria]
3. Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)
4. Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA)
5. Chronic recurrent multifocal osteomyelitis (CRMO)

Conditions 1–5 have been reported with oral manifestations. Then there are two other periodic syndromes:

6. Blau syndrome
7. Cyropyrin-associated periodic syndrome (CAPS) {this covers a spectrum of severity and was previously subdivided into: neonatal onset multisystem inflammatory disease [NOMID; which is also known as chronic inflammatory neurological cutaneous articular (CINCA) syndrome]; Muckle-Wells syndrome (MWS), and familial cold auto-inflammatory syndrome (FCAS)}

Genotyping analyses are registered at the Internet web site http://fmf.igh.cnrs.fr/infevers (Sarrauste de Menthiere *et al*, 2003) which contains nearly 300 sequence variants in the related genes (MEFV, TNFRSF1A, MVK, CARD15, PSTPIP1 and CIAS1) (McDermott, 1999, 2002, 2004; McDermott and Aksentijevich, 2002; Touitou *et al*, 2004).

Clinical features

The common features of the auto-inflammatory syndromes are recurrent spontaneously relapsing and

Table 2 The main auto-inflammatory syndromes

Disease	*Acronym*	*Main inheritance*	*Gene (and protein defect)*	*Main features apart from fever and rashes*	*Therapies available*
Oral features recorded					
Periodic fever, aphthous-stomatitis, pharyngitis, adenitis	PFAPA	Not known to be inherited	None known	Regularly occurring attacks of pharyngitis, adenitis, mouth ulcers	Corticosteroids Cimetidine Tonsillectomy
Familial Mediterranean fever	FMF (MIM249100)	Usually AR AD forms are recognized	MEFV (pyrin) located at chromosome 16p13	Short-lived (2–3 days) episodes of serositis, synovitis, amyloidosis	Colchicine
Hyperimmunoglobulinaemia D and periodic fever syndrome	HIDS (MIM260920)	AR	MVK (mevalonic kinase) located at chromosome 12q24	Attacks of abdominal pain, diarrhoea, arthralgia, mouth ulcers lasting up to a week. Precipitated by vaccinations	Simvastatin, Anakinra Etanercept
Mevalonate aciduria	(MIM260920)	AR		Psychomotor retardation, failure to thrive, progressive cerebellar ataxia, dysmorphic features, progressive visual impairment	
Tumour necrosis factor receptor-associated periodic syndrome	TRAPS (MIM142680)	AD	TNFRS1A (TNF-receptor 1) located at chromosome 12p13	Abdominal pain, migratory myalgia, rash, periorbital oedema, mouth ulcers, amyloidosis	Corticosteroids Etanercept
Pyogenic sterile arthritis, pyoderma gangrenosum, acne	PAPA (MIM604416)	AD	PSTPIP1/CD2BP1 (CD2-binding protein)1 located at chromosome 15q24	Arthritis, headache, abdominal pain, mouth ulcers	Anakinra Etanercept Infliximab
Chronic recurrent multifocal osteomyelitis	CRMO	AD	LPIN2 and Lipin2 at chromosome 18q21	Chronic recurrent multifocal osteomyelitis	Antimicrobials
Oral features not recorded					
Blau syndrome	(MIM186580)	AD	CARD15 or NOD2 (CARD15) at 16q12	Arthritis, uveitis	Corticosteriods Infliximab
Cyropyrin-associated periodic syndrome which has historically been subdivided into:	CAPS		CIAS1 (cyropyrin) located at 1q44		Anakinra
Neonatal onset multisystem inflammatory disease	NOMID (MIM607115)	Sporadic new mutations		Progressive chronic meningitis, learning disability, hearing and vision loss, severe skeletal abnormalities	
Muckle-Wells syndrome	MWS (MIM191900)	AD		Urticarial rash, Deafness, AA amyloidosis	
Familial cold auto-inflammatory syndrome	FCAS (MIM120100)	AD		Cold induced urticarial rash and conjunctivitis	

MIM, Mendelian Inheritance in Man classification; from OMIM [http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM; accessed 17 November 2007). AR, autosomal recessive; AD, autosomal dominant.

remitting inflammatory events which do not produce high-titre autoantibodies or antigen-specific T cells (Kastner, 2003; Galeazzi *et al*, 2006).

In general, patients with the auto-inflammatory syndromes are well between recurrent episodes of illness. The clinical syndromes are usually characterized by fluctuating or recurring episodes of fever and systemic inflammation, particularly affecting the serosal surfaces, joints, eyes and skin. Although many of the individual symptoms of these diseases overlap, there are distinctions in their inheritance, the pattern of clinical features and attack frequency. All these disorders are compatible with normal life expectancy, but a proportion of patients develop potentially fatal systemic AA amyloidosis. Ulcers have occasionally been reported to affect the mouth and/or other mucosae.

Oral health in auto-inflammatory syndromes

Oral ulceration which may clinically resemble recurrent aphthous stomatitis (aphthous-like ulcers), is the main oral sign seen in some of the periodic syndromes, particularly PFAPA – when it may be associated with pyrexia, pharyngitis and lymphadenopathy (Ataş *et al*, 2003; Saulsbury and Wispelwey, 2005; Pinto *et al*, 2006; Scully and Hodgson, 2008).

Diagnosis in auto-inflammatory syndromes

The diagnosis in these syndromes relies on a high index of clinical suspicion from clinical features, a positive family history particularly in the autosomal dominant forms, ethnic background, physical examination and exclusion of other more common diseases that may present with similar symptoms.

Most patients have unremarkable basic blood investigations when well but a raised white blood cell count, erythrocyte sedimentation rate (ESR) and CRP during attacks. A genetic test to look for the gene mutation should then be obtained. Genetic testing in these syndromes is usually very helpful but needs to be interpreted with caution. For example in FMF the gene carriage rate in some populations (particularly those arising in the Eastern Mediterranean) is high. Most heterozygotes are healthy carriers but up to 15% of patients with classical FMF have only one detectable mutation (Lachmann *et al*, 2006). Equally some homozygotes are entirely asymptomatic. In addition there are low penetrance mutations/polymorphisms in *MEFV*, *TNFRSF1A* and probably the other fever genes which can be disease-causing in some individuals or may be of no clinical significance. Furthermore, genetic sequencing often does not cover the whole gene and may miss unusual or novel mutations.

Management in auto-inflammatory syndromes

Many of the syndromes have a specific treatment, often based on understanding the problems caused by the genetic defect.

Auto-inflammatory syndromes in which oral lesions have been reported

Auto-inflammatory syndromes known to be relevant to oral health include PFAPA, FMF, HIDS, TRAPS, PAPA and CRMO, and there is a suggested association of FMF with Behçet's disease (BD).

Periodic fever, aphthous-stomatitis, pharyngitis, adenitis (PFAPA, Marshall's syndrome)

Periodic fever, aphthous-stomatitis, pharyngitis, adenitis is not a familial condition but has a number of characteristic features. Attacks usually appear before the age of 5 years as recurrent fever with aphthous-like stomatitis, pharyngitis and cervical lymphadenitis (Feder, 2000). It is slightly more common in boys. The aetiopathogenesis of PFAPA is unclear but the lack of second cases in siblings or other close contacts and lack of clustering in season or geographical areas suggest heredity and infection are unlikely (Long, 1999; Padeh *et al*, 1999; Thomas *et al*, 1999).

Aphthous-like ulcers affect 40–70% of patients, pharyngitis 72% of patients and cervical adenitis 88% of patients but the condition can readily be misdiagnosed as FMF (Ataş *et al*, 2003). The cardinal features of PFAPA that are both required and discriminatory are that the patient is well between episodes which have a strikingly regular periodicity (usually an interval of 4–6 weeks), there is an unheralded onset and there is a rapid rise to a high fever ($>39°C$) sustained over 3–6 days (Tasher *et al*, 2006).

Aphthous-like stomatitis reported with PFAPA has not been described as distinctively different from the common recurrent aphthous stomatitis (RAS) but we could identify neither reports nor clinical photographs of the ulcers in the dental literature (Pinto *et al*, 2006), which raises the possibility that perhaps this disease is underdiagnosed by dental clinicians or misdiagnosed by doctors. The associated pharyngitis and cervical adenitis are also vaguely described (Long, 1999, 2005). Long-term sequelae of PFAPA do not appear to have been reported; however, most children eventually grow out of it.

Diagnostically, mild leucocytosis and raised ESR, fibrinogen and serum immunoglobulin D (IgD) have been found, but there are no specific laboratory abnormalities defined (Padeh *et al*, 1999).

Periodic fever without other systemic manifestations or sites of disease has a short list of differential diagnoses. Recurrent fever can be associated with primary or acquired immunodeficiency disorders (especially cyclic neutropenia), Still's disease, Crohn's disease, the inherited periodic fever syndromes and BD should be excluded.

Patients with PFAPA often respond well to a single dose of corticosteroids at the start of the attack, whereas others have a remarkable response to tonsillectomy or cimetidine (Feder, 1992; Dahn *et al*, 2000), presumably via an effect on cellular immunity.

Familial Mediterranean fever

Familial Mediterranean fever is an autosomal recessive inflammatory disease, which occurs worldwide but predominantly affects populations arising from the Eastern Mediterranean basin particularly the non-Ashkenazi Jews, Armenians, Turks and Levantine Arabs. The prevalence of FMF has been estimated to be between 1/250 and 1/500 in non-Ashkenazi Jews and 1/1000 in the Turkish population. The gene frequency is as high as 1 in 5 among Turkish and North African Jewish populations and the vast majority of heterozygotes are asymptomatic (Livneh *et al*, 2001).

Clinical features of FMF include fever (100%), peritonitis (86%), pleuritis (56%), arthritis (34%) and myalgias (27%). There is also a high rate of cutaneous manifestations (47%) with the characteristic ankle rash of erysipelas-like erythema; oedema and recurrent mouth ulcers but no significant association between the ulcers and the genotype (Koné Paut *et al*, 2000).

The only effective treatment for FMF is colchicine, a serendipitous discovery made in 1972. Regular prophylactic treatment with colchicine at a dose of 1–2 mg daily prevents or substantially reduces the clinical manifestations of FMF in at least 95% of cases. Colchicine is thought to modulate neutrophil function by binding to tubulin-inhibiting motility and exocytosis of the intracellular granules and diminishing neutrophil chemotaxis *in vitro* and *in vivo*.

Behçet's disease has similar features and is a rare, chronic, multisystem inflammatory disorder common in the same Mediterranean populations as is FMF. The prevalence of BD is higher in the FMF patient population than in other populations known to be rich in BD. Both BD and FMF have some pathophysiological features in common and they appear to result from the inappropriate activation of neutrophils. Clinical manifestations of both diseases can mimic each other and the coexistence of both diseases in the same patient has been reported; nevertheless, FMF and BD do appear to be distinct entities (Ben-Chetrit *et al*, 2002). Neither FMF nor TRAPS is genetically associated with BD (Espinosa *et al*, 2005). The FMF gene MEFV appears to be a susceptibility and modifier gene in BD (Touitou *et al*, 2000; Atagunduz *et al*, 2003; Imirzalioglu *et al*, 2005; Rabinovich *et al*, 2007).

Hyperimmunoglobulinaemia D and periodic fever syndrome

Hyperimmunoglobulinaemia D and periodic fever syndrome is an autosomal recessive inherited auto-inflammatory syndrome caused by a deficiency of the enzyme mevalonate kinase (MVK) (Grose *et al*, 1996; Frenkel *et al*, 2000). Although the majority of cases reported have been from the Netherlands and France, cases have now been reported worldwide. Affected patients suffer fevers every few weeks from infancy, sometimes accompanied by malaise, headache, diarrhoea, abdominal pain, vomiting, rashes, arthralgia, arthritis, lymphadenopathy, hepatosplenomegaly, and oral and genital ulcers. Attacks are characteristically precipitated by routine vaccinations or minor infections and last 4–7 days. Granulocytosis, elevated acute phase reactants and raised serum IgD are common; cytokines appear responsible for a raised CRP and serum amyloid levels (Drenth *et al*, 1994, 1996). Meavalonate kinase (MK) is involved in cholesterol and isoprenoid synthetic pathways but how MK deficiency leads to fever and elevated serum IgD is not understood (Frenkel *et al*, 2000).

A severe phenotype, mevalonic aciduria in which there is no enzyme residual activity is characterized additionally by learning disability and dysmorphic features.

Tumour necrosis factor receptor-associated periodic syndrome

Tumour necrosis factor receptor-associated periodic syndrome is a rare autosomal dominant disease, initially called 'familial Hibernian fever' because the first recognized cases were from 'Hibernia' – the classic Latin name for Ireland – meaning 'wintry'. Most patients subsequently reported have also been of northern European descent but there have been ever increasing cases in various ethnic groups from Western Europe, and among Jews, Arabs and Japanese (McDermott, 1999; Hull *et al*, 2002).

The TNFR S1A gene encodes the receptor TNFR1. Mutations in the TNFRS1A gene were initially thought to typically disrupt the cysteine-rich extracellular portions of the receptor region but it is now clear they are much more varied. Novel mutations are still being reported and to date more than 35 true mutations have been described. There are also more than 10 polymorphisms. One of these R92Q is present in 1–2% of Caucasians but is also the single commonest disease causing mutation generally resulting in milder disease. Interestingly, TNFRS1A mutations are more common in the population than is the classic phenotype, suggesting that there are as yet unidentified modulating factors. There are also sporadic cases that present with a clinical history compatible with TRAPS, but in which no TNFRSF1A mutation has been defined, suggesting further genetic heterogeneity in the syndromes (Aksentijevich *et al*, 2001). Rare *de novo* mutations have also been reported (Aganna *et al*, 2002) as have complex cases with mutations of genes other than TNFRSF1A (Stojanov *et al*, 2004).

The auto-inflammatory phenotype of TRAPS may be due to impaired down-regulation of membrane TNFR1 and diminished shedding of potentially antagonistic soluble receptor in response to a given stimulus, and thus increased activity of TNF-α. However, defective shedding of TNFRSF1A can only partially explain the pathophysiological mechanism of TRAPS, as some mutations have normal shedding and other mechanisms including defective receptor trafficking, abnormalities of apoptosis and abnormal receptor trimerization have been postulated.

TRAPS affects males and females equally and the median age of onset is 3 years (range 2 weeks to 53 years). Classic TRAPS is characterized clinically by

recurrent fever, abdominal pain, migratory myalgia with an overlying tender erythematous plaque-like rash, and periorbital oedema or other ocular complaints (conjunctivitis, uveitis, iritis). The disease symptoms vary from person to person, as do the length of episodes and time between them. A less common feature is chest pain caused by pleurisy or pericarditis. AA amyloidosis, the main serious complication, affects around 20% of patients and is more common among patients with cysteine mutations and most commonly targets the kidneys and the liver (Aksentijevich *et al*, 2001). Aphthous-like mouth ulcers have been reported in two patients (Saulsbury and Wispelwey, 2005; Scully and Hodgson, 2008).

The diagnosis of TRAPS is based on the finding of a TNFSFR1A mutation in combination with a suggestive family history, clinical picture or physical examination and evidence from blood tests showing signs of inflammation during an episode (raised ESR, CRP, haptoglobin, fibrinogen or ferritin, and neutrophilia, thrombocytosis, low haemoglobin and polyclonal gammopathy). The presence of an acute-phase reaction seems to be a constant finding and thus measuring this during attacks could become a diagnostic step. The main differential diagnosis is FMF, and the diagnosis rests heavily on demonstration of a TNFR gene defect (Dodé *et al*, 2002). Nonspecific anti-inflammatory agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids in dosages greater than 20 mg day^{-1}, may help relieve symptoms. However, colchicine neither relieves nor prevents attacks (Masson *et al*, 2004).

There is no reliably effective definitive treatment for TRAPS but the pathogenic hypothesis involving defective TNFRSF1A shedding suggests that medications targeting TNF-α or IL-1β, or blocking the downstream signal transduction pathway, should been considered. Development is most advanced for the strategies that neutralize TNF-α on the cell surface or in the soluble phase which include:

Etanercept (Enbrel) – a recombinant protein composed of an immunoglobulin backbone and two soluble TNF-α receptors, given by subcutaneous injection twice-weekly. This is effective in many patients and tends to be given long term as intermittent use is likely to induce development of neutralizing antibodies (Nigrovic and Sundel, 2001; Drewe *et al*, 2003, 2004; Nowlan *et al*, 2006; Jacobelli *et al*, 2007).

Infliximab (Remicade) – a recombinant chimeric monoclonal antibody composed of a human antibody backbone with a mouse idiotype (the region that binds TNF-α), given by intravenous infusion is not used as there are anecdotal reports of infliximab exacerbating the condition (Church *et al*, 2006).

Adalimumab (Humira) – an anti-TNF-α monoclonal antibody given by subcutaneous injection every other week is a potential therapy but there are no reliable reports of its efficacy.

Anakinra (Kineret) – an IL-1 receptor antagonist is likely to be helpful, but has only been described in one brief report (Simon *et al*, 2004).

The possibility of serious adverse reactions to cytokine modulators, including neutropenia, infections, malignancies and others (Bandolier, 2006), means that treatment is most appropriately carried out in collaboration with a doctor with experience in the use of these medications.

Pyogenic, sterile arthritis, pyoderma gangrenosum, acne

Pyogenic, sterile arthritis, pyoderma gangrenosum, acne manifests as a pauciarticular, non-axial, destructive, corticosteroid-responsive arthritis from childhood; pyoderma gangrenosum, and severe cystic acne in and beyond adolescence. Other less commonly associated features included adult-onset insulin-dependent diabetes mellitus, proteinuria, abscess formation at the site of parenteral injections and cytopenias attributable to sulfonamides (Lindor *et al*, 1997).

The gene mutations in PAPA affect the CD2-binding protein 1 (CD2BP1), important in actin reorganization during cytoskeletal-mediated events. This gene and its murine orthologue, proline-serine-threonine phosphatase interacting protein (PSTPIP1), are adaptor proteins known to interact with PEST-type protein tyrosine phosphatases (PTP). The genes for PAPA syndrome and familial recurrent arthritis (FRA) are both found at chromosome 15q, suggesting that they are the same disorder (Wise *et al*, 2002). Differing degrees of joint destruction, and cervical ankylosis in people with the E250Q mutation demonstrate PAPA syndrome's variable expression, which includes micrognathia (Tallon and Corkill, 2006).

Reportedly effective treatments for PAPA have included etanercept and infliximab (Cortis *et al*, 2004; Stichweh *et al*, 2005).

Chronic recurrent multifocal osteomyelitis

Chronic recurrent multifocal osteomyelitis is a severe form of chronic sterile osteomyelitis in children and adolescents. Characterized by a prolonged, fluctuating course with recurrent episodes of pain over several years, CRMO is most often seen in tubular bones, predominantly the metaphyses of the long bones, the clavicle, and less frequently the spine and pelvic bones, and it may be multifocal (Jurik, 2004; Girschick *et al*, 2007).

Chronic recurrent multifocal osteomyelitis may rarely affect the skull (Wedman and van Weissenbruch, 2005) and jaws – usually the mandible (Weihe *et al*, 2000; Lavis *et al*, 2002; Schuknecht and Valavanis, 2003; Deutschmann *et al*, 2005; Compeyrot-Lacassagne *et al*, 2007). Diffuse sclerosing osteomyelitis of the mandible (DSOM) is considered a localized form of CRMO (Compeyrot-Lacassagne *et al*, 2007).

Chronic recurrent multifocal osteomyelitis appears associated with a gene on chromosome 18q [different from RANK, which is mutated in familial expansile osteolysis (FEO)] (Golla *et al*, 2002).

Chronic recurrent multifocal osteomyelitis must be differentiated from infective osteomyelitis and malignant neoplasms but bacterial culture is typically negative, and histopathological and laboratory findings are nonspecific. However, clinical findings and radiography,

if necessary supplemented by computerized tomography (CT) and/or magnetic resonance imaging (MRI) are usually helpful; the appearance suggests subacute or chronic osteomyelitis. Scintigraphy is also recommended in CRMO, and when multi-focal systemic disease is suspected, such as in SAPHO [synovitis (inflammatory arthritis), acne (pustulosa), pustulosis (psoriasis, palmoplantar pustulosis), hyperostosis (acquired) and osteitis (bland osteomyelitis) syndrome] (Schuknecht and Valavanis, 2003). The latter appears related to CRMO (Schilling and Kessler, 2000).

Chronic recurrent multifocal osteomyelitis may respond to NSAIDs (Weihe *et al*, 2000; Abril and Ramirez, 2007; Girschick *et al*, 2007), bisphosphonates (Compeyrot-Lacassagne *et al*, 2007) or infliximab (Deutschmann *et al*, 2005).

Conclusions

Aphthous-like ulceration has been reported as one manifestation in some of the auto-inflammatory syndromes, including PFAPA, FMF, HIDS, TRAPS and PAPA. Associations of other aphthous-like ulcers including BD, Reiter's syndrome, Crohn's disease, systemic lupus erythematosus, and cyclic neutropenia (Livneh *et al*, 1996) support an immunopathological aetiology.

Author contributions

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