

An 8-Year-Old Girl with Urticaria Since Birth

TL LEE, KW CHAN, YL LAU

Abstract

This is a case report about an 8-year-old girl misdiagnosed as simple urticaria since birth. She has been given antihistamine and paracetamol for her symptoms but with no improvement. The diagnosis of CINCA syndrome was made clinically and confirmed by gene mutation analysis. This article aims to alert general practitioners to the symptoms of neonatal onset urticaria, headache and arthralgia/arthritis as the diagnostic triad of this syndrome.

Key words

Arthritis; CINCA syndrome; NOMID; Urticaria

An eight-year-old Chinese girl presented to us because of recurrent fever, skin rash and headache with vomiting (Figures 1a & 1b). She was noticed to have skin rash since birth, which persisted throughout her childhood with on-and-off bouts of flare-up and never completely subsided (Figure 1c). She was treated as having urticaria by multiple dermatologists and was given antihistamine and topical steroid but with no improvement. The skin rash was urticarial but not itchy or painful. There was no residual pigmentation of skin. The skin rash could occur at any part of the body. She started to have recurrent low grade periodic fever and morning headache since 3 years old. The headache usually occurred in the morning and relieved after vomiting. She complained of left hip and knee arthralgia since 5 years old. Her symptoms became more severe and frequent and she was admitted to our paediatric unit at 8 years old for further investigations.

Bilateral uveitis were noted on slit-lamp examination as well as bilateral papilloedema with blurred disc margin (Figures 1d & 1e). MRI brain detected a few tiny T2-weighted hyperintense foci in bilateral frontal lobes (Figure 1f). The opening pressure upon lumbar puncture was >40 cmH₂O. Pleocytosis (white cell count 289/mm³) was noted in cerebrospinal fluid, but Gram's smear and Ziehl-Neelsen stain as well as bacterial, fungal and acid-fast bacilli cultures were negative. Her ESR was 75 mm/hr and C-reactive protein 8 mg/dl. ANA, anti-dsDNA, anti-ENA and ANCA were negative; however lupus anticoagulant was present on repeated testing. The anti-cardiolipin Ig G and Ig M were not elevated. Immunoglobulin D was 73.7 mg/l. Moderate bilateral sensorineural hearing loss was detected. Skin biopsy showed mild perivascular inflammatory infiltrates, consisting of lymphocytes, histiocytes and occasional neutrophils in the dermis. There was no evidence of vasculitis. She was clinically diagnosed as Chronic Infantile Neurological Cutaneous and Articular (CINCA) or Neonatal Onset Multisystem Inflammatory Disease (NOMID) syndrome. The diagnosis was confirmed by identifying a heterozygous G>A missense mutation in exon 3 (cDNA nucleotide position 907) of CIAS1 gene by PCR-direct sequencing of genomic DNA. The mutation causes an amino acid substitution of aspartic acid with asparagine at position 303 (codon GAT>AAT,

Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong, China

TL LEE (李子良) FHKCPaed, FHKAM(Paed)
KW CHAN (陳冠榮) BSc, MPhil
YL LAU (劉宇隆) MD, FHKAM

Correspondence to: Dr. TL LEE

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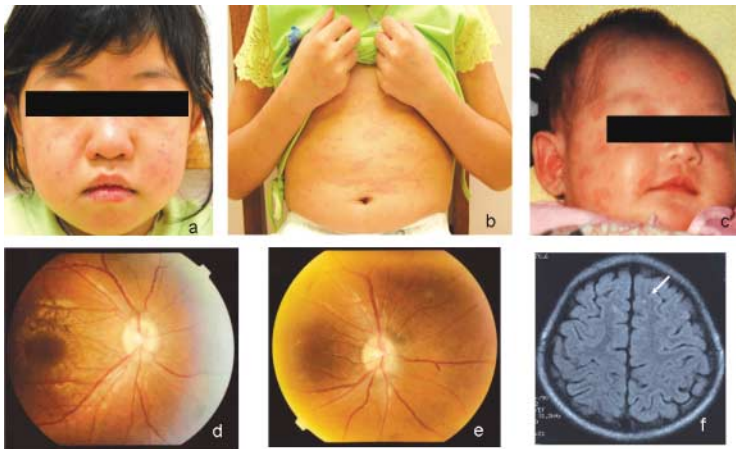


Figure 1 (a) Urticaria on the face; (b) trunk and limbs and (c) during neonatal period; (d & e) bilateral papulooedema and (f) T2-weighted hyperintense foci in left frontal lobe.

D303N). RT-PCR analysis indicated that both normal and mutant alleles were expressed at mRNA level. This mutation in CINCA has been reported previously.¹

CINCA/NOMID syndrome has been reported in more than 60 patients. It is a rare congenital inflammatory disorder characterised by a triad of (i) neonatal onset of cutaneous symptoms, (ii) neurological symptoms, and (iii) joint manifestations with recurrent fever and inflammation.² The first symptom of skin rash occurs at birth or in the first 6 months of life. A progressive neurological impairment results from chronic meningitis and secondary cerebral atrophy. Progressive visual defect and perceptive deafness frequently occur with increasing age. Joint symptoms manifest as recurrent flares. The course of the disorder is one of chronic relapsing inflammatory disease with fever, sometimes hepatosplenomegaly and lymphadenopathy. Presence of antiphospholipid antibodies, as in our patient, has not been reported before. The exact cause, pathophysiology and treatment of CINCA/NOMID syndrome remains unknown. This syndrome may be part of a spectrum of clinical phenotypes including Muckle-Wells syndrome and familial cold autoinflammatory syndrome, which also involve NALP3/cryopyrin/CIAS1 gene mutation.^{3,4} No therapeutic approach has been effective in altering the course of disease but a recent report indicated

potential usefulness of recombinant human IL-1 receptor antagonist anakinra.⁴ The differential diagnoses include systemic onset juvenile idiopathic arthritis, hyperimmunoglobulinemia D syndrome, sweet syndrome, mastocytosis and Langerhan's cell histiocytosis.

CINCA/NOMID syndrome can be readily diagnosed clinically and genetic diagnosis is available for confirmation.

References

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