

AUTO-INFLAMMATION AS A CAUSE OF URTICARIA

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INTRODUCTION

Our understanding of auto-inflammation and the associated clinical syndromes is expanding rapidly – advances in genetic testing have revealed many monogenic auto-inflammatory diseases. While classic auto-inflammatory conditions such as Familial Mediterranean Fever have been recognised as distinct diseases for centuries, the relatively recent concept of auto-inflammation has led to better insight being gained into many distinct immune disorders and their classification. Auto-inflammatory conditions can present with a wide range of symptoms, which overlap with the presentation of allergic disease, and multiple organ systems can be involved. A basic understanding of auto-inflammation is therefore required if generalists, particularly allergologists, are to be prompted to a correct diagnosis, and triage to optimal treatment for these potentially devastating conditions.

INDEX CASE

A five-year-old Caucasian girl has presented to a multidisciplinary team of paediatric allergologists, immunologists and a paediatric rheumatologist with recurrent urticarial rashes since early infancy (see Figure 1). Her younger sister experienced similar, but less severe, symptoms. Her family had consulted numerous specialists over the preceding years, but extensive allergy testing and symptomatic treatment provided neither a clear diagnosis nor a sustained improvement. Her rashes appeared to be exacerbated by cold or pressure and appeared to worsen during times of infection. A delay in her speech development

prompted a hearing test that demonstrated mild to moderate sensorineural deafness. She suffered recurrent upper respiratory tract infections and otitis media, necessitating myringotomies. On occasion, she had experienced difficulty walking, especially going down stairs in the morning. At age four, after complaining of eye pain, she was diagnosed with and treated for blepharitis by an ophthalmologist; however, resolution was slow, and the eye pain recurred intermittently. Her parents noted a deterioration in her mood and general condition, with urticaria, describing her as grumpy and lethargic, and with diffuse body pain. Additional clinical features were: allergic rhinitis (AR); chronic recurrent intermittent abdominal pain and diarrhoea. There was a strong family history of deafness and urticaria.

She was asymptomatic at the time of the visit, and her clinical examination was completely normal, apart from mild speech difficulties. However, the history and previous clinical findings indicated the likely diagnosis was an auto-inflammatory condition in the spectrum of Familial Cold Auto-inflammatory or Muckle Wells syndrome – one of the Cryopyrin Associated Periodic Syndromes (CAPS), where the pathology is driven by an overproduction of active IL-1 β . The patient was referred for genetic testing because about 60 per cent of patients with CAPS have a specific mutation in the NLRP3 gene that codes for a protein in the inflammasome.¹ The results in her case were negative, but in view of her strong clinical picture, the team opted for a trial of therapy with Kineret (Anakinra) – a specific IL-1 inhibitor given subcutaneously once a day. It is dramatically



Figure 1: Diffuse urticarial rashes and dermatographism in the index case during an acute flare. (Pictures published with consent)

effective in CAPS and a response would support a diagnosis of IL-1 β -mediated auto-inflammation. A dramatic improvement in her condition was noted with Anakinra, with no urticaria, and there was a sustained improvement in her wellbeing and systemic symptoms, including increased energy, appetite and mood. Her parents were ecstatic at the response, describing it as 'life changing'.

WHAT IS AUTO-INFLAMMATION?

The concept 'auto-inflammation' was first discussed in 1999, in the context of Familial Mediterranean Fever (FMF) and Tumour Necrosis Factor Receptor Associated Period Fever syndrome (TRAPS), after the discovery of the pathogenic mutations responsible for these inherited conditions.^{2,3} Auto-inflammation describes dysregulation of the innate immune system and it is characterised by spontaneous episodes of systemic or localised inflammation caused by cells of the myeloid lineage (e.g. macrophages and neutrophils) and without identifiable auto-antibodies or antigen-specific T-lymphocytes.⁴ In this sense, pure monogenic auto-inflammatory disease represents the opposite scale of the immune dysregulation spectrum to monogenic autoimmune diseases such as the Immunodysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome, where the gene defect involves failure of antigen-specific immune tolerance generated by regulatory T-cells (see Figure 2).⁵ Nearly 20 years later, more than 20 monogenic auto-inflammatory conditions are described, and a larger number of polygenic auto-inflammatory conditions have been identified.⁴ In fact, many conditions previously identified

as autoimmune – such as systemic Juvenile Idiopathic Arthritis (sJIA) and Crohn's disease – are being conceptualised with an important auto-inflammatory component.⁶

THE INFLAMMASOMES

The inflammasomes (see Figure 3) are intra-cellular protein complexes that are formed in response to microbial and danger signals and mediate the release of the pro-inflammatory cytokine Interleukin 1 β .⁷ In the classic inflammasome-related conditions, known as the CAPS, for instance, mutations in the NOD-like receptor 3 gene (NLRP3) cause gain-in-function of the NLRP3 inflammasome and an overproduction of inflammatory cytokines IL- β . Excessive production of IL-1 β leads to an exaggerated automated inflammatory response and triggers the production of downstream cytokines such as IL-6. This results in clinical manifestations that range from the mild Familial Cold Urticarial syndrome (FCAS) to the more severe Muckle Wells syndrome (MWS) characterised by fever, urticarial rash and sensorineural deafness. The most devastating CAPS is NOMID (Neonatal Onset Multisystem Inflammatory Disease), alternatively known as Chronic Infantile Neurologic, Cutaneous and Articular (CINCA) syndrome, which is characterised by destructive arthritis, deafness, progressive chronic meningitis and intellectual impairment (see Table I). Mevalonic aciduria/HIDS (Hyper-IgD syndrome) is a condition of excessive IL-1 β signalling which is triggered by a metabolic disorder: a mutation in the mevalonate Kinase gene results in high levels of Mevalonic acid, a precursor in the cholesterol pathway, which in turn, via unclear mechanisms, results in excessive



Figure 2: List of known monogenic auto-inflammatory diseases as well as a conceptualisation of the relative pathological involvement of non-specific innate immune dysfunction (auto-inflammation) and antibody or cell-mediated autoantigen-directed autoimmunity in rare and more common immunopathologies.

TABLE I: REPRESENTATIVE AUTO-INFLAMMATORY CONDITIONS SHOWING PATTERN OF INHERITANCE, EPISODE DURATION, CLINICAL FEATURES AND TREATMENT OPTIONS.

	FMF	HIDS	TRAPS	MW, FCAS, CINCA
Mode inheritance	AR	AR	AD	AD
Age of onset	< 20	Childhood	Variable	Infancy/neonatal
Length of episode	1–4 days	3–7 days	Several days	Variable
Abdominal pain	Very common	Very common	Common	Rare
Musculoskeletal	Monoarthritis	Arthralgias	Myalgias	Destructive arthritis
Chest pain	Pleuritis	Unusual	Yes	No
Rash	Rare	Very common, papular, maculopapular	Common, erysipelas-like	Urticaria, exanthema
Other	Pericarditis, scrotal attacks, splenomegaly	Headaches, cervical nodes, HSM	Orbital oedema	Cold sensitivity, dysmorphism, papilloedema
Amyloidosis	Yes	Yes	Yes	Yes
Treatment	Colchicine	None effective, ?TNF inhibitor	Steroids, TNF inhibitors	Steroids, IL 1 inhibitor

IL-1 β signalling.⁸ Similarly, mutations in the pyrin gene and the resultant dysfunction of the pyrin inflammasome, result in the clinical phenotype of Familial Mediterranean Fever.³

OTHER MECHANISMS OF AUTO-INFLAMMATION

While the most classic periodic fevers are associated with inflammasome dysfunction, other components of the innate system of downstream signalling from the inflammasome may also be involved in auto-inflammation (see Figure 4 and Table I). Abnormalities in NF- κ B activation cause Crohn's disease and Blau syndrome;⁶ Protein Folding Disorders are implicated in the pathogenesis of TRAPS² and spondyloarthropathies; complement disorders in Haemolytic Uremic syndrome; Cytokine Signalling disorders in Cherubism; and Macrophage Activation disorders in Familial HLH.⁸ Disorders of excessive type-1 interferon signalling have been associated with CANDLE syndrome⁹ and Aicardi Goutières syndrome.¹⁰ CANDLE syndrome is thought to be caused by proteasome dysfunction; proteasome degradation of ubiquitinated inflammasomes is a key regulatory method of this innate signalling pathway.

These conditions fulfil a different clinical phenotype from the inflammasome-related conditions and a full description of these conditions is beyond the scope of this article. On the other hand, some conditions which have very clear features of auto-inflammation are at this stage not possible to classify according to disease mechanism. PFAPA (Periodic Fever Aphthous Stomatitis, Pharyngitis and Adenitis), for instance, is the most common auto-inflammatory condition in children; it presents in young children as clockwork-regular attacks of fever, pharyngitis, aphthous stomatitis and cervical adenitis. Attacks come regularly every three to six weeks and last 3–7 days, with completely asymptomatic intervening periods.¹¹

HOW TO RECOGNISE AN AUTO-INFLAMMATORY SYNDROME: THE CLINICAL SPECTRUM

While the spectrum of auto-inflammatory diseases can be broad, certain combinations and patterns occur with increased frequency and are more likely to predict auto-inflammatory characteristics. Urticaria is a common feature of CAPS, NLRP12 FCAS, TRAPS, sJIA and HIDS.¹² Distinguishing between the

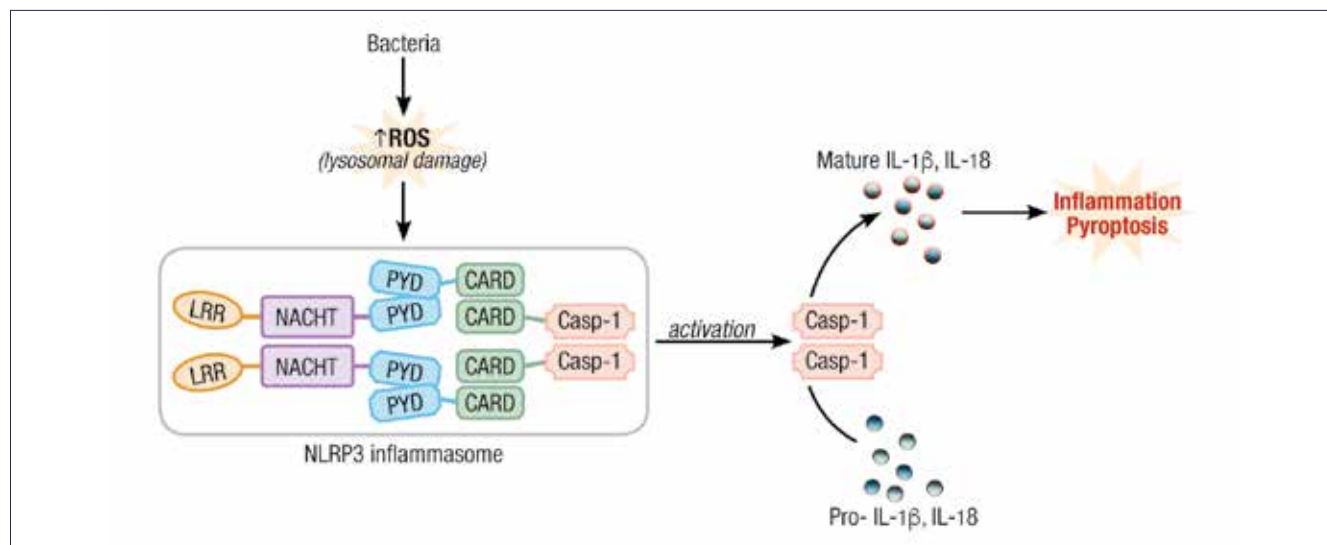


Figure 3: The inflammasomes

Inflammasomopathies	• Intrinsic e.g. cryopyrinopathies • Extrinsic e.g. FMF • Complex e.g. gout
NF-κB activation	• Crohn's disease • Blau syndrome
Protein folding	• TRAPS • Spondyloarthropathies
Complement	• HUS
Cytokine signalling	• Cherubism
Macrophage activation	• Familial HLH

Figure 4: Classification of auto-inflammatory conditions by innate immune defects

different phenotypes of chronic urticaria and urticaria associated with auto-inflammation can be difficult, and is the key reason for allergologists to be aware of these systemic conditions. Chronic autoimmune and auto-inflammatory urticaria can both have physical inducibility, but chronic urticarias tend to be more intensely pruritic, respond better to antihistamines, and individual wheals tend to disappear within 24 hours. Auto-inflammatory urticaria tends to be associated with fever, arthralgia and longer duration, frequently with a family history.

In the case of the CAPS, urticarial rashes, arthritis, conjunctivitis and sensorineural deafness are key features.¹² Cold exposure is a well-known trigger and attacks are shortlived (1–2 days) in FCAS and MWS but continuous in NOMID.

TRAPS presents with longer periods of fever (up to six weeks) in addition to conjunctivitis, periorbital swelling, pleuritis, pericarditis, myalgia, arthralgia, abdominal pain and erythematous rash (often overlying areas of myalgia or arthritis). Familial Mediterranean Fever presents with shortlived attacks (1–3 days), with arthritis, peritonitis or pleuritis and erythematous rashes, especially over the lower limbs. Hyper IGD syndrome presents in infancy with recurrent attacks of rash (from petechial to urticarial), fever, cervical lymphadenopathy, joint pains, abdominal pain and vomiting or diarrhoea.

A number of auto-inflammatory conditions are known to cause sterile bone inflammation. Chronic Recurrent Multifocal Osteomyelitis (CRMO), PAPA (Pyogenic Arthritis with Pyoderma Gangrenosum and Acne), DIRA (Deficiency of IL1 Receptor Antagonist) and DITRA (Deficiency of Interleukin Thirty-six Receptor Antagonist) are well recognised as conditions presenting with fever, pustular skin lesions and sterile bone abscesses.¹³

Clinical combinations that warrant the consideration of auto-inflammatory conditions include those with recurrent discrete attacks of fever, often self-limiting, with skin rashes (from urticarial-like lesions to diffuse erythematous exanthems), arthritis or sterile osteomyelitis, serositis and abdominal pain (see Table II). Eye inflammation, deafness and neurological involvement are also associated with several auto-inflammatory conditions. The periodic nature of these conditions is highly suggestive, especially when symptoms cluster together. In some of these conditions periodic attacks are so regular that attacks can be accurately anticipated. Laboratory tests which demonstrate high CRP and inflammatory markers during the time of an attack, which improve spontaneously after the resolution of symptoms, can be a telling sign. However, in more severe conditions such as NOMID or conditions characterised by prolonged attacks, such as TRAPS, inflammatory markers may remain elevated. In milder variants, inflammatory markers may not be very helpful. Clinical classification criteria for many of these conditions have been proposed.¹⁴

TABLE II: WARNING SIGNS FOR AUTO-INFLAMMATION

WARNING SIGNS FOR AUTO-INFLAMMATION
Recurrent urticaria or erythematous rash plus any of the following:
Fever (self-limiting, with a predictable recurrence)
Arthritis
Sterile osteomyelitis
Serositis
Abdominal pain
Raised inflammatory markers during attacks
Additional features:
Sensorineural deafness
Family history

TREATMENT OF AUTO-INFLAMMATORY DISEASES

Given the differences in the mechanisms of inflammation, different auto-inflammatory conditions require different therapeutic approaches. In the case of inflammasomopathies, where IL-1β is overproduced, IL-1β-modulating or -blocking drugs can be instantly and dramatically effective. Three IL-1β-blocking drugs have been developed and approved for use. Unfortunately, these agents are not freely available in South Africa owing in part to a lack of demand, because these conditions are rare, and also because there is a scarcity of skills to diagnose and manage them. Cost is another limiting factor of importing these agents, which range from approximately R20 000 per month for the daily subcutaneous injection of Anakinra to approximately ten times that per month for Canakinumab, which is given monthly. IL-1 inhibitors are also useful in the management of Hyper-IgD syndrome and TRAPS.^{15–17}

OTHER THERAPEUTIC AGENTS USED FOR AUTO-INFLAMMATORY CONDITIONS

COLCHICINE

This is Used frequently in FMF and can be dramatically effective. Colchicine acts by inhibiting neutrophil function and a good response is usually quite helpful in confirming the diagnosis of FMF. It has also been used successfully in other polygenic auto-inflammatory conditions such as gout and Behcet's disease.

TOCILIZUMAB

This IL-6-blocking biologic agent is useful in the management of systemic Juvenile Idiopathic Arthritis.

JANUS KINASE INHIBITORS

Agents in this class include Baricitinib, Tofacitinib and Ruxolitinib. While they have only recently been approved by the FDA for the management of rheumatoid arthritis, reports have emerged of efficacy in interferon alpha type-1-related diseases as well as in the proteasome dysfunction-related auto-inflammatory condition, CANDLE syndrome.

TNF INHIBITORS

TNF inhibitors such as Infliximab, Etanercept and Adalimumab have been used in the management of TRAPs as well as other auto-inflammatory conditions such as Blau syndrome, PAPA and CRMO.

CORTICOSTEROIDS

Used for decades in all forms of inflammatory disease, this agent is frequently used in auto-inflammatory diseases and offers a short-term option to treat acute attacks, especially when more specific agents are not available.

NON-STEROIDSAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

These are used as adjunctive and supportive agents, especially in sJIA and Hyper IGD syndrome; but they are effective only for symptom control.

OTHER MISCELLANEOUS THERAPIES

PFAPA tends to respond dramatically to tonsillectomy, although the reasons for this effect are not clear. Statins are sometimes used in MVK/HIDS because of the nature of the underlying metabolic disorder in cholesterol metabolism.

AMYLOIDOSIS

Apart from the obvious clinical impact of auto-inflammatory disease and the organ systems affected by inflammation, amyloidosis can complicate long-term uncontrolled inflammation. FMF and TRAPS are two conditions where this complication is prominent, and they can have dramatic effects on long-term health. Amyloidosis results from tissue deposition of Serum Amyloid A fractions produced in the liver as an acute-phase reactant. Renal deposition and subsequent kidney failure occurred in 60–80% of patients with untreated FMF after a median duration of 6.4 years (Gattorno and Martini).

CONCLUSION

Auto-inflammatory conditions are increasingly being recognised as multi-faceted diseases. Advances in genetic testing have led to the identification of more than 20 monogenic auto-inflammatory diseases with distinct phenotypes but many overlapping features. Recognising the patterns that suggest auto-inflammation will lead to improvements in diagnosis for patients and enable more appropriate therapeutic interventions. Given the range of specific and often complex and costly therapies, accurate diagnosis is imperative.

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DECLARATION OF CONFLICT OF INTEREST

The authors have no potential conflict of interest related to this article.

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