

CINCA syndrome

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Abstract

Chronic infantile neurological, cutaneous, and articular (CINCA) syndrome, also referred to as NOMID (neonatal, onset multisystemic inflammatory disease), was recently recognized as a unique entity that associates 3 cardinal signs: 1) a maculopapular urticarial skin rash that is often present at birth but whose presence varies with time; 2) articular signs of variable expression including transient swelling without sequelae between crises or unpredictable anomalies of growth cartilage suggestive of a pseudo-tumor, which, when biopsied, reveals disorganized cartilage with no inflammatory cells; 3) central nervous system involvement with headaches. Lumbar puncture almost always provides evidence of chronic meningitis with neutrophils and sometimes eosinophils. Generally, the infants are born preterm and dysmature; a placenta anomaly with inflammation was observed in some cases. The syndrome progresses in a context of chronic inflammation, with bouts of fever of varying intensity. Laboratory tests reveal signs of a non-specific inflammatory syndrome with anemia, polynuclear leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate (ESR) and elevated concentrations of inflammatory proteins. No autoantibodies or immune deficiency are detected. Despite its rarity (about 100 cases have been reported worldwide), this syndrome is increasingly recognized by pediatricians. Mutations of the CIAS1 gene, which is almost exclusively expressed by polymorphonuclear leukocytes and chondrocytes, was recently identified.

Keywords

CINCA, maculopapular urticarial skin rash, articular signs, neurological involvement, chronic inflammation, CIAS1 gene

Name of the disease and its synonyms

CINCA – chronic infantile neurological, cutaneous, and articular – syndrome.

Known as NOMID – neonatal, onset multisystemic inflammatory disease – in America.

Diagnostic criteria/Definition

The CINCA syndrome has recently been accepted as a separate entity. This syndrome associates three essential signs : 1) cutaneous signs, including maculopapular urticarial eruptions that vary over time and that are often

present at birth; 2) joint involvement, also varies over time: sometimes merely articular attacks leaving no persistent anomalies between episodes; other times, primarily abnormalities of growth cartilage arising unpredictably and suggestive of a pseudo-tumor, which, when biopsied, shows disorganized cartilages but no inflammatory cells; 3) involvement of the central nervous system becomes manifest over time, with headaches, sometime neurological signs leading to lumbar puncture. Chronic meningitis is almost always present with neutrophils and sometimes eosinophils.

Children are usually born prematurely and are dysmature. An inflammatory type anomaly of the placenta has been observed in some cases.

The syndrome progresses in the context of chronic inflammation, with episodes of fever of varying intensity. Laboratory analyses document a non-specific inflammatory syndrome with anemia, polymorphonuclear leukocytosis, thrombocytosis, elevated erythrocytes sedimentation rate (ESR) and elevated concentrations of inflammatory proteins. No autoantibodies or immune deficit have been identified to date.

Differential diagnosis

The differential diagnosis includes all the febrile eruptions occurring in children. [Still's disease](#) is very different, as it does not start in the neonatal period, but rather after the age of 6 months. The [hyperimmunoglobulin D syndrome](#) is also clinically different, and does not lead to central nervous system involvement. The diagnosis of the latter is now much easier since it is related to a [mevalonate kinase \(MK\) deficiency](#). If the diagnosis is suspected, the MK activity must be assessed in leukocytes. This deficiency is associated to a mutation in the *MK* gene, present in about half cases. The other recurrent fevers are discussed according their clinical status: [Familial Mediterranean Fever](#) in particular. Prolonged unexplained fever can also be related to a cytokine secreting mass, most often benign, for which surgical removal can lead to the cure of the fever. The archetype is the [Castleman's disease](#) in its monocentric type. The [Marshall's syndrome](#), which is very frequent in pediatrics consists of sudden attacks of fever, sometimes preceded by chills, with aphts, adenopathies, pharyngitis. Laboratory investigations show non-specific inflammation during attacks, but remain normal between attacks. The attacks last 4 to 6 days. The intervals between attacks are of 2 to 6 weeks, and the child remains perfectly healthy. Two other syndromes must be discussed with CINCA: [Familial Cold Urticaria](#) (FCU) and [Muckle-Wells](#) syndrome (MWS). Both are characterised by mutations of the *C1AS1* gene. FCU is characterised by urticaria occurring at cold exposure, with sometimes fever, arthralgia. MWS associates rash, fever, sometimes arthritis, and deafness occurring during late childhood (after age of 18 months), with a risk of secondary amyloidosis. The similar genetic background of CINCA, FCU and MWS renders these three diseases nosologically similar, although the clinical aspect remains most often very different.

Frequency

Despite its rarity, (about 100 cases have been reported worldwide), this syndrome is becoming better recognized by pediatricians.

Management and treatment

Therapeutic attempts have been disappointing. Non-steroidal anti-inflammatory drugs are indicated, corticosteroids might be necessary, provided that their administration is as innocuous as possible. Neither disease-modifying anti-rheumatic drugs (DMARDs) nor immunosuppressants have been shown to be effective. Intravenous immunoglobulins should be avoided as they can induce a major meningeal reaction.

Etiology

Mutations of the *C1AS1* gene, which codes for a pyrin-like protein, was recently identified. This gene is almost exclusively expressed by polymorphonuclear leukocytes and chondrocytes.

Genetic counseling

Generally, all these cases are sporadic. Sometimes there is a familial vertical transmission of the autosomal dominant type.

Prenatal diagnosis

Prenatal testing is not done.

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