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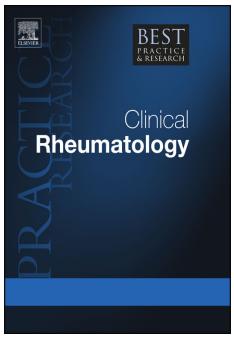

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Helen J. Lachmann, MA MB BChir MD FRCP FRCPath

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The Periodic Fever Syndromes

Helen J Lachmann MA MB BChir MD FRCP FRCPath

National Amyloidosis Centre and Centre for Acute Phase Proteins
Division of Medicine
University College London
Royal Free Campus
Rowland Hill Street
London NW3 2PF

h.lachmann@ucl.ac.uk

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ABSTRACT

The periodic fever syndromes are autoinflammatory diseases. The great majority present in infancy or childhood and are characterized by recurrent episodes of fever and systemic inflammation that occur in the absence of autoantibody production or identifiable infection. The best recognised disorders include CAPS, FMF, TRAPS, and MKD. Understanding of the molecular pathogenesis of these disorders provides unique insights into the regulation of innate immunity.

Diagnosis relies on clinical acumen, and is supported by genetic testing. With the exception of FMF, which is prevalent in populations originating from the Mediterranean, these syndromes are rare and easily overlooked in the investigation of recurrent fevers.

Disease severity varies from mild to life threatening and one of the most feared complication is AA amyloidosis. Effective therapies are available for many of the syndromes including colchicine, IL-1 blockade, anti TNF therapies and there is increasing interest in blocking interferon pathways.

KEY WORDS:

Periodic fever syndromes, autoinflammation, cryopyrin associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), NLCR4, tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS), Mevalonate kinase deficiency (MKD), Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), Majeed Syndrome, LPIN-2, Deficiency of IL-1 receptor antagonist (DIRA), Deficiency of IL-36 receptor antagonist (DITRA), Blau, Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE), STING-associated vasculopathy of infancy (SAVI), Aicardi-Goutieres Syndrome, Deficiency of adenosine deaminase 2 (DADA2), Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA),

A Introduction

The periodic fevers syndromes are a group of disorders of innate immunity that can cause multisystem inflammation presenting as unexplained fluctuating or recurrent episodes of fever usually accompanied by inflammation affecting the joints, eyes, skin or serosal surfaces. The term autoinflammatory was coined in 1999 as: “clinical disorders marked by abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition”(1).

Over the last 20 years at least 30 separate genes have been implicated in the hereditary diseases (infevers, http://fmf.igh.cnrs.fr/ISSAID/infevers) as well an increasing number of polygenic and/or acquired syndromes. It is now clear that autoinflammation can result from a variety of pathogenic mechanisms including: inflammasomopathies with dysregulated production of interleukin 1 as seen in Familial Mediterranean fever (FMF) and the cryopyrin associated periodic fever syndrome CAPS ; intracellular stress resulting in production of reactive oxygen species, aberrant autophagy and activation of kinases as seen in the TNF

associated periodic syndrome (TRAPS) and mevalonate kinase deficiency (MKD); defective regulatory mechanisms affecting cytokine signalling or loss of function of inhibitors as seen in deficiency of IL-1 receptor antagonist (DIRA) and deficiency of IL-36 Rn (DITRA); enhanced NF kappa B signalling as seen in Blau syndrome; increased interferon signalling in SAVI and CANDLE or deficiency of enzymes such as adenosine deaminase 2(2). In addition to inherited forms the most prevalent disease seen in paediatric practice is PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis).

A Recognising Autoinflammatory Diseases

As with all rare diseases diagnosis relies on a high index of suspicion. As a group, the systemic autoinflammatory diseases deserve considerable disease awareness as, almost uniquely they combine severe disease, often with early onset, and a risk of irreversible long term complications with, for the most often seen syndromes, excellent responses to highly specific and well tolerated, albeit often expensive, treatments. Unfortunately there are still considerable diagnostic delays and many patients will have seen five or more hospital specialities before a diagnosis is made(3).

Investigation of the patient with a suspected autoinflammatory disease is often challenging as the differential diagnosis is wide and somewhat age dependent(4). As in most areas of medicine, the mainstay is a good clinical case history and physical examination. Many conditions can mimic autoinflammatory diseases. Immunodeficiency including cyclic neutropenia, occult or recurrent infections are important differential diagnosis as well as malignancy and atypical connective tissue diseases. It is vital to ascertain that symptomatic attacks are accompanied by a marked inflammatory response, as this is a hallmark of systemic autoinflammatory disease. It is especially important to cover family history and

ethnicity in detail. A patient diary is often valuable in assessing the frequency and duration of attacks as well as symptoms and any evidence of precipitating factors.

The clinical picture will give a clue as to which hereditary periodic fever syndrome might cause the symptoms but in the clinical presentation of the different diseases can overlap considerably. Furthermore, at least 40% of patients with a probable autoinflammatory disease do not fit with any of the known diseases. The understanding of these "undifferentiated" disorders need to be improved. However, the increasing knowledge of the pathogenesis of autoinflammatory diseases in combination with the development of functional assays and the potential for therapeutic trials of cytokine inhibitors can permit better treatment.

A Inflammasonopathies

B Cryopyrin-associated periodic syndromes (CAPS)

C Pathogenesis

CAPS is due to gain of function mutations in NLRP3 a key component of the IL-1 inflammasome. Mutations result in constitutive over-activation of the inflammasome and thus caspase 1 mediated cleavage of pro IL-1 to active IL-1 β(5). Although IL-1 production is regulated at multiple levels from gene expression onwards, CAPS provides clear evidence both that cleavage by caspase 1 is the key step in production of IL-1 β and also that over production of IL-1 β itself drives increased gene expression of components of the entire IL-1 pathway thereby enhancing its own production(6). The NLRP3 inflammasome can be activated by a range of factors, including potassium efflux, mitochondrial reactive oxygen species, changes in extracellular calcium levels and lysosomal release of cathepsin B, and crystals such as uric acid thus implicating this pathway in a variety of acquired diseases such as gout, type 2 diabetes, atherosclerosis and fibrotic lung diseases.

Most of the disease causing mutations are found in NLRP3 exon 3 encoding the NACT domain but mutations are also recognised in other exons. In severe disease mutations are frequently private whereas in mild spectrum disease more than half of reported patients are heterozygous for one of three common mutations: R260W, T348M or A439V(7). Although CAPS is classically inherited in an autosomal dominant pattern, a substantial proportion of patients with clinical features of CAPS have somatic rather than germline mutations. Somatic mutation has been reported both in up to 50% of cases of severe disease and in 10% of much more typical mid-spectrum disease (Rowczenzio D *et al* Frontiers in Immunology 2015 in press).

C Clinical features

CAPS is a rare disease affecting one to three per million with no gender or ethnic predisposition. It was historically considered as three distinct clinical diseases: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological, cutaneous and articular syndrome (CINCA)/neonatal-onset multisystem inflammatory disorder (NOMID). These are now recognised as a severity spectrum rather than separate entities. Excess IL-1 production produces chronic inflammation which manifests from birth as fever, fatigue and characteristic urticarial rash and red eyes. Irreversible damage can include sensorineural hearing loss with childhood onset, vision loss due to inflammation affecting the eye at any level from the cornea to the optic nerve, skeletal deformities, cognitive disability and systemic AA amyloidosis(7). Acute symptoms can occur intermittently, often precipitated by cold or damp environments. Many patients will have daily symptoms with a typical diurnal pattern and worsening symptoms as the day progresses which has a major impact on quality of life (8).

The symptoms of CAPS are sufficiently characteristic that validated diagnostic criteria have been developed. Evidence of raised inflammatory markers (CRP/SAA) plus two or more of six CAPS-typical signs/symptoms: urticaria-like rash, cold-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms (arthralgia/arthritis/myalgia), chronic aseptic meningitis and skeletal abnormalities (epiphyseal overgrowth/frontal bossing) provides a specificity of 94% and a sensitivity of 81% in diagnosing CAPS and performs well for all CAPS subtypes(9).

C Treatment

Outcomes in CAPS were completely revolutionised by the recognition of the role of IL-1 blocking agents in the early 2000s (10). Three separate anti IL-1 agents are currently licenced for the treatment of CAPS: anakinra (recombinant IL-1 receptor antagonist) from aged eight months(11), rilonacept (anti IL-1 TRAP) from aged 2 years(12) and canakinumab (a fully human monoclonal antibody with high specificity for IL-1 β) from aged two years(13). All of these biologics are given by subcutaneous injection and all have shown remarkable efficacy in completely abolishing CAPS associated symptoms and signs with normalisation of the acute phase response and dramatic improvements in quality of life. There are a few case reports of reversal of deafness in children with treatment and it is hoped that prompt initiation of treatment in childhood may prevent disease associated damage in the first place. Long term treatment has been used for 15 years with excellent responses in terms of clinical disease and quality of life. Safety data to date has been encouraging although treatment is undoubtedly associated with an increase in infections and a small risk of modest neutropenia. Live vaccinations are contraindicated while on treatment although there is no concrete evidence of harm. Significant local reactions to pneumococcal vaccination has been reported

in canakinumab treated individuals(14). Data on pregnancies exposed to anakinra and canakinumab are just starting to emerge. There is most experience with anakinra although the number of cases remains very limited. There is some concern about the development of the renal tract as there have been two cases of renal agenesis in anakinra exposed pregnancies (neither mother had CAPS) but no other fetal anomalies have been reported(15).

B Familial Mediterranean Fever (FMF)

C Pathogenesis

Mutations in MEFV, a 10 exon gene located on chromosome 16 (16p13.3), were found to be associated with FMF in 1997(16, 17). The gene encodes a 781 amino acid protein, pyrin and more than 310 MEFV sequence variants have been reported (http://fmf.igh.cnrs.fr/infevers/), although by no means all variants are associated with a disease phenotype. The majority of patients have two mutations although up to 20% of patients are reported to be heterozygote. A few mutations are associated with genuinely dominant inheritance, particularly in atypical populations including the British(18). The most frequently seen pathogenic variants are all located in exon 10: M694V, M694I, M680I, V726A, R761H, A744S; and of these M694V is both the most common and associated with the most severe phenotype.

Evidence-based recommendations have been developed for the use of genetic testing in the diagnosis of FMF by the Single Hub and Access point for Pediatric Rheumatology in Europe (SHARE) initiative, highlighting that the diagnosis of FMF is clinical and that disease associated with homozygous M694V is often more severe(19).

Current evidence suggests that, unusually for a recessive disease, mutations are gain of function. Pyrin is activated when dephosphorylated at Ser208/Ser242 allowing interactions with microtubules which are critical for formation of the pyrin inflammasome and thus oligomerisation of procaspase 1 and release of Il-1 β. Mutations in exon 10 appear to result in

reduced binding of RhoA effector kinases and thus decreased phosphorylation of pyrin facilitating formation of the pyrin inflammasome(20).

The carrier frequency, of up to one in five in high risk populations, has long fuelled speculation that the FMF trait may have conferred a survival benefit. Work published in 2014 suggesting that pyrin is an indirect sensor of a wide variety of bacterial toxins, including diarrhoeal toxins, and potentially also Yersinia Pestis, that perturb actin polymerization dynamics by modifying Rho GTPases provides a potential mechanism by which activating mutations could augment the innate immune response(21).

C Clinical features

Familial Mediterranean fever (FMF) is by far the most common of inherited autoinflammatory diseases. It is recognised worldwide but is much more prevalent among populations originating from the Eastern Mediterranean.

The symptoms of FMF are recurring attacks of fever and serositis lasting 12 to 72 hours. Peritonitic abdominal pain occurs in 80% of attacks and can resemble appendicitis. Indeed 40% patients undergo laparoscopy before the diagnosis is made. Pleuritic chest pain is seen in 15-30% of the patients and is unilateral. Acute non-erosive arthritis, usually affecting one or two large joints of the lower limb or the sacroiliac joints is seen rarely. Pericarditis and testicular involvement are rare. An erysipelas-like erythema during attacks is seen in about 25% of pediatric patients. This is usually located between the knee and the dorsum of the foot and can be associated with arthritis. There is a brief but marked inflammatory response during an attack and subclinical inflammation is common between attacks(22). A variety of diagnostic criteria for adults and children have been published but few have been fully validated (23).

One of the most remarkable features of FMF is that a disease characterised by recurrent severe attacks of multisystem inflammation does not result in serious long term complications more often.

The recurrent inflammatory attacks in FMF cause intense acute symptoms and confer a markedly increased relative risk of developing AA amyloidosis and eventually end stage renal disease. Prior to the colchicine era this was a major cause of mortality particularly around the Mediterranean. Other potential complications of FMF include destructive arthritis, adhesions, subfertility and vasculitis. Fortunately these remain very rare and, with long term prophylactic treatment, recent studies suggest that both complications and mortality for FMF appear very close to age matched healthy controls(24).

C Treatment

Recent guidelines have been published on the management of FMF(25). The treatment of FMF is lifelong colchicine (26-28). It is important to explain that it is only effective as long-term prophylaxis and that colchicine provides no useful analgesia in acute attacks(29). On appropriate doses most patients will be symptom-free and the risk of amyloidosis almost completely disappears. Children usually need a higher dose per kilogram than adults (30). Colchicine can sometimes, especially in higher doses, give gastrointestinal side effects. A temporary reduction in the colchicine dose and a lactose free diet can relieve the gastrointestinal symptoms. Cohort studies suggest that colchicine in pregnancy is safe and should not be discontinued. Failure to respond to colchicine should prompt a careful review of compliance but IL-1 inhibitors have been demonstrated in trials to be effective therapy in resistant cases (31-33) and canakinumab was licenced for this indication in 2017 as a result of the CLUSTER study (manuscript in preparation). Acute FMF attacks can be treated with non-steroid anti-inflammatory drugs (NSAID). Corticosteroids do not have an effect on the

classical manifestations but are effective in protracted myalgia, a rare vasculitic complication of FMF(34).

B Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA)

Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) is an autosomal dominant disease with variable penetrance which has only been reported in a small number of kindreds. It is caused by mutations in the PSTPIP1 (proline serine threonine phosphatase interacting protein 1) gene on chromosome 15 and 25 diseases associated mutations have been described to date. The mechanisms by which these cause inflammation are not clear. However, PSTPIP1 directly interacts with pyrin, the mutated protein in FMF. Some PAPA-associated mutations have been shown to significantly increase binding of PSTPIP1 to pyrin and may activate the pyrin inflammasome via p38 mitogen-activated protein kinases signalling. PSTPIP1 appears to play a role in the organization of cytoskeletal structures in white cells and thus in cell migration, with pyrin modulating the dynamics of these interactions(35).

PAPA tends to present between 1 and 16 years of age with an oligoarticular pyogenic arthritis, sometimes after a mild trauma. Severe cystic acne often develops at puberty. Pyoderma gangranosum-like ulcerative lesions occur in some patients as does suppurativa hidradenitis (sometimes described as a separate clinical entity Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH))(36). There is no established treatment for this rare disorder. PAPA is only partly responsive to treatment with oral and intraarticular steroids. Case series have shown variable results on anti-TNF treatment as perhaps more effectively with anti-IL-1 treatment(37). The treatment is usually better against the arthritis than the skin manifestations.

B NLCR4 related disease

De novo gain-of-function mutations of NLRC4, causing a potential lethal autoinflammatory syndrome with a diverse phenotype including fever, severe enterocolitis, urticarial type rash and macrophage activation syndrome were first reported in two separate publications in 2014(38, 39). NLRC4 is an inflammasome component which acts as an intracellular sensor of pathogen associated molecular patterns. It is activated by NAIP-mediated recognition of a variety of bacterial constituents including flagellin or components of bacterial type 3 secretion systems. How these dominant mutations result in over activation of the inflammasome is not yet entirely clear but the report of a clinical response to anti IL-1 treatments supports this as the disease mechanism.

A Disorders resulting in intracellular stress responses

B TNF receptor associated periodic syndrome (TRAPS)

C Pathogenesis

The TNF-receptor associated periodic fever syndrome (TRAPS) is an autosomal dominant disease. It was initially called familial Hibernian fever and renamed in 1999 after the discovery of causative mutations in the gene for the tumor necrosis factor receptor superfamily member 1A, TNFRSF1A, on chromosome 12(1). The majority of sequence variants underlying TRAPS lie within exons 2 to 4, and there appears to be over representation of missense substitutions which disrupt structurally important cysteine-cysteine disulphide bonds in the extracellular domain (Infevers database: http://fmf.igh.cnrs.fr/ISSAID/infevers/). The mechanism(s) by which heterozygous TNFRSF1A mutations cause TRAPS remain unclear and probably differ between variants(40). The first case of somatic mosaicism causing TRAPS has recently been described(41).

The two commonest TNFRSF1A variants, P46L and R92Q are present in approximately 10% of West Africans and 2% of Caucasians respectively. The vast majority of carriers of these two variants are entirely well, and how they cause inflammatory disease in a minority remains obscure(42).

C Clinical features

TRAPS has an estimated prevalence of approximately one to two per million. It has been more frequently reported in Caucasians but this almost certainly reflects ascertainment bias. TRAPS is a far less distinct disease entity than familial Mediterranean fever; attacks can be discrete or near continuous and are often prolonged, lasting several weeks and accompanied by a variety of features including: fever (88%), non peritonitic abdominal pain (74%), rash (63%), eye manifestations (43%), pleuritic pain (32%), headache (28%) and lymphadenopathy (14%) (43). Symptoms are almost universally accompanied by a marked acute phase response and leucocytosis. The median age at presentation is 7 years and attacks characteristically are more discrete in children. Most attacks last from less than a week to 3 weeks but a minority of patients have continuous diseases with exacerbations. Slightly over a quarter of patients are aware that attacks can be precipitated and the best recognised precipitants are emotional stress; menstrual cycle; fatigue; infections; exercise and vaccinations. Untreated TRAPS carries a risk of AA amyloidosis which in a recent series was 18% of adult patients(44).

C Treatment

Descriptions of the treatment of TRAPS are largely based on retrospective cohorts but there have been a few placebo controlled studies(45). SHARE has produced recommendations for management in 2015(46).

Not all attacks need disease modifying treatments and NSAIDs provided some degree of symptom relief in approximately 75% of patients but are rarely effective in terminating inflammatory episodes. Corticosteroids are useful in terminating attacks but the effect tends to wane over time. Most patients require doses in the order of 0.5 to 1 mg/kg and long term use carries a high risk of corticosteroid side effects.

Etanercept has been used in a prospective study which demonstrated significant improvement in symptoms and inflammatory parameters but most patients eventually discontinue the drug due to declining effect(47). IL-1 blockade with Anakinra is highly effective (48) and the remarkable response of TRAPS to IL-1 therapies has been confirmed by an open labelled study with canakinumab(49) and in the placebo controlled CLUSTER study which used canakinumab in TRAPS, MKD and colchicine resistant FMF (manuscript in submission). This latter study has resulted in the licencing of canakinumab to treat all three by both the U.S. Food and Drug Administration and the Europeans Medicine Agency in 2017.

B Mevalonate Kinase Deficiency (MKD)

C Pathogenesis

Mevalonate Kinase Deficiency (MKD) is a very rare autosomal recessive disease caused by hypomorphic mutations in *MKD*, the gene for mevalonate kinase. Two clinical phenotypes are recognized with severity determined by the activity of their leukocyte intracellular enzyme. In the autoinflammatory disease residual enzyme activity is at about 10% whereas in the inherited disorder of metabolism, mevalonic aciduria, there is almost no detectable enzyme activity. Diagnosis relies on supportive test results: either two MVK mutations or one mutation in combination with an abnormal metabolic studies, either increased urinary mevalonic acid with attacks or reduced mevalonate kinase enzyme activity in leukocytes or fibroblasts. Measurement of serum IgD is neither particularly sensitive nor specific and is no

longer regarded as a useful diagnostic test(50). More than 170 mutations have been reported in association with disease of which two are much the commonest. In the largest series to date V377I was reported in 84% of patients and 12% of patients were homozygotes. The second most frequent mutation was I268T, occurring in 25% of the patients although none were homozygotes(51).

Mevalonate kinase is involved in the sterol and isoprenoid biosynthetic pathway converting mevalonate acid to mevalonate-5-phosphate. The pathologic mechanisms of autoinflammation in MKD is poorly understood but reduced synthesis of isoprenoid lipids downstream of MVK, in particular geranylgeranyldiphosphate are thought to play a central role(52). These are necessary for prenylation (the addition of a hydrophobic compound) of small GTPases including RhoA and Rac1. These small GTPases are involved regulation of the cytoskeleton and trafficking of vesicles, and the prenylation moiety is involved in their localization to membrane. Reduced prenylation of GTPases appear to result in altered autophagy, mitochondrial potential, and redox balance with over activation of the pyrin inflammasome and consequently dysregulated production of IL-1β(53).

C Clinical features

The most common phenotype is a periodic fever syndrome, initially called hyperimmunoglobulin D and periodic fever syndrome (HIDS) and now generally referred to as MKD, which is characterized by an onset in the first six months of life of recurrent three to seven day episodes of fever(51). Fever episodes are provoked by specific triggers in almost 50% of cases, mostly by vaccination, stress, or infection. Typical attacks feature GI upset in 98% (abdominal pain (88%), diarrhoea (84)%, vomiting (69)%), lymphadenopathy (90%), arthralgia (71%), oral aphthae (60%), maculopapular rashes (39%), headache 938%) and eye inflammation (15%). Rarer features include macrophage activation syndrome, retinitis pigmentosa and in 4% of cases AA amyloidosis. The more severe phenotype is mevalonic

aciduria (MA), usually associated with MVK enzyme activity of less than 0.5%. MA is associated with a high rate of stillbirth; survivors present neonatally with severe systemic inflammation, dysmorphic facies, severe failure to thrive, developmental delay, seizures, and hepatic involvement. Without bone marrow transplantation most affected children do not survive.

C Treatment

MKD has proved difficult to treat. Corticosteroids and colchicine are generally disappointing although a few patients with mild disease find long-term colchicine helpful. HMGCoA reductase inhibitors have been tried(54). A formal trial showed no benefit and current understanding of the molecular pathogenies of MKD would suggest that statins should be of no benefit or positively unhelpful but a small number of patients report benefit(51).

In severe disease IL-1 blockade appears most promising and is recommended in recent international expert consensus guidance(45, 51). Unfortunately, therapeutic success is often modest with only 30% complete remission, and 70% partial remission in patients treated with daily anakinra. Canakinumab, a monoclonal antibody against IL-1β, appears to have superior efficacy to anakinra with over half of patients achieving complete response (55) and canakinumab is now licenced for the treatment of MKD. Blockade of IL-6 receptor with tocilizumab has been reported to be highly effective in a very small number of patients who have proved refractory to other treatments(56).

A Defective regulatory mechanisms

B Deficiency of the interleukin-1 receptor antagonist (DIRA)

DIRA is an autosomal recessive disease first reported in 2009 caused by mis-sense and non-sense mutations in IL1RN, the gene encoding the IL-1-receptor antagonist (IL-1Ra) protein(57). Founder mutations have been described in Puerto Rico, the Netherlands, Newfoundland, Palestine/Lebanon and Brazil. The absence of functional protein leads to

unopposed IL-1 receptor activation and thus increased responses to IL-1α and IL-1β. Patients present neonatally with skin pustulosis, joint swelling, painful osteolytic lesions, periosteitis particularly affecting the distal ribs and the long bones and heterotopic bone formation. Patients can develop fevers, often low grade with elevation of acute-phase reactants. Pathergy characteristically develops after mechanical skin trauma. Patients with DIRA respond dramatically treatment with anakinra.

B Deficiency of interleukin thirty-six–receptor antagonist (DITRA)

This extremely rare disease is caused by recessively inherited mutations in IL36RN on chromosome 2 and was first described in a large kindred from North Africa and unrelated European families(58). It is characterized by recurrent episodes of a generalised sterile pustular rash accompanied neutophilia, a marked acute phase response and fever. A few patients have reported nail dystrophies, glossitis and oligoarthritis Age at onset varies from the neonatal period to the sixth decade. Episodes may be precipitated by stress, pregnancy or drugs and can be life threatening**.** Optimal treatment is not yet entirely clear; there are case reports of response to IL-1 blockade(59), anti TNF agents(60), secukinumab(61) and ustikinumab(62).

B Majeed

This autosomal recessive syndrome characterized by chronic recurrent multifocal osteomyelitis (CRMO), congenital dyserythropoietic anemia, and inflammatory dermatosis was first described in 1989(63). The disease was found to be due to mutations in LPIN-2 on chromosome 18 in 2005(64). Lipin-2 has recently been found to play a role in regulation of the IL-1 inflammasone by inhibiting the activation and sensitization of the P2X7 receptor thereby reducing the potassium efflux that is required for inflammasome formation. There is also evidence Lipin-2 regulates synthesis of pro–IL-1β via effects on pMAPK(65). Disease onset is usually in the neonatal period and attacks consist of several days of fever, severe

pain, and the appearance of periarticular soft tissue swelling. Long term complications of growth retardation and flexion contractures are well recognised. Consistent with current understanding of the pathogenesis, good responses to IL-1 blockade have been reported(66).

A Enhanced NF-kappa B signalling

B Blau

Blau syndrome was first described in 1985 as an autosomal dominant syndrome of sarcoid-like granulomatous infiltration of the joints (causing camptodactyly), eyes (causing sight threatening uveitis), skin and sometimes viscera which typically onsets in the two years of life. It is caused by missense mutations in in or near the nucleotide oligomerization domain of NOD2/CARD15, a member of the death-domain superfamily. NOD2 mutations have also been implicated in familial Crohn's disease. In Blau syndrome these gain of function mutations result in increased NF-κβ activation and a pro-inflammatory state. In common with the other dominantly inherited autoinflammatory syndromes of CAPS and TRAPS somatic mosaicism has been reported(67). Treatment is frequently disappointing and there is little consensus on the best choice of agent. The largest case series of Blau associated uveitis to date reports that 68% of patients are treated with a combination of systemic corticosteroids and immunosuppressive drugs and/or biologicals. The most commonly used agents were: systemic corticosteroids, methotrexate, adalimumab, infliximab, mycophenolate mofetil, and in two cases thalidomide and one in canakinumab(68). Anti TNF agents may be the most promising current therapeutic option, with some reports of complete remission(69).

A Interferonopathies

B Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE)

The acronym CANDLE, Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature was proposed in 2010 for an autosomal recessive disease caused by mutations in PSMB8(70, 71). The syndrome was described in 1939 as Nakajo-Nishimura syndrome, with secondary hypertrophic osteoperiostosis, partial lipomuscular atrophy, clubbing, a pernio-like, heliotrope-like or nodular erythema-like rash, periodic fever and joint contractures.

PSMB8 encodes the inducible B5 subunit of the immune proteasome. Proteasomes are involved in proteolysis, generating antigenic peptides for class I MHC presentation and maintenance of cell homeostasis. Failure of proteolysis leads to increased cellular stress. Cytokine profiling and transcriptome analysis are consistent with dysregulation of the IFN pathway. Skin biopsies demonstrate a characteristic extensive dermal and subcutaneous inflammatory infiltrate of mononuclear cells, atypical myeloid cells, neutrophils, eosinophils, and some mature lymphocytes(72). Treatment attempts, including anti TNF agents and the interleukin-6 (IL-6) receptor blocker tocilizumab, have proved only partially effective. A more rational approach is to use Janus Kinase (JAK) inhibitors to reduce IFN gamma-inducible protein 10 production and there is an ongoing trial in CANDLE (ClinicalTrials.gov Identifier: NCT01724580).

B STING-associated vasculopathy of infancy (SAVI)

In 2014 there was a report of a novel inherited autoinflammatory syndrome due to de novo mutations in TMEM173 gene which encodes the stimulator of interferon genes (STING), an endogenous regulator of type I interferon (IFN) signalling. The affected children present in early infancy with systemic inflammation and vasculitic lesions on the skin of the fingers, toes, nose, cheeks, and ears, interstitial lung disease, and peripheral gangrene,(73). Mutations result in a constitutively active STING protein, with uncontrolled secretion and activation of

type I IFN. No therapy has yet been shown to be beneficial but as with CANDLE a trial of JAK inhibitors seems the most rational approach.

B Aicardi-Goutieres Syndrome

The Aicardi–Goutières syndrome was first described in 1984 as an early onset familial encephalopathy(74). Diagnosis is based on: early-onset encephalopathy with extrapyramidal signs and acquired microcephaly; cerebral calcification, particularly in the basal ganglia; cerebral white matter abnormalities; cerebral atrophy; cerebrospinal fluid findings of chronic lymphocytosis and elevated IFN alpha; recurrent fevers; chilblain lesions on the fingers, toes and ears; exclusion of pre-/perinatal infections, in particular the TORCH complex (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus). Some patients display symptoms overlapping with systemic lupus erythematosus and there is also evidence of genetic concordance. A genetic cause is found in more than 90% of patients usually with an autosomal recessive pattern but Aicardi-Goutieres is genetically heterogenous with seven genes identified to date. These included the genes encoding the 3-prime to 5-prime exonuclease TREX1 (AGS1), three non-allelic components of the RNASEH2 endonuclease complex (AGS2, 3 and 4) and the SAMHD1 protein (AGS5)(75). It is postulated that the mutations result in inadequate processing nucleic acid debris, with consequent chronic stimulation of innate and acquired immunity. Treatment is symptomatic.

A Deficiency of adenosine deaminase 2 (DADA2)

This autoinflammatory syndrome resembles polyarteritis nodosa and was first reported in 2014(76). Features included episodes of fever, rashes (including the characteristic livedo racemosa), cutaneous ulcers, hypertension, peripheral neuropathy, and recurrent ischemic lacunar strokes, or, less often, intracranial bleeds. The phenotype can also include cytopenia, hypoglobulinaemia and infections. DADA2 is caused by recessively inherited mutations in the ADA2 gene resulting in low levels of circulating enzyme. ADA2 is an important

regulator of immune development; deficiency is associated with skewed macrophage development towards the M1 pro-inflammatory phenotype. M1 macrophages are known to produce TNF-α, which may explain the effectiveness of anti TNF agents in DADA2(77). Successful allogeneic haematopoietic stem cell transplantation has been reported in a recent cohort of 14 cases(78).

A Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA)

C Pathogenesis

The mechanisms underlying PFAPA are not understood and are assumed to combine polygenic and multifactorial acquired factors. There has been interest in the role that the tonsils play given the responses to tonsillectomy. Published studies looking at tonsillectomy specimens have failed to identify plausible mechanism although one suggested there might be a role for their microbiota which differs from that of healthy controls(79).

C Clinical features

Worldwide this is the commonest autoinflammatory disease of childhood. It classically presents before the age of 5 years and may preferentially affect boys. Diagnostic criteria were defined in 1999: regularly recurring fevers with an early age of onset (<5 years of age), and symptoms in the absence of upper respiratory tract infection with at least one of the following: aphthous stomatitis; cervical lymphadenitis; pharyngitis; exclusion of cyclic neutropenia; completely asymptomatic interval between episodes with normal growth and development(80). Attacks usually last three to seven days, and recur at intervals of two to eight weeks. Characteristically the attacks are so regular as to be predictable ‘sometimes to a point that the parents can predict the time’(81). In most children the disease will remit within a few years or by adolescence but attacks have a serious impact on the quality of life of the child and their family(82).

C Treatment

Corticosteroids reliably abort a flare to the point that a failure to respond within hours should bring the diagnosis into doubt(81). A number of centres use prophylactic colchicine with good effect although rarely complete responses(45). Tonsillectomy resulted in disease resolution in 80–90% of episodes in a case series(83). The effectiveness of tonsillectomy in PFAPA has been examined in a systematic review which concluded that 'the evidence (supporting tonsillectomy) is of moderate quality … due to the relatively small sample sizes of the studies and some concerns about the applicability of the results. Therefore, the parents and carers of children with PFAPA syndrome must weigh the risks and consequences of surgery against the alternative of using medications. It is well established that children with PFAPA syndrome recover spontaneously and medication can be administered to try and reduce the severity of individual episodes'(84).

A Summary

The autoinflammatory diseases are a growing group of diseases characterised by recurrent or continuous inflammation. Although they are rare they have proved remarkable exemplars of both translational and reverse translational medicine. The best recognised syndromes of FMF, CAPS, TRAPS and MKD have seen outcomes transformed by the availability of effective treatments. The finding that all four diseases respond so well to IL-1 inhibition has gone hand in hand with elucidation of previously unsuspected molecular mechanisms regulating cytokine production and activation. With the discovery of more recent extremely rare syndromes it is becoming clear that autoinflammatory phenotypes can be accompanied by both immunodeficiency and autoimmunity demonstrating that the innate immune system does not function independently and that cross talk between the acquired and innate immune systems is significant. There is increasing hope that the remarkable advances in this field in the last 20 years may produce benefits in such common acquired diseases as diabetes, cancer

and, most topically, atherosclerosis as demonstrated in the publication of the CANTOS trial which showed that IL-1 inhibition reduced recurrent cardiovascular events post myocardial infarction, independent of lipid-level lowering(85).

PRACTICE POINTS -
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- *Recognition of the autoinflammatory disorders relies on clinical acumen backed up by genetic testing. In an attempt to improve this there are a number of current initiatives on defining classification criteria for the commoner syndromes*
- *Recent consensus criteria have been published for the management of autoinflammatory diseases in general(46) and FMF in particular(25)*
- *Not all patients with autoinflammatory disease require long-term treatment. In those that do colchicine is the treatment of choice for FMF. Anti IL-1 treatments are almost completely effective in TRAPS, CAPS and DRA and have been used with good responses in colchicine resistant FMF, MKD and Blau.*
- *Stem cell transplantation may be curative in some diseases and should be considered in severe early onset MKD and DAD2*

RESEARCH AGENDA

- Late diagnosis is a major issue and development of algorithms to facilitate disease recognition would be helpful
- Approximately 40% of patients with presumed autoinflammatory disease do not fit into any of the currently known syndromes and his group requires further study.
- Expansion of next generation genetic testing has demonstrated that many uncharacterised patients have sequence variants of unknown or intermediate significance in one or more of the genes known to be associated with autoinflammatory disorders. Genetic advances need to be combined with functional work to explore the significance of novel variants and common sequence variants of unknown significance
- There has been little work yet exploring the role of the microbiome in altering disease presentation and complications.
- In these rare diseases there is a paucity of well controlled trials and this is particularly striking in the interferonopathies
- There is potential for development of small molecule pharmaceuticals which modify pathogenic process above the level of cytokine processing or receptor binding
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