

# Chronic infantile neurocutaneous and articular syndrome (CINCA) rare disease, difficult to prove and to treat

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## Introduction

Chronic infantile neurologic cutaneous and articular (CINCA) syndrome, also known as 'neonatal onset multisystem inflammatory disease,' or NOMID, is a congenital inflammatory disorder characterized by a triad of neonatal onset of cutaneous symptoms (skin rash), chronic meningitis, and joint pain with recurrent fever and inflammation.<sup>1</sup> It was first described by Prieur et al.<sup>2</sup> in 1981. CINCA is the most severe form of the cryopyrin associated periodic syndromes (CAPS) caused by mutations in the CIAS1/NLRP3 gene. About 50% of affected individuals have mutations in this gene. This condition is inherited in an autosomal dominant fashion<sup>3,4</sup> but most of the cases arise by new mutation in CIAS1 gene on chromosome 1q44.<sup>5</sup>

Renal AA-amyloidosis, severe arthropathy and neurological complications and deafness are long-term disabilities with this disease.<sup>6</sup> CINCA syndrome is poorly treatable and steroids do not eliminate the disease and can cause harmful side-effects. But use of IL1 antagonist (anakinra) give promising results in few patients especially genetically negative patients.<sup>7</sup>

## Case report

G,S,A is Libyan female patient; she was 2 years old when she admitted for the first time to medical side of Benghazi children Hospital at 22-10-2008. She was C/O: both knee swelling, abdominal distension, fever for 2 weeks before admission. By revising her Past history: pt product of FTND birth weight 2.5 kg. Mother notice erythematous skin rash soon after birth which increasing and decreasing but never fading. Frequent attacks of mild to moderate fever since infancy Mother notice that the child inactive with large head and she was delay in development comparing with other siblings, she followed private clinic diagnosed as rickets and received multiple courses of vitamin D and calcium (Figure 1).



**Figure 1** Patient at presentation.

## Family history

She is product of non consanguineous marriage with negative family history of similar illness.

## On examination at that time

Pt had large head with frontal posing with left eye ptosis, Urticarial skin rash over face, arms and legs enlargement of cervical, axillary, inguinal lymph nodes. Bilateral knee swelling but no effusion.

## Abdominal examination

Liver palpable 9 cm and spleen 3 cm below costal margin.

## CNS

Gross developmental delay (unable to walk at 2 years of age), with normal speech and mentality.

## Investigation

- a. **CBC:** TLC 13000/cm
- b. **Hb:** 8.1 gm/dl
- c. **Platlet:** 585000/cm
- d. **ESR:** 57 mm/hr CRP +ve RF -ve
- e. **Renal function test and liver function test:** normal.

Slit lamp examination done by ophthalmologist show evidence of uveitis with posterior synechia both eyes but more in left eye. Genetic study for CIAS1 gene mutation done at rheumatology center in Italy it was negative.

## Treatment

Steroid started and patient improved but as steroid tapered the manifestation relapsed so methotrexate added but without effect

so anakinra started at 7 years of age and patient started to improve markedly. Now the patient has good school performance, markedly less severe and less frequent attacks but skin rash still present but in milder form (Figure 2).



**Figure 2** Same patient after 3 years.

## Discussion

Our patient clinically typical CINCA with neurological, cutaneous and articular manifestations and the manifestation started at neonatal period. But when genetic study done it was negative as 50% of CINCA patient gene study is negative,<sup>3</sup> that CIAS1 missense mutations can result in distinct phenotypes with only a few overlapping symptoms and suggest that this gene may function as a potential inducer of apoptosis. The two other auto inflammatory syndromes related to CIAS1 mutations are Muckle-Wells syndrome (MWS) and familial cold auto inflammatory syndrome (FCAS).<sup>8,9</sup>

CIAS1 gene analyses in CINCA syndrome had not yet been available till 2002<sup>5,6</sup> and since that time there is a lot of advancement in precise and many cases which was negative the result become positive now but still there are many subtle undetectable changes which most likely our patient one of them.

The differential diagnosis comprise periodic inflammatory syndromes plus other childhood febrile illness as Kawasaki diseases, infantile cortical hyperostosis (Coffey's disease) Sweet's syndrome, and Weber-Christian disease and systemic onset juvenile idiopathic arthritis which shares many aspects with CINCA but it is rare in the first 6 months of life.

There is no established treatment for the pyrin associated auto inflammatory syndromes Nonsteroidal anti inflammatory drugs and steroids offer temporary clinical relief<sup>10</sup> but newer biologic agents are promising.

anakinra an IL1 antagonist show promising results specially in genetically negative patients with improvement within 6 months of starting treatment in many patients.<sup>11</sup>

## Acknowledgments

None.

## Conflicts of interest

None.

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