Alergia, Asma e Inmunología
Pediátricas
Vol. 31, No. 3 • September-December 2022 pp 90-93
doi: 10.35366/113855

Clinical case

Multisystem inflammatory syndrome in an infant with G6PD deficiency

Síndrome inflamatorio multisistémico en un lactante con deficiencia de G6PD

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How to cite: García-Domínguez M, López-Acosta JR, García-Arroyo I, López-Robles A, Morales-Cuevas JR. Multisystem inflammatory syndrome in an infant with G6PD deficiency. Alergia Asma Inmunol Pediatr. 2022; 31 (3): 90-93. https://dx.doi.org/10.35366/113855

ABSTRACT

Introduction: multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory disorder related to SARS-CoV-2 infection, characterized by a release of cytokines and oxidative stress, due to uncontrolled immune activation, which becomes critical in patients with a compromised antioxidant (AO), such as patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. **Clinical case:** we present a 3-month-old boy with G6PD deficiency who, three weeks after his mother had COVID-19, presented with fever, abdominal pain, dehydration, and shock. By epidemiological contact, positive RT-PCR was obtained for SARS-CoV-2. Laboratory tests showed elevated inflammatory markers, coagulopathy, and significant myocardial compromise. He was treated with intravenous immunoglobulin (IVIG) and systemic steroids with favorable clinical course. **Conclusion:** MIS-C in patients with G6PD deficiency should be identified early to establish immediate treatment and avoid serious complications both due to MIS-C and those that occur in patients with G6PD deficiency.

Keywords: multisystem inflammatory syndrome in children, glucose 6-phosfato dehydrogenase deficiency, COVID-19.

RESUMEN

Introducción: *el síndrome inflamatorio multisistémico en niños (MIS-C) es un trastorno hiperinflamatorio relacionado a la infección por SARS-CoV-2, caracterizado por una liberación de citocinas y estrés oxidativo, debido a la activación descontrolada del sistema inmune, que se vuelve crítico en pacientes con un sistema antioxidante comprometido (AO), como el caso de pacientes con deficiencia de glucosa-6-fosfato deshidrogenasa (G6PD).* ***Caso clínico:*** *presentamos un lactante masculino de tres meses de edad con deficiencia de G6PD. La madre tuvo COVID-19 tres semanas previas. Desarrolló fiebre, dolor abdominal, deshidratación y shock. Debido al contacto epidemiológico se obtuvo prueba nasal RT-PCR positivo para SARS-CoV-2. Los laboratorios mostraron marcadores inflamatorios elevados, coagulopatía y compromiso miocárdico significativo. Recibió tratamiento con inmunoglobulina intravenosa (IGIV) y esteroides sistémicos con evolución favorable.* ***Conclusión:*** *el MIS-C en pacientes con deficiencia de G6PD debe identificarse de manera temprana para establecer un tratamiento inmediato y evitar complicaciones graves, tanto por MIS-C, como las que ocurren en pacientes con deficiencia de G6PD.*

Palabras clave: *síndrome inflamatorio multisistémico en niños, deficiencia de glucosa 6-fosfato deshidrogenasa, COVID-19.*

Received: 03/28/2022. Accepted: 04/28/2022.

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INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an inborn error of metabolism that predisposes to hemolytic crisis due to enzymatic defects of red blood cell when exposed to oxidative agents or triggers (drugs, infections, fava beans). Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory disorder related to SARS-CoV-2 infection was reported in late April 2020.[1] The release of cytokines in MIS-C leads to an excessive inflammatory response and pro-oxidative responses with the leading to reactive oxygen species (ROS) due to uncontrolled immune activation. This response becomes critical in patients with a compromised antioxidant (AO) system such as patients with G6PD deficiency.[2]

PRESENTATION OF CASE

We report a 3-months-old male diagnosed with G6PD deficiency. A history of prematurity of 35 weeks of gestation with respiratory distress and early-onset neonatal sepsis treated with pulmonary surfactant, antibiotics (cefotaxime, vancomycin) and mechanical ventilation for 2 weeks. Presented unconjugated hyperbilirubinemia with negative Coomb's test, treated with phototherapy and an expanded neonatal screening test was performed prior to blood transfusion, which reported deficient G6PD enzymatic activity.

He developed a fever of 38.7 °C two days before admission, inconsolable crying and irritability. COVID-19 is suspected due to a history of maternal COVID-19 three weeks prior with positive nasopharyngeal reverse transcription chain reaction (RT-PCR) for SARS-CoV-2. Upon admission clinically he was fever, pallor, irritable with acute abdomen suspected. He presented increased respiratory effort, dehydration, and hypotension. The patient received hydric resuscitation, oxygen delivery and, antibiotics (cefotaxime-vancomycin). Laboratory test showed Hb 9.2 g/dL, WBC 25,000/mm^3 (PMN 65%), C-reactive protein (CRP) 4.57 mg/dL, erythrocyte sedimentation rate (ESR) 45 mm/h, procalcitonin 10.98 ng/mL, total serum bilirubin 1.54 mg/dL, direct bilirubin 0.57 mg/dL, lactate 3.7 mmol/L, with positive antigen test and RT-PCR for SARS-CoV-2.

On the second day of admission manifesting tachypnea, tachycardia and pallor, due suspicion of hemolytic crisis, laboratory showed Hb 8.4 g/dL, WBC 4.190/mm^3, procalcitonin 19.39 ng/dL, CRP 20 mg/dL, D-dimer 2.07 µg/mL, fibrinogen 454 mg/dL, NT-proBNP 35.000 pg/mL, IgM serology and RT-PCR for SARS-CoV-2 positive. A chest X-ray normal. The diagnosis of MIS-C was made and treatment within immunoglobulin intravenous (IVIG) 2 g/kg, methylprednisolone 2 mg/kg/day and, enoxaparin was started.

The echocardiogram showed normal artery coronary, LVEF 53% and refringent pericardial *(Figure 1)*.

Clinical improvement was observed with normalization of fever and inflammatory biomarkers. He was discharged home in good condition on steroids tapering dose over one week.

DISCUSSION

G6PD deficiency is found worldwide, occurs most frequently in sub-Saharan Africa and the Arabian Peninsula. In Latin America the prevalence varies in the different countries, from 0.5 to 10%. In Mexico, a prevalence of 0 to 2% is estimated.[3] G6PD is a cytoplasmic enzyme, which prevents oxidative damage to cells by decreased ROS, in which the production of nicotinamide adenine dinucleotide phosphate (NADPH) is necessary, which engage in the glutathione cycle, avoiding cell damage by hydrogen peroxide and maintains an intracellular oxidative balance. The majority of G6PD deficiency being asymptomatic, however the hemolytic crisis that may be triggers by intrinsic or extrinsic stressors, e. g., drugs, infections, fava beans. The manifestations depending on the amount of oxidative stress intracellular and the levels of enzyme activity.[2] In 2008, Wu et al, demonstrated *in vitro* that G6PD deficiency cells are more susceptible to HCoV 229E-induced cell death.[4]

SARS-CoV-2 infection is characterized by production of pro-inflammatory cytokines and the development of acute respiratory distress syndrome (ARDS). However, in late April 2020 a severe form in children with shock and Kawasaki-like features was reported and subsequently named MIS-C.[1,5]

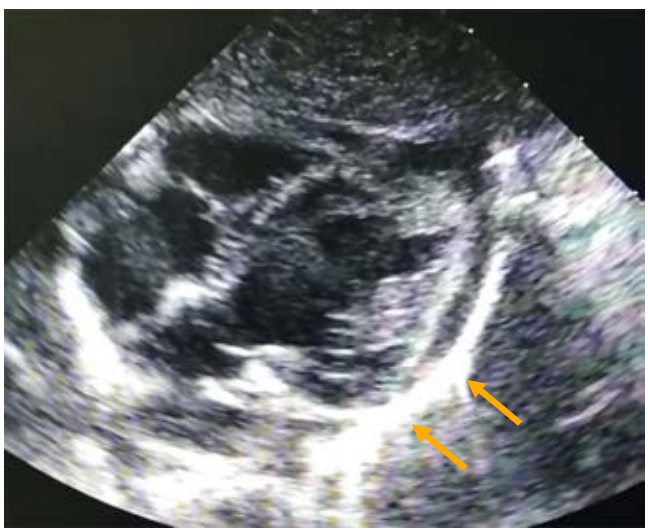

Figure 1: Refringent pericardial without evidence of effusion with normal coronary arteries.

Table 1: Clinical features, treatment and outcome of multisystem inflammatory syndrome in children in patients with G6PD deficiency.

	Age (years)	Sex	Days of fever	Mucocutaneous signs	System involved	Laboratory tests	Echocardiography	Treatment	Outcome
Almoosa[9]	7	Female	3	Rash	G-I, CNS	RT-PCR (+)	Normal	AB, IVIG, DXM, favipiravir, LMWH	Recovery on 6 day
Al-Aamri[8]	10-15	Female	3	KD	G-I, shock, myocarditis, ARDS, AKDI	Anemia, hyponatremia, hypoalbuminemia, ferritin, creatinine and serum glucose ↑ LDH, total serum bilirrubin, and AST/ALT ↑	Mild pericardial effusion, mild regurgitation mitral, moderate to severe left ventricular dysfunction and dilatation	AB, IVIG, MPD, favipiravir, aspirin, tocilizumab, enoxaparin, inotropic therapy	Death on 10 day
Almoosa[9]	11	Male	3	Conjunctivitis Rash Cracked lips and strawberry tongue	G-I, shock.	Anemia, thrombocytopenia, hyponatremia, hypoalbuminemia Troponin, BNP and DD ↑ Biomarkers inflammatory ↑ (ESR, CRP, ferritin), COVID-19 antibody IgG (+)	Normal	IVIG, MPD	Recovery
Almoosa[9]	13	Female	5	Conjunctivitis Rash Erythematous cracked lips Extremity edema	G-I, Shock, myocarditis, coagulopathy, ARDS	Biomarkers inflammatory ↑ (ESR, CRP), leukocytosis, hyponatremia, cardiac enzymes (BNP, troponin) ↑ RT-PCR and IgG SARS-CoV-2 (+)	Mild pericardial effusion, mild mitral regurgitation, depressed left ventricular function	AB, IVIG, MPD, favipiravir, tocilizumab, LMWH, inotropic and pressor therapy	Death on day 6
Al Ameer[7]	13	Female	5	Conjunctivitis Rash Erythematous cracked lips	G-I, shock, myocarditis, ARDS, AKDI, liver failure, ventricular dysfunction	Biomarkers inflammatory ↑ (ESR, ferritin), leukocytosis, anemia, hyponatremia, hypoalbuminemia, cardiac enzymes ↑ RT-PCR and IgG SARS-CoV-2 (+)	Mild pericardial effusion, mild mitral regurgitation, moderate depression in left ventricular function (LVEF 32%)	AB, IVIG, MPD, favipiravir, tocilizumab, anticoagulant therapy, inotropic and pressor therapy	Death on day 15

G-I = gastrointestinal; CNS = central nervous system; RT-PCR = real-time polymerase chain reaction; AB = antibiotic; IVIG: intravenous immunoglobulin; DXM = dexamethasone; LMWH = low molecular weight heparin; KD = Kawasaki disease; ARDS = acute respiratory distress syndrome; AKDI = Acute Kidney Disease Injury; MPD = methylprednisolone; LDH = lactate dehydrogenase; AST/ALT = asparate aminotransferase/alanine transaminase; BNP = brain natriuretic peptide; DD = D-dimer; ERS = erythrocyte sedimentation rate; CRP = C-reactive protein; LVEF = left ventricular ejection fraction.

The population with G6PD deficiency has been particularly affected by the COVID-19 pandemic.[2,6]

Nowadays there are few case reports of MIS-C in patients with G6PD deficiency, with different outcomes *(Table 1)*.

Al Ameer et al, report first case of G6PD deficiency with MIS-C mimicking Kawasaki disease (KD). With a history of fever, gastrointestinal symptoms, and organ failure with an increased biomarker inflammatory. Ineffective response treatment with IVIG, steroids, antiviral, and biologic therapy.[7] Al-Aamri et al, report another case like KD shock syndrome that developed multiorgan dysfunction without response to established treatment.[8]

Almoosa et al, in a report of ten cases, three G6PD patients developed MIS-C. The first patient with multiorgan failure, elevated cardiac enzymes and left ventricular dysfunction died after 15 days without response to treatment with IVIG, steroids and biological therapy. The other two cases showed adequate response to treatment.[9]

CONCLUSIONS

G6PD deficiency is especially susceptible to stress factors that lead to hemolytic crises and free radical production, a situation that is aggravated if MIS-C develops. Clinical suspicion of MIS-C in these patients should be made when fever persists for more than 3 days, with inflammatory markers and cardiovascular compromise to establish aggressive treatment, since unfavorable results are observed with greater delay in diagnosis and treatment.

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