A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy

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ABSTRACT

Chronic Infantile Neurological Cutaneous and Articular (CINCA) syndrome, also called Neonatal Onset Multisystemic Inflammatory Disease (NOMID) is characterised by the triad of cutaneous rash, chronic meningitis and arthropathy. It is a chronic inflammatory illness that starts most often at birth and persists for the whole lifespan of the patient. Attempts at therapy have been disappointing. The long-term prognosis is poor, with progressive deafness and visual impairment, and worsening of the central nervous system manifestations. Some cases of death have been reported secondary to infection, vasculitis and amyloidosis. Usually observed as sporadic cases, some familial association is recognised.

Introduction

Systemic onset juvenile idiopathic arthritis (JIA) during the first year of life is quite rare. It is most often observed in girls and occurs generally after the age of 6 months (1). Other types of chronic arthritis with systemic manifestations can be observed during the first year of life. Among these, a syndrome of neonatal onset can be recognised, the autonomy of which was underlined by Prieur and Griscelli in 1981 (2). The first description in 1950 was that of an "adult toxoplasmosis in one family" with all features now identified in the syndrome including cerebral involvement with calcifications of the faulx and dura (3).

At this point the syndrome is well known in paediatrics and about one hundred cases have been identified in the world (4-19). It exhibits a typical triad: cutaneous symptoms often present at birth, central nervous system involvement with chronic meningitis, and joint manifestations. The course is characterised by chronic inflammation with recurrent bouts of fever. This syndrome is known as Chronic Infantile Neurological Cutaneous and Articular (CINCA) syndrome in Europe (20, 21) and as Neonatal Onset Multisystemic Inflammatory Disease (NOMID) in North America (22).

Perinatal events

A cutaneous rash is present at birth in two-third of the cases. After an uneventful pregnancy, half of all CINCA patients are born with a weight lower than normally expected for the duration of the pregnancy. In some, umphaloceles or umphalitis can be observed. In one infant, the placental histological study showed vascular thrombosis, microcalcifications and polymorphonuclear cell infiltrates (20). Although the clinical aspect at birth is often that of a neonatal infection, no infectious agent has yet been identified.

Clinical manifestations

Skin manifestations are observed in all cases. Seventy-five percent of the newborns present a rash at birth. It is recognised in the other cases within the first weeks of life. It can be confused with a systemic JIA rash, but is more pronounced, and characterised most accurately as a non-pruritic persistent urticaria which is migratory during the course of a a single day. It is present for the life of the patient. The skin biopsy shows a normal epidermis, mild inflammation in the dermis and perivascular infiltration mostly by polymorphonuclear cells. No immunoglobulin or complement deposits are seen by fluorescence study.

Central nervous system involvement is the second characteristic manifestation. They are not always suspected during the first years of follow up. They can manifest as seizures, or transient episodes of hemiplegia. Spasticity of the legs is often mentioned. Headaches are

very frequent after some years. Neurological features reflect the chronic meningeal irritation due to a cellular infiltration with polymorphonuclear cells responsible for a chronic meningitis. Extensive studies to demonstrate a chronic infection have been negative. Exceptionally, this chronic meningitis may not be present (15, 19).

Joint manifestations represent the third most typical feature. The severity of joint involvement may vary considerably between patients. In some, the joint symptoms manifest as arthralgia with transient swelling but no radiological modifications. In other cases, particularly when the joint symptoms start during the first year of life, a severe arthropathy occurs symmetrically and consists of patellar overgrowth and epiphyseal and metaphyseal modifications, often linked with a growth cartilage overgrowth resulting in hard bony enlargement without any suggestion upon palpation of synovial thickening. Synovial fluid effusion can occur, probably in association with a local non-specific reaction to the epiphyseal disturbances. Synovial fluid, when present, is sterile and contains predominantly polymorphonuclear cells. Progressive joint contractures involving the knees must be treated early in order to maintain a good functional status.

Sensory organ involvement seems to appear with increasing age. Eye involvement is noticed in most cases. In the worst cases, it can lead to a progressive visual defect and sometimes to blindness. Optic disc changes are the commonest features, consisting of optic disc edema, pseudopapilledema and optic atrophy. Chronic anterior uveitis is seen in about 50% of the cases, but no synechia nor glaucoma, as reported in a recent review of 31 patients (23). Progressive perceptive deafness in varying degrees is observed in older patients. Hoarseness is frequent.

Radiological manifestations

Where present, radiological manifestations consist of a unique form of modification of the bones and joints (24). A typical arthropathy is observed in about half of the cases. In these cases, the manifestations of joint involvement are clinically present during the first year of life. In rare cases a very early periosteal reaction has been observed (24). A spontaneous bone fracture at one year may be observed (personal observation). The most distinctive changes occur in the metaphyses and epiphyses at the ends of the long bones, affecting (in decreasing frequency) the knees, ankles, wrists and elbows. A premature patellar ossification is frequent with a subsequent overgrowth of the patella. Epiphysis can appear large with irregular ossification *en mie de pain* ("bread-crumb"), often resulting in an overgrown and grotesque bone extremity. A growth cartilage puff is possible, giving a tumoral aspect with an irregular frame.

The most frequent location of growth cartilage anomalies is on the upper extremity of both tibias, but abnormalities can be observed elsewhere. Hips, shoulders, and spine seem to be relatively unaffected. Skull anomalies associate increased cranial volume, frontal bossing and late closure of the anterior fontanelle. Brain imaging often reveals mild ventricular dilatation, prominent sulci and increased extra-axial fluid spaces. Calcification of the faulx and dura can be seen in the oldest patients, reflecting the chronic inflammation of the meninges (20).

Disease course and follow up

Inflammatory relapses with bouts of fever occur in all patients. The skin rash is permanent, and lymph nodes and hepatosplenomegaly are often present during flare ups. Laboratory investigations reveal hypochromic anemia, leucocytosis with a predominance of polymorphonuclear neutrophils and eosinophils, high platelet counts, elevated ESR and high levels of acute phase reactants. There are usually no auto-antibodies.

The course of the disease is chronic with persistence of the manifestations for the whole lifespan of the patient. No remission has yet been reported. Non-steroidal anti-inflammatory drugs can relieve the pain but have no effect on the inflammatory features. Glucocorticostroids reduce fever and pain, without any effect on skin lesions, central nervous system disease or joint manifestations. Attempts with more aggressive medications such as slow acting anti-rheumatic drugs or cytotoxics have been very disappointing. Physiotherapy, splinting and occupational therapy are a very important part of the management of the disease.

Long-term follow-up reveals a progressive worsening of symptoms. Central nervous system involvement worsens and clinical manifestations such as headaches and seizures can be troublesome. The intellectual development may remain normal, but a low IQ in some patients can occur with time. In children with a severe arthropathy, the progression of the bony lesions can lead to monstrous deformity impairing the functional capacities. Sensory organ involvement can end with blindness and complete deafness. Secondary amyloidosis was observed in some patients, probably as a consequence of chronic inflammation. The causes of death have been documented as bacterial infection (8), vasculitis (5, 7), and secondary amyloidosis (personal observation).

Morphological characteristics

A progressive growth retardation is observed in most patients. One of the first reported cases was published as “dwarfing” (4). The cranial morphology demonstrates a peculiar aspect consisting of overall enlargement and frontal bossing. A saddleback nose is frequent and was already recognised in the earliest publication (3). The extremities may have an aspect of shortening of the hands and feet with clubbing of the fingers and sometimes a wrinkled aspect of the palms and soles. These common morphological features create a sibling-like resemblance in patients from various countries in the world.

Pathophysiologic and nosologic considerations

Chronic inflammatory syndromes starting early in life are now better understood. Their clinical specificities have been suspected and even recognised for many years (1, 25). They encompass some well-known entities in paediatrics such as the mucocutaneous syndrome

(Kawasaki's disease), infantile cortical hyperostosis (Caffey's disease), Sweett's syndrome, and Weber Christian disease. Other entities are now clearly distinguishable from systemic onset juvenile idiopathic arthritis by the discovery of their genetic background. Recurrent fever with hyperIgD, a disease associating febrile attacks, cutaneous symptoms, transient arthritis which starts before the age of one year in two-thirds of the cases, is caused by mutations of the gene of the mevalonate kinase (26, 27). The genetic linkage of early onset sarcoid arthritis, also known as "familial granulomatous arthritis (arteritis)" (28) or Blau syndrome (29) is located on chromosome 16 (30). Mutations of the 55 kDa TNF receptor (TNFR1) characterise a group of autoinflammatory diseases called TRAPS (TNF Receptor Associated Periodic Syndromes) (31). The gene of the Muckle-Wells syndrome, a hereditary inflammatory disorder with recurrent fever, urticaria and arthritis with progressive deafness and the development of AA-type amyloidosis is linked to chromosome 1q44 (32).

The CINCA syndrome appears to be original in many respects. The neonatal cluster of manifestations with infectious-like symptoms suggests the possibility of an intra-uterine or neonatal infection. Extensive evaluations for viral, fungal or bacterial agents have been negative. No immune deficiency could be documented. The most striking findings are cartilage anomalies with epiphyseal modifications, growth retardation, anomalies of ossification of the skull, saddle-back nose, hoarseness suggesting laryngeal localisation and progressive deafness. Interestingly, growth cartilage histology obtained from the modified growth plate shows a complete disorganisation of the cartilage cell columns, an irregular metachromasia of the cartilage substance and no inflammatory cell infiltrates, in contrast with pathological specimen from other tissues in which a non-specific inflammatory reaction with polymorphonuclear cell infiltrates is observed (21). Some indications for a cartilage target have been suggested by the presence of a toxic effect of the serum from these patients on normal human growth cartilage cells in culture (33). However, the precise mechanism of this disease remains unknown. The occurrence of familial cases, although much rarer than sporadic cases, suggests a genetic background, which may or may not be related to other familial hereditary inflammatory disorders.

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