Chronic Infantile Neurocutaneous and Articular Syndrome (CINCA) Rare Disease, Difficult to Prove and to Treat

Case Report

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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 [1]. It was been first described by *Prieur et al.* [2] 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 [3,4] but most of the cases arise by new mutation in CIAS1 gene on chromosome 1q44 [5].

Renal AA-amyloidosis, severe arthropathy and neurological complications and deafness are long-term disabilities with this disease [6]. 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 [7].

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 Dand 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 enlargment 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 uveit is 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).

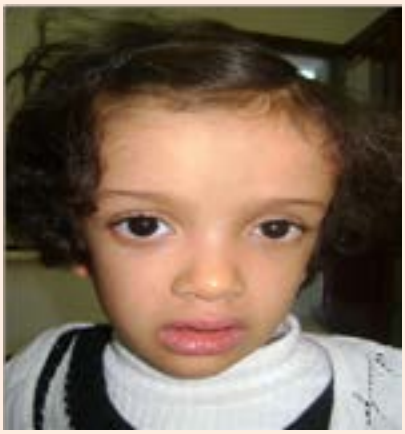

Figure 2: Same patient after 3 years.

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 [3], 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) [8,9].

CIAS1 gene analyses in CINCA syndrome had not yet been available till 2002 [5,6] 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 [10] 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 [11].

References

1. OMIM (2006) CINCA Syndrome. Online Mendelian Inheritance in Man.
2. Prieur AM, Griscelli C (1984) Nosologic aspects of systemic forms of very early onset juvenile arthritis. Aprops of 17 cases. Sem Hop 60(3): 163-167.
3. Hoffman H (2007) Neonatal-onset Multisystem Inflammatory Disease. National Organization for Rare Disorders.
4. Cleveland Clinic (2009) Periodic Fever Syndrome.
5. Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, et al. (2002) Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet 71(1): 198-203.
6. Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, et al. (2002) De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated auto inflammatory diseases. Arthritis Rheum 46(12): 3340-3348.
7. Frenkel J, Wulffraat NM, Kuis W (2004) Anakinra in mutation negative NMID/CINCA syndrome: comment on the articles by Hawakins et al and Hoffman and patel. Arthritis Rheum 50(11): 3738-3739.
8. Dodé C, Le Dû N, Cuisset L, Letourneur F, Berthelot JM, et al. (2002) New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. Am J Hum Genet 70(6): 1498-506.
9. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD (2001) Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet 29(3): 301-305.
10. Hawkins PN,Lachmann HJ, Aganna E, McDermott MF (2004) Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. Arthritis Rheum 50(2): 607-612.
11. Hawkins PN, Bybee A, Aganna E, McDermott MF (2004) Response to anakinra in a de novo case of neonatal-onset multisystem inflammatory disease. Arthritis Rheum 50(8): 2708-2709.