Title:

Early onset urticaria – a marker of cryopyrin associated periodic fever syndrome

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Running head: Early onset urticaria – a marker of CAPS
EARLY ONSET URTICARIA – A MARKER OF CRYOPYRIN ASSOCIATED PERIODIC FEVER SYNDROME

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A one-year-old boy presented with an asymptomatic fleeting erythematous rash, recurring since 6 hours after birth, without fever and poorly responsive to high-dose antihistamines. The lesions, which disappeared within hours, appeared when he was undressed or bathed, suggesting cold as a trigger. He was otherwise well, growing and developing normally, with no relevant personal or family history. Examination showed multiple small scattered urticarial rash on his trunk and extremities (Fig. 1).

Investigations revealed low haemoglobin 109 g/L (117-137), raised white blood cells 19.6 x10⁹/L (5.0-16.0), platelets 512 x10⁹/L (150-400), CRP 32 mg/L (0-10) and ESR 85 mm/hr (0-9). Other than a slightly low IgD 0.03 g/L (0.05-0.20), immunoglobulins were within normal limits. Histology from a representative lesion showed a neutrophilic urticarial dermatosis characterised by perivascular and interstitial neutrophilic infiltrate with leukocytoclasia but without vasculitis or dermal oedema (Fig. 2).

These findings prompted further investigations which demonstrated a raised serum amyloid A protein at 15.5 mg/L (<5-10mg/L) and a previously described pathogenic heterozygous mutation in exon 3 of NLRP3. Asp303Asn (D303N), which was absent in his parents and
siblings, signalling a diagnosis of cryopyrin associated periodic syndrome (CAPS). Treatment with anakinra led rapidly to complete resolution of the symptoms and serological abnormalities, and he remains well at 2.5 years of age.

CAPS, sometimes termed the cryopyrinopathies, is an hereditary periodic fever syndrome caused by dominantly inherited or de novo gain-of-function mutations in the NLRP3 gene located on chromosome 1q44, which encodes the intracellular protein cryopyrin (formerly NALP3). Activation of cryopyrin, a constituent of the multiprotein inflammasome complex, results in downstream activation of caspase 1 leading to over-production of interleukin IL-1ß, a potent inflammatory cytokine that drives the characteristic fever, vasodilation and systemic inflammation.¹

Three subtypes of CAPS are recognised but there is considerable clinical as well as genetic overlap. Familial cold autoinflammatory syndrome (FCAS) is the mildest variant with cold-induced episodes of fever with rash, arthralgia, headaches and occasionally conjunctivitis. In Muckle-Wells syndrome (MWS) there is additionally, but variably, sensorineural hearing loss and amyloidosis in adulthood (25%). Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic, cutaneous, articular syndrome (CINCA) is the most severe form with about 20% mortality before adulthood. It presents in the neonate or infant with spontaneous urticarial rash and fever; later patients develop central nervous symptoms, sensorineural hearing loss, ocular changes (80%) and disabling arthropathy.² Although the course of CAPS is unpredictable, sporadic occurrence, early onset (<6 months), and urticaria not provoked by cold are associated with a higher risk of severe neurological complications.³

The relatively mild presentation and provocation by cold in our patient are in keeping with the FCAS end of the CAPS spectrum, but the very early onset is a concern. Furthermore, the D303N mutation in NLRP3 gene has been reported in association with MWS and CINCA but
not FCAS.\textsuperscript{2,4} It is not possible to accurately predict the risk of neurological complications and neurosensory hearing loss in a young patient with CAPS, since the precise features severity of the disease may vary substantially within a single family, let alone among the numerous different causative mutations. \textbf{Cold trigger and autosomal dominant inheritance have been reported as predictors of better prognosis, but} All these patients require close long term monitoring including audiometry, ophthalmology and neurological review and early IL-1 blocking treatment to minimize the risk of long-term complications.\textsuperscript{3}

Our case highlights the importance of considering autoinflammatory syndromes when a child presents with very early onset, asymptomatic, fleeting urticarial lesions, unresponsive to antihistamines, even without other features of systemic inflammation. \textbf{A perivascular neutrophilic infiltrate on histology supports a diagnosis of CAPS.} Prompt diagnosis allows the use of specific treatment with anti-IL-1 agents,\textsuperscript{5} which dramatically improves quality of life in most cases and hold great hope for improving outcomes long-term.

\textbf{Conflict of interest:} nil
References:


Figure Legends:

**Figure 1:** Multiple scattered urticarial rash on the lower limbs

**Figure 2:** Histopathology from a representative lesion showing perivascular and interstitial neutrophilic infiltrate with leukocytoclasis but without vasculitis or dermal oedema. Haematoxylin and eosin, original magnification x 400
Multiple scattered urticarial rash on the lower limbs

70x99mm (300 x 300 DPI)
Histopathology from a representative lesion showing perivascular and interstitial neutrophilic infiltrate with leukocytoclasis but without vasculitis or dermal oedema. Haematoxylin and eosin, original magnification x 400

648x543mm (96 x 96 DPI)
MCQs:

Learning objective

To demonstrate up-to-date knowledge in the pathogenesis of cryopyrin associated periodic syndrome.

Question 1

1. Mutation in which of the following genes causes cryopyrin associated periodic syndrome?

   a) MEFV  
   b) MVK  
   c) IL1RN  
   d) NLRP3  
   e) IL36RN

Answers to question 1:

   a) Incorrect, mutation in MEFV gene causes familial mediterranean fever  
   b) Incorrect, mutation in MVK gene causes Hyperimmunoglobulinemia D with Periodic Fever Syndrome (HIDS) or Mevalonate Aciduria (MA)  
   c) Incorrect, mutation in IL1RN gene is implicated in Deficiency of Interleukin-1ß (IL-1ß) Receptor Antagonist (DIRA)  
   d) Correct, mutation in NLRP3 gene causes cryopyrin associated periodic  
   e) Incorrect, mutation in IL36RN is implicated in Deficiency of Interleukin-36-Receptor Antagonist (DITRA)

Question 2:

Learning objective: To demonstrate up-to-date knowledge in the management of cryopyrin associated periodic syndrome.

The drugs used in the treatment of cryopyrinopathies are targeted against which of the following interleukins?

   a) IL-6  
   b) IL-8  
   c) IL-5  
   d) IL-1
e) IL-17

**Answers to Question 2:**

a) Incorrect. The drugs targeted against IL-6 are used in treatment of certain rheumatic disease such as Castleman’s disease and rheumatoid arthritis.

b) Incorrect. The drugs used in treatment of cryopyrinopathies are not targeted against IL-8

c) Incorrect. The drugs targeted against IL-5 are tried in the treatment of eosinophilic disorders.

d) Correct. The drugs such used in treatment of cryopyrinopathies are targeted against IL-1

e) Incorrect. The drugs targeted against IL-17 are used in psoriasis