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Caso Clínico

Severe pericarditis as the first manifestation of a combination of genetic autoinflammatory disease and genetic anemia. Case report

Irene Benítez[1], Zoilo Morel Ayala[2], Dora Lacarrubba[3], Jorge Rios[4], Hassel Jimmy Jiménez[4]

[1]Universidad Católica "Nuestra Señora de la Asunción", Instituto de Previsión Social, Hospital Central, Departamento de Pediatría. Asunción, Paraguay.
[2]Universidad Católica "Nuestra Señora de la Asunción", Instituto de Previsión Social, Hospital Central, Departamento de Reumatología. Asunción, Paraguay.
[3]Consultorio de Genética. Centro Integral Dermatológico. Asunción, Paraguay.
[4]Sanatorio Británico. Asunción, Paraguay.

ABSTRACT

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Glucose 6 Phosphate Dehydrogenase (G6PD) Deficiency, Cryopyrin-associated periodic syndrome (CAPS), Pericarditis, hemolytic anemia.

Corresponding author
Email:
zoiloma@hotmail.com
(Z. Morel)

Pericarditis is one of the most common pericardial diseases. The activation of the NLRP3 (nucleotide-binding andoligomerization (NOD) like receptor (NLR) containing pyrin domain (NLRP) 3) inflammasome is central in the genesis of autoinflammatory pericarditis. Cryopyrin-associated periodic syndrome (CAPS) is a rare, heterogeneous disease associated with NLRP3 gene pathogenic variants and increased interleukin-1 (IL-1) secretion. Glucose-6-phosphate dehydrogenase (G6PD) deficiency in erythrocytes causes acute haemolytic anaemia during distress or chronic non responsive to iron anemia X-linked. We present the case of a male 1-year-9-months-old patient, with pericarditis and hemolytic anemia, diagnosed as inherited X-linked Glucose 6 Phosphate Dehydrogenase Deficiency p.[Val68Met;Asn126Asp] haplotype, and a heterozygous pathogenic variant in the NLRP3 gene: c.1315G>A/p.Ala439Thr compatible with Autosomal Dominant Cryopyrin Associated Periodic Syndrome. This is the first Paraguayan patient with a "de novo" autoinflammatory condition coexisting with a glucose 6-phosphate dehydrogenase deficiency.

Pericarditis severa como primera manifestación de una combinación de enfermedad autoinflamatoria genética y anemia genética. Reporte de caso

RESUMEN

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Palabras clave
Deficiencia de glucosa 6 fosfato deshidrogenasa (G6PD), Síndrome periódico asociado a criopirina (CAPS), Pericarditis, anemia hemolítica.

La pericarditis es una de las enfermedades pericárdicas más frecuentes. La activación del inflamasoma NLRP3 (receptor de unión a nucleótidos y oligomerización (NOD) similar a (NLR) que contiene el dominio pirina (NLRP) 3) es central en la génesis de la pericarditis autoinflamatoria. El síndrome periódico asociado a la criopirina (CAPS) es una enfermedad heterogénea y poco frecuente asociada con variantes patogénicas del gen NLRP3 y aumento de la secreción de interleucina-1 (IL-1). La deficiencia de glucosa-6-fosfato deshidrogenasa (G6PD) en los eritrocitos causa anemia hemolítica aguda durante algún distrés, o anemia crónica no respondedora a hierro, ligada al cromosoma X. Presentamos el caso de un paciente de sexo masculino de 1 año y 9 meses de edad, con pericarditis y anemia hemolítica, diagnosticado de deficiencia de glucosa 6 fosfato deshidrogenasa

Editor Responsable: María Isabel Acosta
Universidad Nacional de Asunción, Facultad de Ciencias Médicas, Reumatología. San Lorenzo, Paraguay.

Autor para correspondencia
Correo electrónico: zoiloma@hotmail.com (Z. Morel)

ligada al cromosoma X, haplotipo p.[Val68Met;Asn126Asp], y variante patogénica heterocigota en el gen NLRP3: c.1315G>A/p.Ala439Thr, compatible con síndrome periódico autosómico dominante asociado a criopirina. Se trata del primer paciente paraguayo con un cuadro autoinflamatorio "de novo", coexistente con una deficiencia de glucosa 6 fosfato deshidrogenasa.

INTRODUCTION

Pericarditis is one of the most common pericardial diseases. The most frequent causes of acute pericarditis correspond to viral etiology, tuberculosis and "idiopathic". However, in children those related to post-cardiac surgery, kidney diseases, neoplasms and autoimmune or autoinflammatory pathologies are also very frequently described, the latter being currently the most common in cases of recurrent or idiopathic pericarditis[1-3].

It has been demonstrated that the activation of the NLRP3 (nucleotide-binding andoligomerization (NOD) like receptor (NLR) containing pyrin domain (NLRP) inflammasome[3] is central in the genesis of autoinflammatory pericarditis, with the consequent overproduction of IL-1, the main cytokine in this inflammation[4-6].

Cryopyrin-associated periodic syndrome (CAPS) is a rare, heterogeneous disease entity associated with NLRP3 gene and increased interleukin-1 (IL-1) secretion[7-9].

There is a spectrum of autoinflammatory diseases in CAPS: familial cold auto-inflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and chronic infantile neurological cutaneous articular (CINCA) syndrome, that is also called neonatal-onset multisystem inflammatory disorder (NOMID), deafness autosomal dominant 34 (DFN34) and keratitis fugax hereditaria (KFH)[7-9].

Hemolytic anemias are a diverse group of disorders with wide clinical and molecular heterogeneity[10]. Glucose-6-phosphate dehydrogenase (G6PD) deficiency in erythrocytes causes acute haemolytic anaemia upon exposure to fava beans, drugs, or infection[11].

We present the case of a child with severe acute pericarditis and pathogenic variant in both NLRP3 gene and G6PD gene.

CASE

Male, 1 year 9 months old, only child of a young couple. Maternal grandfather and mother with progressive congenital hearing loss, mother with mild anemia; premature first cousin with sequelae associated with prematurity and second degree maternal aunt with congenital heart disease. This was an unplanned pregnancy, the mother reports having mild COVID-19 in the second trimester of pregnancy. Normal prenatal ultrasounds. Scheduled cesarean delivery, birth weight: 3400g. Regular pediatric consultations and complete vaccination schedule. Between January and December 2022, 6 infectious symptoms occurred, the last 3 of which were difficult to resolve and led to the use of intravenous antibiotics. During these examinations, hemoglobin of 9.6 g/dL was found, which did not improve with iron supplementation. Currently, He is admitted to the ER due to progressive abdominal pain, which is accompanied by intermittent constipation. Laboratory test and ultrasound test were reported as normal. Given the persistence of symptoms, a CT scan of the chest and abdomen was performed, which revealed increased fluid in the pericardium.

During hospitalization, He was admitted to the PICU in a severe general condition, in shock, tachycardic, with weak pulses, marked paleness, slow capillary refill, drowsy, with barely audible heart sounds. Laboratory values confirmed the presence of severe systemic inflammation (Table 1). Echocardiogram: severe pericardial effusion. Emergency pericardial puncture was performed. He required support with vasoactive drugs for 24 hours, mechanical ventilation for 6 days, and pleural drainage tube for 8 days. A pericardial surgical toilet was subsequently performed through the sub-xiphoid pericardial window, wtih serosanguineous fluid. Infectious diseases were studied, with negative cultures (pericardial fluid and blood cultures). He received IVIG 2 g/kg + methylprednisolone 30 mg/kp/day for 5 days due to signs of acute pericarditis, continuing with oral prednisone, with progressive decrease until complete suspension.

A diagnostic whole exome sequencing was required, which reported a pathogenic p.[Val68Met;Asn126Asp] haplotype in G6PD gene, compatible with the diagnosis of inherited X-linked Glucose 6 Phosphate Dehydrogenase Deficiency and a heterozygous pathogenic variant in the NLRP3 gene: c.1315G>A/p.Ala439Thr compatible with Autosomal Dominant Cryopyrin Associated Periodic Syndrome.

Faced with these diagnoses, the patient was approached in a multidisciplinary manner, and will start canakinumab.

Tabla 1 Laboratory findings.

Variable	Cutt off	1er day in PICU
Hemoglobin (g/dL)	11-16	7.5
Hematocrit (%)	37-50	25
Platelets (cell/uL)	150000-450000	650000
CRP (mg/L)	< 6	48
Procalcitonin (ng/mL)	< 0.1	10
D-Dimer (ng/mL)	<500	>15.000
Pro BNP (pg/mL)	≤ 125	2353
IL-6 (pg/mL)	< 6	162
Coombs	Negative	Negative
ANA	Negative	Negative

DISCUSSION

We present the case of a patient with CAPS, having started with severe pericarditis and shock, without fever. CAPS generally manifests before the age of 2 years, and in those patients who developed symptoms before the age of 6 months, predicted a more severe clinical outcome, with a spectrum of clinical manifestations that mainly encompasses urticarial rash, fever and musculoskeletal involvement., but they can also present neurological involvement (40%) with headaches, papilledema and chronic meningitis, Eye involvement, with conjunctivitis, optic atrophy, and decreased vision, DFN34 is associated with hearing loss. In the long term, the presence of amyloidosis may be observed. No differences in sex are described[7-9,12-15].

Cuisset L et al found an estimated prevalence in France equal to 1/360 000[16]. This is the first case published in our country.

The Eurofever/PRINTO clinical classification criteria for CAPS includes: Presence of at least two of five: Urticarial rash; Cold/Stress-triggered episodes; Sensorineural hearing loss; Chronic aseptic meningitis; Skeletal abnormalities (epiphysial overgrowth/frontal bossing)[13].

Our patient does not currently meet the clinical criteria to be included in the CAPS classification; however, it is important to take into account the spectrum of presentation of pathologies with NLRP3 pathogenic variants, which could probably lead to changes in classifications over time.

More than 100 NLRP3 variants are classified as pathogenic/likely pathogenic with strong genotype-phenotype correlation along the disease continuum, and most of them are mainly concentrated in exon 3[9]. In our patient, He was carrying an heterozygous NLRP3: c.1315G>A/p.Ala439Thr mutation.
There are different registries in the world regarding autoinflammatory diseases with multiple genetic mutations, among them, The Eurofever project, supported by the European Agency for Health and Consumers[17]; The Autoinflammatory Diseases Alliance (AIDA) Network[18]; The registry of Hereditary Auto-inflammatory Disorders Mutations (Infevers database)[19]; The Autoinflammatory Diseases Alliance Registry of monogenic autoinflammatory diseases[20]; The Primary Immunodeficiency Database in Japan[21].

Pericarditis is the most common cardiac involvement of monogenic periodic fever syndromes, while some forms may present with myocarditis. Amyloidosis, the most significant complication of autoinflammatory syndromes, may lead to deterioration in cardiac functions[5,6,22].

We have to take into consideration that this patient had two coexisting genetic conditions, which is observable in 4% of pediatric patients. The CAPS was no possible to be suspected before this particular event, but the genetic anemia should have been tested after no response to iron supplementation. Which could have led to an earlier treatment.

The treatment of recurrent pericarditis is based on NSAIDs, corticosteroids and colchicine, and in refractory cases the use of anti-IL1 is described[23]. However, accounting for the pivotal role of IL-1ß in the pathogenesis of CAPS, three therapeutic options, all blocking the action of IL-1ß, are currently approved: anakinra, a recombinant IL-1 receptor antagonist, the IL-1 trap rilonacept and canakinumab, a monoclonal anti-IL-1ß antibody[24-26]. Our patient is about to start canakinumab. This is the first Paraguayan patient with a “de novo” autoinflammatory condition coexisting with a glucose 6-phosphate dehydrogenase deficiency inherited from the mother.

CONCLUSION

In the presence of fever without focus and no apparent infectious cause; of pericarditis without an infectious and/or recurrent cause, monogenic autoinflammatory causes should be investigated. And, in hemolytic anemia or anemia not responsive to iron supplementation, primary genetic causes must be ruled out.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

I.B., J.R.: summarized the case. Z.M., I.B., D.L., H.J.J.: wrote the work.

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