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CINCA Syndrome: about a Series of 5 Cases

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Abstract **Original Research Article**

CINCA is a chronic auto-inflammatory syndrome of childhood characterized by a combination of skin, joint and neurological involvement, including sensory organs, due to a mutation in the NLRP3 gene responsible for uncontrolled activation of innate immunity. Our objective is to establish the epidemiological, clinical, genetic, therapeutic and evolutionary characteristics of the CINCA syndrome. ***Materials & Methods***: Retrospective analysis spread over 16 years (2000 to 2016) of 05 cases of CINCA syndrome, followed up at the pediatric rheumatology department and consultation at the Rabat children's hospital. ***Results:*** There were 03 boys and 02 girls, the mean age at diagnosis was 2 years and 02 months. 01 patient was from consanguineous parents (1st degree). Clinical signs were recurrent fever in all patients, osteoarticular involvement in 80% with patellar hypertrophy in 01 patient, skin involvement in 80%, neurological involvement in 60%, no sensory involvement, dysmorphic facies in 60% of cases, and staturo-ponderal retardation in 60%. None of the patients had renal amyloidosis. Biological tests revealed an inflammatory syndrome in all our patients, and joint radiographs showed a modelling disorder of the lower femoral metaphyses associated with osteoporosis in one patient, and epiphyseal remodelling with irregular ossification of the patellae in another. A genetic study was carried out in only 01 cases, revealing a mutation in the CIAS 1 gene. Biotherapy was not used in view of the clinical and biological improvement with NSAIDs and/or corticosteroids. CINCA syndrome is rare but can be serious and often goes unrecognized. Diagnostic and therapeutic management must be rapid in order to avoid serious complications, particularly ocular and renal, and to improve vital and functional prognosis.

Keywords: CINCA syndrome, autoinflammatory, Gene NLRP 3, Anti-interleukin 1.

INTRODUCTION

First described in 1981, CINCA Syndrome (Chronic Infantile Neurological Cutaneous and Articular Syndrome) is a chronic autoinflammatory syndrome of childhood characterized by a combination of cutaneous, articular and neurological involvement, including sensory organs [1]. CINCA syndrome represents the most severe phenotype of CAPS (Cryopyrin-Associated Periodic Syndromes) or cryopyrinopathies, which are a continuum of three diseases of increasing severity: Familial cold urticaria, Muckle-wells syndrome and Cinca syndrome, described independently by clinicians but brought together by genetics as due to mutations in the same gene: the NLRP3 /CIAS1 [2]. It's a rare syndrome, transmitted in the autosomal dominant mode, but generally most cases are sporadic due to de novo mutations [3]. It belongs to the group of auto-inflammatory diseases (AIDs), which are characterized by episodes of clinical and biological inflammation secondary to excessive activation of the innate immune response, independent of the adaptive immune response. They are associated with deregulation of inflammation mediated by pro-inflammatory cytokines, primarily interleukin-1 (IL-1) [4]. There is great variability in terms of severity within this syndrome. Some patients present the full pathognomonic clinical picture with early onset, while others have a more attenuated clinical phenotype and better quality of life [5].

PATIENTS AND METHODS

It is a 16-year retrospective study of 5 cases of CINCA syndrome, managed in Pediatrics 4 and the Pediatric Rheumatology Consultation. Patients are recruited through medical emergencies, referred by pediatricians or by specialists (ophthalmologists, neurologists, infectious diseases). The work was carried out using the archive register of the the pediatric rheumatology department and consultation at the Rabat children's hospital. The diagnosis was based on Anne Marie Prieur's criteria (Table 1).

Table 1: Anne Marie Prieur's diagnostic criteria for CINCA syndrome [6]

Skin rash	**pseudo-urticarial type**
	And at least one of the two signs:
Arthropathy	Symmetrical hypertrophy radiologically manifested by epiphyseal and/or metaphyseal changes of the long bones, early and irregular ossification of the patella.
Central nervous system damage	Secondary to chronic polynuclear meningitis

RESULTS

From 2000 to 2016, (16 years), we identified 05 cases of CINCA syndrome among the 87130 hospitalizations .in the P4 department at the Rabat Children's Hospital, representing an overall hospitalization incidene of 0.005%. The Average age of study population was 2 years 2 months, with extremes ranging from 4 months to 4 years,and was predominantly male, with an M/F sex ratio of 1.5. The age of onset of symptoms ranged from 03 to 06 months with a mean age of 04 and ½ months. All our patients had a recurrent fever (100%).04 patients (80%) had joint involvement: arthralgia of the large joints (elbows, wrists, knees and ankles), functional impotence in 01 patient (20%), arthritis in 02 children CINCA(40%), and patellar hypertrophy and synovitis in 01 case (20%).Skin involvement in the form of urticarial lesions was observed in 04 children (80%), neurological involvement was present in three cases (60%), manifesting as aseptic meningitis. Ocular damage and deafness were not observed in any case. Staturo-ponderal retardation was present in 03 patients (60%). Other clinical signs were observed in our series: a dysmorphic syndrome with bulging forehead, nasal ensellurement and protruding eyes was observed in 03 patients (60%), abdominal pain was present in a single patient (20%), cervical or axillary adenopathy was found in 03 patients, and recurrent pharyngitis was observed in a single case.

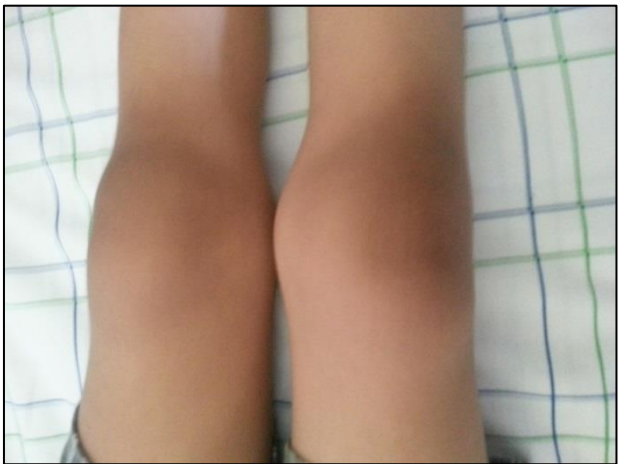

Figure 1: Patellar hypertrophy in a patient from our series

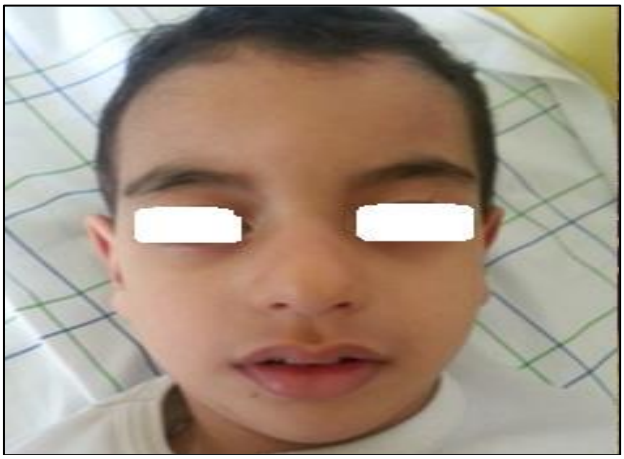

Figure 2: Dysmorphic syndrome in a patient from our series Nasal bridge and bulging forehead

Biologically, the inflammatory syndrome was present in all patients in our series: the Sedimentaion rate (ERS) was accelerated in 100% of cases, and exceeded 60 mm at 1 hour in 03 cases, 60%. The mean value was 62.2 mm at the first hour, with 20 mm being the lowest and 110 mm the highest. CRP was elevated in 80% of

cases, with extremes ranging from 44.6 to 140mg/l. Inflammatory anemia was present in all our patients (100%), hyperleukocytosis was detected in 03 cases (60%), thrombocytosis in 02 cases (40%).

Renal function was normal in all our patients. The immunological testings, which included rheumatoid factor and antinuclear antibody assays, was negative in cases of juvenile idiopathic arthritis or other inflammatory or systemic diseases. Lumbar puncture showed aseptic meningitis in 03 patients, while the rest of the infectious assays was normal in all our patients.

Front and side thoracic X-rays were systematically taken in all our patients and were strictly normal.

Joint radiographs returned normal in 03 patients, and showed a modelling disorder of the lower femoral metaphyses associated with osteoporosis in one patient, and epiphyseal remodelling with irregular ossification of the patellae in another.Genetic testing for mutations was carried out in only 01 cases, and revealed a mutation in the ICAS 1 gene.

DISCUSSION

Epidemiology

A rare entity, CAPS syndrome has mainly been described in Caucasians and more recently in Asians.

Its incidence is estimated at one case in a million. According to a recent epidemiological study, the number of patients diagnosed in France is around 150 [7]. In Morocco, we are unable to establish the actual prevalence of the disease, due to underestimation of this pathological entity. The first clinical manifestations of CINCA syndrome appear from birth, hence the former name NOMID [1]. For the five cases in our series, the age of onset ranged from 03 to 06 months, with an average of 04 and ½ months, with an early neonatal onset in one case: urticarial skin lesions trivialized by the parents. This syndrome affects both sexes, is a sporadic disease with autosomal dominant transmission, no data in the literature on sex distribution. In our series, the M/F sex ratio was 1.5.

Pathophysiological Aspects

As mentioned, CINCA syndrome represents the most severe phenotype of the three cryopyrinopathy entities, which are due to mutations in the NLRP3/CIAS1 gene encoding the NLRP3 protein, formerly known as cryopyrin [8]. This intracellular protein is highly expressed in monocytes and polynuclear cells [3, 9].

Cryopyrin mutations induce the formation of a hyperactive inflammasome in response to minor stimuli (stress, cold), leading to excessive IL-1b production and the consequent inflammatory skin, neurological and joint manifestations of CAPS. The remarkable efficacy of treatments inhibiting IL-1b has confirmed the central role of IL-1b in the pathogenesis of CAPS [8]. Since its initial description, around a hundred cases have been reported in the literature, the majority sporadic due to de novo mutations, but there are a few familial forms of autosomal dominant transmission [10]. Whether sporadic or hereditary, a mutation in the ICAS1 gene is found in approximately 60% of cases, suggesting genetic heterogeneity [10].

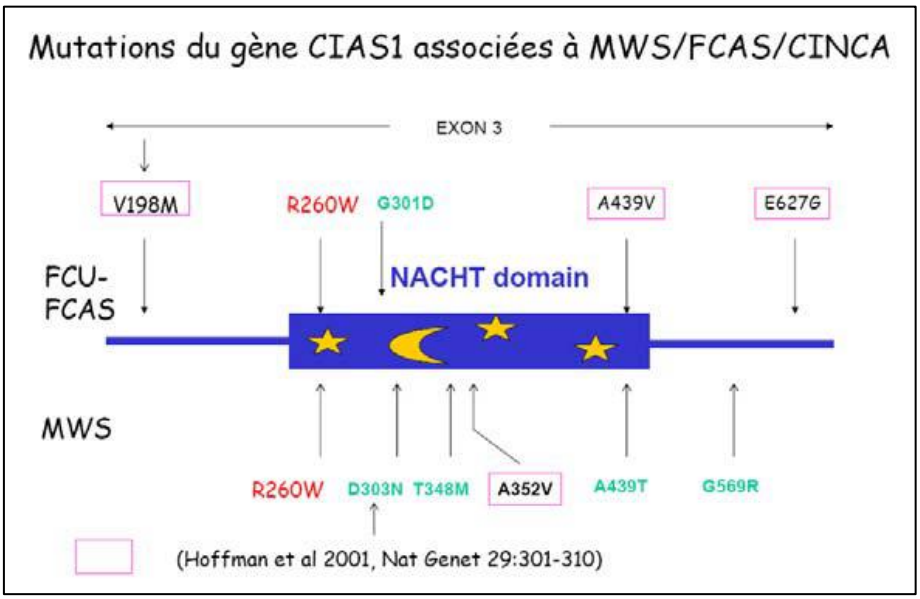

Figure 3: Diagram showing mutations in the CIAS1 gene [11]

Clinical Description

The disease usually presents in the first hours/days of life with an urticarial rash, a persistent increase in reactive proteins in the acute phase of inflammation and an inconstant fever. Typical facial features are a frontal bump and nasal ensellurement; in

our series, facial dysmorphia was noted in 3 out of 5 of our patients. The urticarial rash is generally non-pruritic and migrates during the day, without vascular alterations. Involvement of the central nervous system is manifested by chronic aseptic meningitis, which can lead to cerebral atrophy or severe intellectual impairment. Sensory damage includes inflammatory eye disease (uveitis, papillary damage, optic neuritis leading to blindness) and often progressive sensorineural deafness. Early degenerative arthropathy often affects the large joints, causing deformity and contractures. In our series, only one of five patients presented with patellar hypertrophy, two with arthritis and one with functional impotence [6].

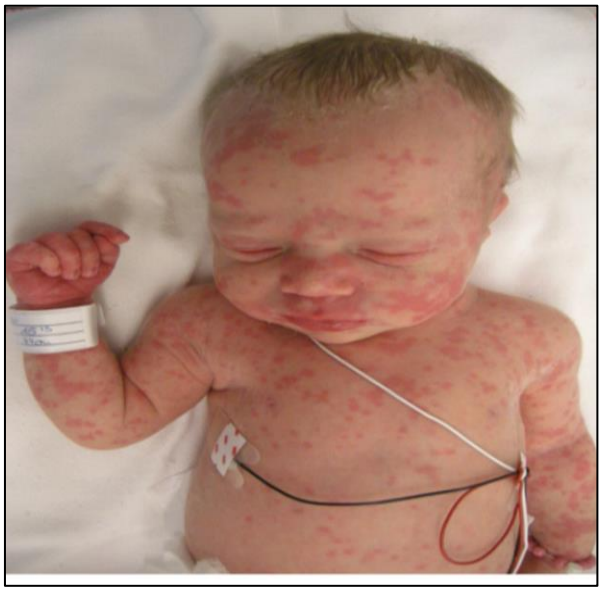

Figure 4: Neonatal skin rash in a case of CINCA syndrome [12]

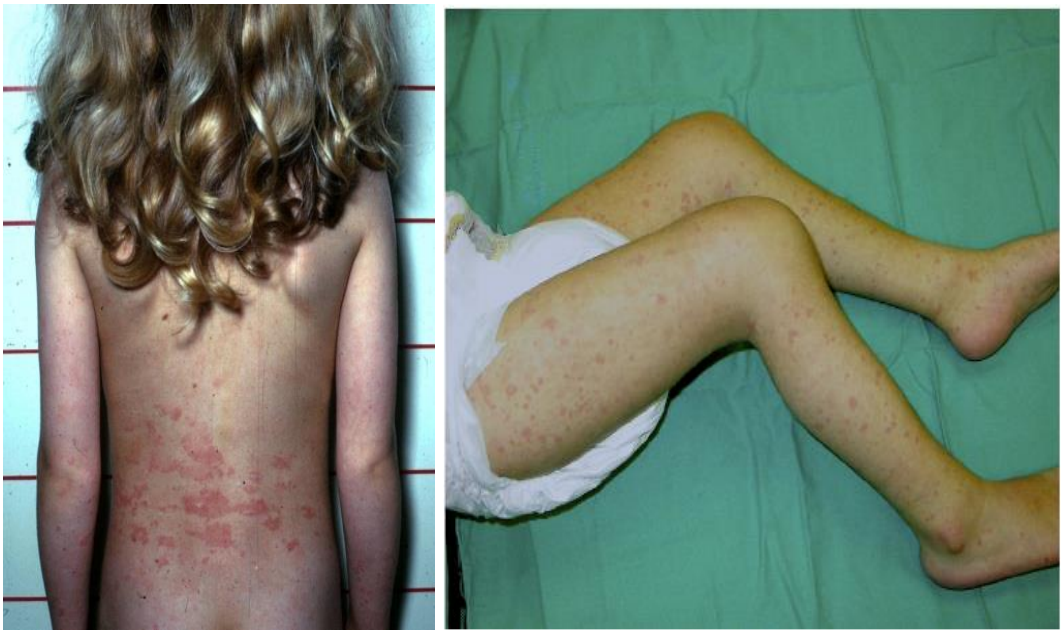

Figure 5: Skin lesions in patients with CINCA syndrome [13]

Diagnostic Methods:

Experts agree that the clinical presentation of CINCA is sufficient to establish the diagnosis. Laboratory tests reveal a non-specific inflammatory syndrome with anemia, granulocyte-predominant hyperleukocytosis, elevated sedimentation rate and high levels of C-reactive protein. No autoantibodies or immune deficiencies are detected. MRI of the brain reveals signs of meningitis, with possible inflammatory involvement of the inner ear. Ophthalmological examination may reveal papilledema [6]. Genetic testing can generally detect de novo NLRP3 mutations, but is not mandatory for diagnosis. In the event of a negative result from standard genetic testing, somatic mosaicism of *NLRP3* should be investigated.

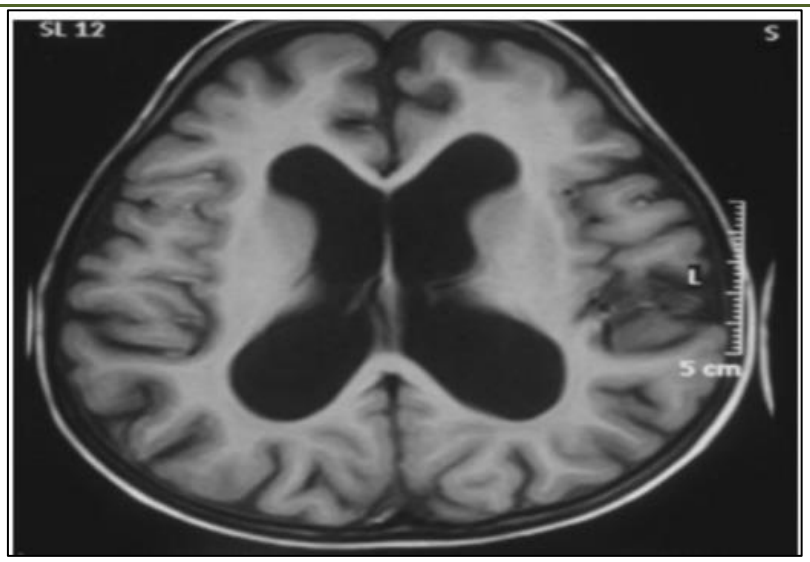

Figure 6: Brain MRI showing typical passive dilatation of the ventricles, with cerebral atrophy in a child with CINCA syndrome [14]

Therapeutic Methods:

Non-steroidal anti-inflammatory drugs are used in the majority of cases. Corticosteroids are often used at a dose of 0.5 to 1mg/kg/day, with variable but often moderate efficacy. They have a partial effect on fever and pain, but prolonged treatment is necessary, leading to corticosteroid dependence and numerous side effects. Anakinra (an interleukin-1 receptor antagonist) and canakinumab (a monoclonal antibody against IL1 beta) have been shown to be effective against inflammatory signs, as well as intracranial hypertension and hearing loss [6]. The long-term efficacy and tolerability of anakinra in CINCA syndrome have been described in two separate studies conducted in France and Italy, respectively [15, 16], whose data demonstrated that anakinra was effective in the long term and provided a spetacular improvement in quality of life [15], although joint involvement, in its hypertrophic form, was unaffected [8]. Physiotherapy is essential in cases of hypertrophic joint damage, to limit tendon retraction and reduced mobility [17].

CONCLUSION

CINCA syndrome is part of the auto inflammatory diseases, which represent a new entity unknown to the majority of healthcare personnel. Consequently, it is difficult to establish the incidence of these diseases. It is vital that paediatricians or general practitioners (family doctors) who are likely to see young infants and children, familiarize themselves with the clinical aspects of these diseases in order to recognize them, order the appropriate paraclinical examinations, institute early treatment and refer them rapidly to specialized centers.

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