



Periodic Syndrome Associated to Cryopyrin: About 10 Cases

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Abstract

NLRP3 gene responsible for an uncontrolled activation of the innate immunity. Objective is to study epidemiological, clinical, genetic, therapeutic and evolutionary characteristics of CAPS.

Material and methods: It is a retrospective analysis over 20 years (2000 to 2020) of 10 cases of CAPS, followed by the P-IV service and the pediatric rheumatology consultation at the Rabat children's hospital.

Results: The mean age at diagnosis was 3 years and 7 months with a masculine predominance of 70%. 06 patients were born to consanguineous parents (first degree). Clinical signs were a recurrent fever in 90%, osteo-articular involvement in 90% with patellar hypertrophy in 04 patients, skin signs were found in all patients 100%, neurological involvement in 70%, sensorial disabilities in 10%, dysmorphic facies in 80%, and failure to thrive in 80%. None of our patients had renal amyloidosis. An inflammatory syndrome was present in all patients 100%. Radiography of joints showed a modeling disorder of the femoral metaphysis in 02 patients, osteoporosis in 02 others, epiphyseal remodeling, and irregular ossification of patella in 01 patient. The genetic studies could only be done to one patient, and it revealed a CIAS1 mutation. NSAIDs and corticosteroids were prescribed to 07 patients with good evolution, and 02 patients received bi-therapy, after NSAIDs and steroids treatment failure, with clear improvement.

Conclusion: CAPS are rare diseases, and they are largely unknown. Diagnostic and therapeutic management should be early and prompt to avoid irreversible complications and improve the quality and expectancy of life.

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Introduction

Cryopyrin-Associated Periodic Syndromes (CAPS) are monogenic autoinflammatory diseases comprising a spectrum of 3 phenotypes of increasing severity: Familial Cold Urticaria (FCAS), Muckle Wells Syndrome (MWS), and chronic infantile neurological cutaneous joint syndrome (CINCA/NOMID). Their transmission is autosomal dominant in the first two syndromes (FCAS and MWS), where as in CINCA it is essentially a neomutation [1]. In Morocco, CAPS are part of MAI, which represents a new entity unknown by all health personnel. Therefore, it is difficult to establish an incidence of these diseases. Delayed diagnosis prolongs the course of the disease. It is essential that pediatricians or general practitioners (family physicians) who are likely to see young infants and children, become familiar with the clinical aspects of these diseases in order to recognize them, and in addition to request adequate paraclinical examinations, to initiate early treatment and to refer them rapidly to specialized centers.

The aim of our research is to define the etiopathogenic, clinical, paraclinical, therapeutic and evolutionary particularities of CAPS.

Results

Our series consisted of 7 boys and 3 girls with a sex ratio (M/F) of 0.4. The mean age of the patients at diagnosis was 3 years with extremes ranging from 4 months to 6 years. The age of onset of symptoms in the 10 patients ranged from birth to 17 months. 6 patients were from consanguineous marriages.

The most common signs in our case series are: recurrent fever which was present in 09 patients and lasted from 2 to 5 days, skin involvement which was present in all patients, and joint involvement also present in 09 patients manifested by arthralgia, arthritis, functional impotence, patellar hypertrophy, synovitis and joint retraction.

Neurological involvement was present in 7 patients. Delayed height and weight were present in 8 patients, and a dysmorphic syndrome with a bulging forehead, nasal saddle and protruding eyes was noted in 9 patients.

Biologically, all patients had an inflammatory syndrome with an accelerated SV and an elevated CRP. Lumbar puncture was performed in 09 patients and showed aseptic meningitis in 04 cases.

The genetic study could only be done in one case and revealed a mutation of the CIAS1 gene.

Radiological: Chest X-rays were performed in all patients and were strictly normal. Joint radiography was performed in all 10 patients and showed patellar hypertrophy in 03 patients, modelling disorder of the inferior femoral metaphysis associated with osteoporosis, epiphyseal remodeling with irregular ossification of the patellas in one patient, bone demineralization with modelling disorder of the metaphysis of all limbs in another. Abdominal and renal ultrasound were performed in all patients and were normal except in 02 patients: one had polysplenia and the other a homogeneous hepatomegaly. A CT scan was performed in only one patient and was normal except for a scaphocephaly.

Therapeutically: NSAIDs were used because of joint involvement in 05 patients. Oral corticosteroid therapy was prescribed in 04 patients. Biotherapy (Anakinra) was used in 02 patients

due to the failure of NSAID and CTC treatment. The clinical and biological evolution was favorable in 08 of our patients with a mean follow-up of 3 years. No patient presented complications related to the treatment or neurosensory complications or renal amyloidosis.



Table 1&2: Photos of our patient showing diffuse joint hypertrophy.



Table 3&4: Photos of our patient showing a genu valgum with swelling at the knee (left) and swelling of the wrists and MCP and IPP (right).

Discussion

Among the very many auto-inflammatory syndromes of monogenic origin currently known, cryopyrinopathies are among the very first entities whose genetic origin has been identified, whose pathophysiology has been studied and they are one of the first to have benefited from a targeted anti-IL-1 therapeutic approach [1].

The NLRP3 gene encodes cryopyrin, formerly known as CIAS1, a protein that plays an essential role in the inflammatory response of the human body. Mutations in the gene encoding cryopyrin enhance its function, resulting in increased inflammasome activity and thus increased IL-1 β production. Excess IL-1 produces inflammation, which manifests itself as fever, fatigue, a characteristic urticarial-like rash, and red eyes. Uncontrolled, chronic inflammation can cause sensorineural hearing loss, ophthalmic involvement, skeletal deformity, and secondary renal amyloidosis. The age of onset differs from one syndrome

to another: CINCA, which represents the most severe form of CAPS, is characterized by an early onset, sometimes prenatal; MWS has a later onset in childhood or adolescence; familial cold urticaria, which is the least severe form of the spectrum, may have a later onset and is usually present only after exposure to cold [1].

It is estimated that CAPS occurs in 1 in 1 million people worldwide [2]. A retrospective analysis of genetic data in France, over a period of 08 years, estimated the prevalence of the NLRP3 mutation to be 1/360000 in the country, and it was noted that all patients were of Caucasian origin [3]. In Germany, a prospective surveillance of children was conducted over a period of 03 years. The incidence was estimated to be very low corresponding to 2-7 new patients with age ≤ 16 years per year [4].

In our setting, we diagnosed 10 cases of CAPS over a 20-year period. We cannot establish a real prevalence of the disease, given the underestimation related to the lack of awareness of this entity by general practitioners and pediatricians.

Cryopyrin-Related Periodic Syndromes (CAPS) are related to mutations of the same gene but group 3 syndromes of increasing severity: Familial Cold Urticaria (FCAS) being the least severe, Muckle Wells Syndrome (MWS) and Chronic Infantile Neurological Cutaneous Joint Syndrome (CINCA) also called neonatal-onset multisystem inflammatory disease (NOMID) which is the most severe syndrome of the spectrum [1].

CAPS are monogenic diseases due to autosomal dominant transmission of mutations in the NLRP3 gene (formerly known as cold induced auto-inflammatory syndrome 1 or CIAS1), which encodes the NLRP3 protein also called cryopyrin, part of an IL-1 β activating complex called the NLRP3 inflammasome [5].

The transmission is usually familial in FCAS and MWS [6], but it is sporadic or de novo in patients with CINCA/NOMID [2]. In fact, there is no detectable mutation in the NLRP3 region in 50-60% of patients with a CINCA/NOMID phenotype [7].

The clinical manifestations of CAPS are, in fact, a continuum of overlapping phenotypic features, hence the term 'spectrum'. CAPS were considered, historically, as 3 distinct entities: FCAS, MWS, CINCA/NOMID; today they are recognized as a spectrum of increasing severity instead of different entities.

In general, CINCA/NOMID children present in the first days of life a chronic urticarial rash with mild fever and prolonged elevation of acute phase reactants. The cutaneous rash is non-pruritic, and it changes its distribution throughout the day without vascular alterations. In our case series, 10/10 patients presented skin lesions.

Typical dysmorphic facies: frontal hump, wide cephalic perimeter, nasal ensellurement. In our case series, 08 patients presented a dysmorphic facies.

Osteoarticular symptoms: 60% of CINCA/NOMID patients present major arthropathies concerning mainly the large joints such as the knees [8]. These arthropathies usually begin in childhood, causing deformities that persist into adulthood, resulting in early degenerative arthropathies, joint contractures and consequently short stature [9].

A small proportion of CINCA patients develop pseudotumor cartilage hypertrophy that affects regions of growth plate and progressively worsens over time [10]. In our case series, 08/10 of the patients presented osteoarticular symptoms.

Neurological symptoms include chronic irritability, intellectual impairment, headache, morning sickness, vomiting and rarely seizures. Untreated, CINCA patients develop CNS damage due to chronic inflammation. Chronic aseptic meningitis can cause increased intracranial pressure, leading to hydrocephalus, cerebral atrophy and chronic papilledema. In our case series, 7/10 of the patients presented neurological symptoms, 5 of which presented aseptic meningitis, and 02 presented convulsions.

Ocular : conjunctivitis is the most frequent manifestation of inflammation, persistent papilledema is frequent, it leads to optic nerve atrophy with progressive loss of visual acuity if not treated [5][11]. Anterior uveitis may contribute to progressive loss of vision. Only one patient in our series showed ocular atrophy.

Persistent cochlear inflammation can lead to sensorineural hearing loss, which usually appears in the first years of life [12].

Only one patient in our case series showed sensorineural hearing loss.

The most severely affected patients have a progressive staturponderal growth retardation without hormonal deficiency, and a delay in pubertal development. Hepatosplenomegaly and peripheral adenopathy may be present intermittently. In our case series, 8/10 of the patients presented a delay in their weight and height.

On the paraclinical level, the inflammatory syndrome is an important element in orienting the diagnosis, but it does not confirm it because of its lack of specificity. The sedimentation rate is accelerated and the C-reactive protein is increased. The blood count shows a predominantly neutrophilic hyperleukocytosis, a normocytic normochromic anemia, and thrombocytosis. SAA serum amyloid A was elevated.

In our patients, SV was accelerated in all patients, CRP was elevated in 07/10 patients, microcytic hypochromic anemia was noted in 09 patients, hyperleukocytosis in 08 patients, and thrombocytosis in 02 patients.

Concerning the infectious workup, lumbar puncture is among the complementary examinations that should be requested in case of suspected CINCA syndrome or MWS in search of hyperproteinorachy and study of CSF cellularity. Lumbar puncture may reveal aseptic meningitis with neutrophils which may orient the diagnosis towards CINCA syndrome or MWS. In our series, aseptic meningitis was present in 04 patients.

The immunological workup is done in order to distinguish autoinflammatory diseases from autoimmune diseases. The search for autoantibodies is negative in AIDs. This is the case for our series too. Look for proteinuria or microalbuminuria which may indicate renal glomerular damage secondary to amyloidosis. In 2007, Russo reported elevated liver transaminases in 2 patients [13]. None of the patients in our series had proteinuria, microalbuminuria or liver involvement.

Radiologically, FCAS and MWS patients did not show any abnormalities on knee radiographs. In a study by Hill et al. in 2007, radiographs of 20 patients showed bone abnormalities in 11 cases. These abnormalities included hypertrophy and deformation of the femur and patella. The mechanism is probably represented by endochondral formation of abnormal bone. Early patellar ossification and proliferation are typical although rare. In our series, joint radiography was normal in 04 patients, and

showed patellar hypertrophy in 04 patients, patterning disorder of the femoral metaphyses associated with osteoporosis in one patient, epiphyseal remodeling with irregular ossification of the patellas in one patient, and bone demineralization with patterning disorder of the metaphyses of all limbs in another.

After a few years of evolution, a cerebral atrophy can be objectified on cerebral CT, the ventricles appear distended, dilated and the scissures accentuated.

No neurological complications were detected in the patients of our series.

The diagnosis of CAPS is clinical, based on the presence of characteristic signs and molecular genetic examination can confirm this diagnosis. The NLRP3 mutation may be unidentifiable in almost half of CINCA patients, 25% of MWS patients, and 10% of FCAS patients[14]. Nevertheless, somatic mosaicism can be found using techniques such as Sanger sequencing and massively parallel sequencing [15]. The absence of genetic confirmation of the NLRP3 mutation does not exclude the diagnosis of CAPS. In our series, the genetic study could only be done in one patient and revealed a mutation in the ICAS1 gene.

The discovery of NLRP3 mutations in CAPS patients and the explanation of cryopyrin function has prompted researchers to try therapies targeting IL-1.

Currently, several treatments blocking the pathway involved in IL-1 activation have been developed. Treatments that have dramatically changed the prognosis of CAPS over the last decade[16], especially in CINCA patients, the most severe phenotype of CAPS.

After the spectacular efficacy of Anakinra (Kineret®), the first drug used to treat CAPS, two other anti-IL-1 drugs were allowed to be marketed in the USA and Europe: Canakinumab (Ilaris®) and Rilonacept (Arcalyst®), the latter having withdrawn its marketing authorization in Europe [17]. All 3 drugs have demonstrated their efficacy and their ability to improve the quality of life of CAPS patients.

Measures to avoid cold and temperature changes (air conditioning) are useful since they have been identified as triggering agents in FCAS patients and some MWS patients. Access to psychological support should be facilitated for CAPS patients, as for any patient with a chronic pathology. The musculoskeletal manifestations of CAPS can result in joint and muscle pain, joint swelling, joint stiffness and vicious postures, and severe deforming arthropathies.

The management of these manifestations involves: physical therapy, rehabilitation and functional readjustment; orthotics, occupational therapy; prosthetic orthopedic surgery for severe arthropathies. Neurosensory manifestations may require hearing aids or eye surgery (glaucoma, cataract...). Neurological manifestations may require neurosurgeons to set up a ventriculoperitoneal shunt because of threatening intracranial hypertension; screening for cognitive disorders, which condition the prognosis of MWS and CINCA patients, must be systematic, and early management of these disorders involves specialists in psychomotricity, speech therapy, and specialized educators. The treatment of complications of secondary amyloidosis is the responsibility of nephrology, and visceral surgery in case of hepatic amyloidosis.

Early and aggressive treatment in CAPS patients is crucial to avoid irreversible organ damage. The prognosis of CAPS, espe-

cially CINCA: the most severe phenotype of the spectrum, has dramatically improved after the availability of anti-IL-1 drugs, as it was affected by several complications namely renal amyloidosis which can cause chronic renal failure, and intellectual disability which develop in the first years of life. Improvement in height and weight delay, CNS inflammation, and deafness have been reported in some patients. Unfortunately, some manifestations in CINCA patients especially, such as bone hypertrophy and deformation are not reversible. In our case series, the evolution is favorable in 8 patients, 6 patients are under NSAIDs and/or corticotherapy, and 2 patients are under kineret®. No cases of amyloidosis were detected in our patients. One death of a single patient in an unspecified context.

Conclusion

Cryopyrinopathies (CAPS) are rare and not well-known diseases. In order to provide an effective and well conducted diagnostic and therapeutic approach to the child, it is necessary that pediatricians or family physicians who are likely to see young infants and children manage to make the diagnosis and initiate treatment early. Biotherapy is very promising and can improve the vital and functional prognosis.

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