







# AUTOIMMUNE HEMOLYTIC ANEMIA ASSOCIATED WITH COVID-19 IN AN INFANT: A CASE REPORT

Jesly Doria-Atencia<sup>1</sup>, Karen Tous-Barrios<sup>1</sup>, Mauricio Guerrero-Román<sup>1</sup>, Ayslin González-Cabarcas<sup>2</sup>,  
Hernando Pinzón-Redondo<sup>3</sup>, Joel Doria-Atencia<sup>1</sup>, Dilia Fontalvo-Rivera<sup>1</sup>

<sup>1</sup>University of Sinú School of Medicine, Cartagena, COLOMBIA

<sup>2</sup>Fundación Hospital Infantil Napoleón Franco Pareja, Clinic of Hematology, Cartagena, COLOMBIA

<sup>3</sup>Fundación Hospital Infantil Napoleón Franco Pareja, Clinic of Infectology, Cartagena, COLOMBIA

## ABSTRACT

Autoimmune complications such as autoimmune hemolytic anemia (AIHA), an uncommon entity in pediatric patients, have been associated with infectious diseases. Knowledge of the pathophysiological mechanisms that contribute to the immune dysregulation caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection is highly important, and clarifying the hypotheses about the molecular mimicry linked to these complications is essential to overcome potentially life-threatening hematologic manifestations in the underestimated pediatric population during the pandemic. A 10-month-old male with respiratory and gastrointestinal symptoms due to a SARS-CoV-2 infection documented by a molecular biology test developed severe anemia symptoms with an autoimmune hemolytic etiology. Management with corticosteroids improved his clinical condition and hematologic parameters. AIHA is a pathology with a broad presentation spectrum. Many illnesses are associated with triggers of AIHA; however, only a few related to Coronavirus disease-2019 (COVID-19) in infants have been described. This case report reminds us to consider the AIHA condition as a possible complication of COVID-19 in children under five years old.

**Keywords:** Anemia, autoimmunity, molecular mimicry, SARS-CoV-2

## INTRODUCTION

Coronavirus disease-2019 (COVID-19) was first described in 2019 in Wuhan, China, and is associated with severe acute respiratory syndrome (SARS); it was declared a pandemic in March 2020 by the World Health Organization (WHO) (1).

According to the Korean Center for Control and Prevention of Diseases, 6.3% of COVID-19 cases occur in children under 19 years old, although the pediatric population is not likely to develop severe forms of the disease (2). Emerging evidence indicates that, despite initial statements, young children have a great risk of contracting SARS coronavirus-2 (SARS-CoV-2) infection. However, the epidemiology of this illness in the pediatric population, especially in children under five years old, is not clear (3).

Studies have highlighted the connection between viral infection and autoimmunity (4). Autoimmune disease after infection has been reported in adults. Autoimmune hemolytic anemia (AIHA) is one such disease in which antibodies cause hemolysis (5). AIHA can be idiopathic or related to a microorganism infection, such as the Epstein-Barr virus or *Mycoplasma pneumoniae* (6).

Other causes have also been identified, such as drug-dependent and independent antibodies. Drug-dependent antibodies involve hapten-mediated antibodies, which recognize a mixed epitope composed of erythrocyte parts and drug non-covalently bound to red blood cells, which includes penicillin and ceftriaxone. The second group induces AIHA via adsorption and immune dysregulation such as methyl dopa and fludarabine (7, 8). Two children who developed AIHA after vaccination were described. The patients were a 20-month-



**Address for Correspondence:** Fontalvo-Rivera Dilia, University of Sinú School of Medicine, Cartagena, COLOMBIA

e-mail: diliafontalvor@gmail.com

ORCID iDs of the authors: JDA: 0000-0002-7910-4456; KTB: 0000-0002-1698-4724; MGR: 0009-0006-4850-2941;

AGC: 0000-0003-4586-6898; HPR: 0000-0003-4295-717X; JoDA: 0000-0002-3732-2658; DFR: 0000-0002-2833-9896.

Received: 01.06.2023 Accepted: 12.09.2023

**Cite this article as:** Doria-Atencia J, Tous-Barrios K, Guerrero-Román M et al. Autoimmune hemolytic anemia associated with COVID-19 in an infant: a case report. Turk Med Stud J 2023;10(3):132-5.



OPEN ACCESS



old girl and a 21-month-old boy. The girl experienced two hemolytic episodes; one after oral polio vaccination, and the other after mumps, rubella, and measles vaccinations received simultaneously. The boy experienced hemolysis after revaccination against diphtheria-pertussis-tetanus, hepatitis B, *Haemophilus influenzae*, and polio simultaneously (9).

Until now, the majority of AIHA cases secondary to SARS-CoV-2 infection have been reported in adults, with only a few in pediatric patients (5). The following case report concerns an infant who developed AIHA after COVID-19.

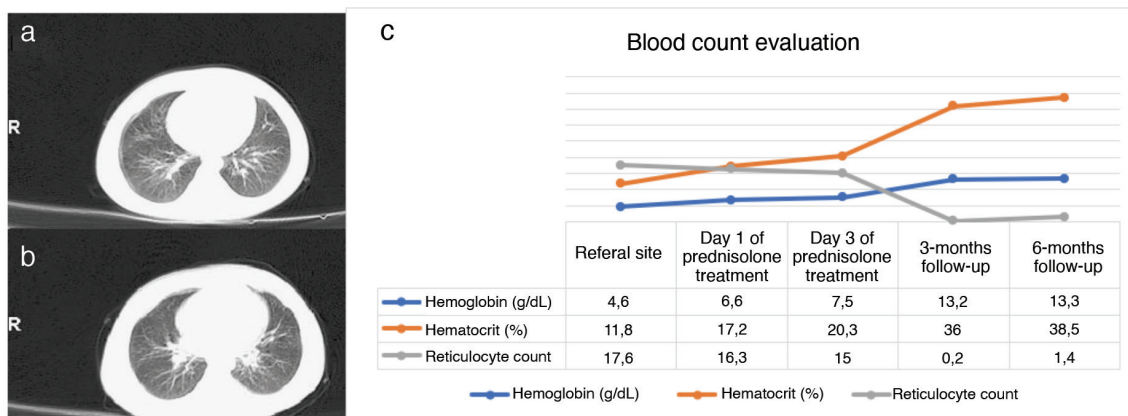
### CASE REPORT

A 10-month-old male from a rural area of the Caribbean coast of Colombia presented with a clinical picture of a one-month evolution consistent with diminished physical activity and regression of psychomotor skills. The caregiver noticed mucocutaneous pallor. Previously, the patient presented with a dry cough and liquid depositions over an approximate four-day period that coexisted with the beginning of the deterioration of the infant's general well-being. On physical examination, anthropometric measurements were evaluated as 8 kg for weight and 77 cm for height, with z-scores of -1.48 and +1.22, respectively. The z-score for weight-for-length was -3.39, according to child growth standards by the WHO (10). Considering these measurements, the patient was at risk of poor nutrition.

The child also presented with reactive cervical adenopathies, an active respiratory process, and an ejective systolic murmur of grade II/VI secondary to severe anemia. Upon evaluation at the local primary care center, fever was not documented, though several paraclinical studies were performed in which several abnormalities were noted: hemoglobin 4.6 g/dL, mean corpuscular volume (MCV) 113  $\mu\text{m}^3$ , 14% reticulocytes, and lactic dehydrogenase (LDH) positivity. A blood transfusion was performed with packed red blood cells leukoreduced to

10 mL/kg without adverse reactions post-transfusion and with an increment of hemoglobin to 7.2 g/dL, decreasing after 24 hours to 6.6 g/dL. Considering the family history of unspecified anemia in his mother and maternal grandmother, qualitative antiglobulin, anti-IgG, and anti-C3d tests were requested, which showed a positive result. The patient was referred to "Fundación Hospital Infantil Napoleón Franco Pareja" where, due to respiratory and gastrointestinal symptoms, reverse transcription-polymerase chain reaction for SARS-CoV-2 was performed. Extension paraclinical studies were performed (Table 1) to support diagnostic imaging, such as a chest X-ray, which showed evidence of a reticular interstitial pattern without other relevant clinical findings. A thoracic computed tomography scan revealed vascular engorgement and thickening of the perilobular septa (Figures 1a, b). Doppler ultrasound did not indicate anomalies.

A qualitative polyspecific human antiglobulin anti-IgG and anti-C3d direct tests were negative, with an MCV of 106  $\mu\text{m}^3$ , a rise in reticulocytes (17.2%), low hyperbilirubinemia (1.99 mg/dL), high indirect bilirubin (1.46 mg/dL), and elevated glucose-6-phosphate dehydrogenase (16.8  $\mu\text{g}/\text{mL}$ ). A new transfusion of packed red blood cells was indicated, and COVID-19 was confirmed by molecular testing. Post-transfusion paraclinical results showed qualitative anti-IgG and anti-C3d positivity, elevated LDH (853 U/L), and falsely elevated MCV due to agglutination and reticulocytosis. The patient was treated with nutritional support, 1 mg/kg of prednisone orally per day, and transfusion was indicated to manage the patient's hemoglobin stabilization after three days of treatment (Figure 1c). He was discharged with multidisciplinary outpatient follow-up and oral corticoid medication. Three months later, the patient's weight increased to 9 kg with a z-score of -0.97 and his height to 78 cm with a z-score of +0.16. However, the risk of poor nutrition persisted, as his z-score for weight-for-length was -1.9, according to WHO standards (10). Anthropometric parameters were still



**Figure 1:** CT scan and evolution in blood count with corticoid therapy. The coronal cut of the CT scan, the parenchymal window, denotes a tendency toward an increase in interlobular septa (a), and vascular engorgement (b). All these findings are described as indeterminate in SARS-CoV-2 infection. The figure shows the evolution in blood count results for hemoglobin, hematocrit, and reticulocyte count before and after corticoid therapy. Hemoglobin and hematocrit levels increased 72 hours after oral corticosteroid therapy. Three and six months after hospitalization, the blood count parameters were normalized with remission of symptoms (c).

SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, CT: Computed tomography

recovering six months later, and multidisciplinary follow-up is being continued.

## DISCUSSION

In this clinical case, AIHA overlapped with an active SARS-CoV-2 infection without any platelet or coagulation alteration. The qualitative polyspecific anti-human globulin test was negative at admission, which might be a false-negative due to technical difficulties such as cellular concentration, inadequate centrifugation, sample concentration, incubation temperature, or host reasons such as rheumatoid factor, mediated hemolysis for IgA or IgM (6). With this negative result, it was impossible to make a proper diagnosis. The antiglobulin test was repeated, improving the technique, with qualitative anti-IgG and anti-

C3d positivity. The initially altered blood count (hemoglobin, hematocrit, and reticulocytes) parameters stabilized between 48 and 72 hours after the use of oral corticoids (Figure 1c). MCV was also normalized.

Other infectious and noninfectious etiologies of AIHA were discarded, as were medications. In this case, the epidemiological nexus was SARS-CoV-2 infection, a cause not considered in pediatric patients and even less in infants.

Hematological complications of COVID-19 are few and primarily related to idiopathic thrombocytopenia purpura and Evans syndrome. The mechanism that mediates the autoimmune response to COVID-19 remains unclear. The possible abnormal expression on the endothelial surface of host protein epitopes has been proposed as a cause (4). Another hypothesis is

**Table 1: Blood analysis of the patient.**

Paraclinical test for infectious etiology	
Epstein-Barr, VCA IgM antibody	2.7 (negative)
Epstein-Barr, EBNA IgM	0.1 (negative)
<i>Mycoplasma pneumoniae</i>	IgG (-) IgM (-)
Parvovirus B19	IgG (-) IgM (-)
HIV-1 and HIV-2	Non-reactive
Cytomegalovirus (CMV)	IgG (-) IgM (-)
SARS-CoV-2 RT-PCR	Positive
SARS-CoV-2 antibodies	IgG positive IgM negative
VDRL	Non-reactive
Immunoglobulins	
IgA	96 mg/dL (10-100)
IgG	1669 mg/dL (330-1160)
IgM	104 mg/dL (40-170)
Others	
Ferritin	641 ng/mL (7-140)
D-dimer	2.46 mg/mL (<0.25 mg/dL)
Bilirubin	Total bilirubin 1.99 mg/dL Indirect bilirubin: 1.46 mg/dL Direct bilirubin: 0.53 mg/dL
Coagulation time	Prothrombin time test: 12 seconds (control 13) Partial thromboplastin time: 23.7 seconds (control 27.4)
Qualitative antiglobulin test	Negative (admission) Positive (control at 48 hours)
Troponin I	0.004 ng/mL (Negative)
Lactic dehydrogenase (LDH)	853 U/L (170-580)
Erythrocyte sedimentation rate (ESR)	23 mm/h (0-10)
Ureic nitrogen (BUN)	8.1 mg/dL (5-18)
Creatinine	0.55 mg/dL (control 0.46)
Blood smear	Erythroid line: Moderate hypochromia and polychromatophilia, macrocytes +, microcytes ++. Leukocyte line: Without alterations. Platelet line: Without alterations.
Hemoglobin electrophoresis	Hemoglobin: type A: 97.8% type A2: 2.2%
Glucose-6-phosphate dehydrogenase	16.8 ug/mL (3.4-8.8)
Antinuclear antibodies (ANA)	Negative

RT-PCR: Reverse transcription-polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, VCA: Viral capsid antigen, EBNA: Epstein-Barr nuclear antigen, HIV: Human immunodeficiency virus, BUN: blood urea nitrogen

regarding molecular mimicry between ankyrin-1 (ANK-1) and the spike protein, which is the most supported cause of AIHA to date. ANK-1 is a protein that participates in the differentiation and formation of the skeleton of red blood cell membranes. Defects in this protein are associated with hemolytic anemia, such as hereditary spherocytosis; this protein 100% shares an immunogenic-antigenic epitope with the spike protein of SARS-CoV-2 (11).

Immune alteration due to SARS-CoV-2 in severe cases can produce multisystem inflammatory syndrome in children (MIS-C). Moreover, complications such as hemolytic anemia may occur even in children under five years old (3).

Although it has been documented in adults, few pediatric cases have been published before. One study about this condition in pediatric patients included seven patients, four of whom also had B-lymphoid malignancies previously discovered or already diagnosed during hemolytic syndrome (12). Cases such as this one have been reported, but not in children under five years old.

Autoimmune hemolytic anemia is a rare condition in childhood, and the incidence is underestimated. In 2011, a French study reported an annual incidence of 1 to 3 cases per 100,000 people and approximately 0.2 cases per 1,000,000 people under 20 years of age (13). In another study, eight children with systemic complications for COVID-19 were reported, providing evidence of the similarities between the pathology and autoimmune diseases (4, 14). The immune response is mediated by two pathways: warm antibodies and cold antibodies. The most common pathway in pediatric patients is the disease via warm antibodies. Because viral infections have been associated with immune disruption, this entity is deadly, and it is essential for pediatricians to be aware of it; strict multidisciplinary follow-up is required (15).

The parents of this patient were informed about his clinical situation and showed receptivity to the current medical treatment. The patient was discharged with 1 mg/kg/d of prednisone by mouth and poor adherence to management. However, at the 3- and 6-month follow-ups, his anthropometric and neurological state had improved, and normalization of cellular counts and inflammatory markers occurred.

This was a case of an infant without comorbidities who was previously healthy. Anthropometric measurements of the patient one month prior to the disease were in the normal range according to WHO standards (10). The findings suggest an association between COVID-19 and AIHA, making it necessary to explore and consider AIHA as a possible hematologic and immune complication.

It is necessary to clarify the pathophysiological pathways implicated in the dysregulation of the immune system

during SARS-CoV-2 infection, such as the molecular mimicry hypothesis. More research on this topic is needed. To date, all AIHA patients with COVID-19 have shown great recovery.

**Ethics Committee Approval:** N/A

**Informed Consent:** Informed consent was obtained.

**Conflict of Interest:** The authors declared no conflict of interest.

**Author Contributions:** Surgical and Medical Practices: J.D.A., K.T.B., M.G.R., A.G.C., H.P.R., Concept: J.D.A., K.T.B., M.G.R., A.G.C., H.P.R., D.F.R., Design: J.D.A., D.F.R., Data Collection and/or Processing: J.D.A., K.T.B., M.G.R., A.G.C., H.P.R., Jo.D.A., D.F.R., Analysis and/or Interpretation: J.D.A., K.T.B., M.G.R., A.G.C., H.P.R., D.F.R., Literature Search: J.D.A., K.T.B., Jo.D.A., D.F.R., Writing: J.D.A., Jo.D.A., D.F.R.

**Financial Disclosure:** The authors declared that this study received no financial support.

## REFERENCES

- Pollard CA, Morran MP, Nestor-Kalinowski AL. The COVID-19 pandemic: a global health crisis. *Physiol Genomics* 2020;52(11):549-57. [Crossref]
- Brodin P. Why is COVID-19 so mild in children? *Acta Paediatr* 2020;109(6):1082-3. [Crossref]
- Bhuiyan MU, Stiboy E, Hassan MZ et al. Epidemiology of COVID-19 infection in young children under five years: a systematic review and meta-analysis. *Vaccine* 2021;39(4):667-77. [Crossref]
- Salle V. Coronavirus-induced autoimmunity. *Clin Immunol* 2021;226:108694. [Crossref]
- Rosenzweig JD, McThenia SS, Kaicker S. SARS-CoV-2 infection in two pediatric patients with immune cytopenias: a single institution experience during the pandemic. *Pediatr Blood Cancer* 2020;67(9):e28503. [Crossref]
- Berentsen S. New insights in the pathogenesis and therapy of cold agglutinin-mediated autoimmune hemolytic anemia. *Front Immunol* 2020;11:590. [Crossref]
- Vehapoglu A, Gökknar N, Tuna R et al. Ceftriaxone-induced hemolytic anemia in a child successfully managed with intravenous immunoglobulin. *Turk J Pediatr* 2016;58(2):216-9. [Crossref]
- Fattizzo B, Barcellini W. Autoimmune hemolytic anemia: causes and consequences. *Expert Rev Clin Immunol* 2022;18(7):731-45. [Crossref]
- Seltsam A, Shukry-Schulz S, Salama A. Vaccination-associated immune hemolytic anemia in two children. *Transfusion* 2000;40(8):907-9. [Crossref]
- World Health Organization (WHO). Child growth standards. 2023. Available from: <https://www.who.int/tools/child-growth-standards/standards/weight-for-age>. [Crossref]
- Angileri F, Légaré S, Marino Gammazza A et al. Is molecular mimicry the culprit in the autoimmune haemolytic anaemia affecting patients with COVID-19? *Br J Haematol* 2020;190(2):e92-3. [Crossref]
- Lazarian G, Quinquenel A, Bellal M et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol* 2020;190(1):29-31. [Crossref]
- Ladogana S, Maruzzi M, Samperi P et al. Diagnosis and management of newly diagnosed childhood autoimmune haemolytic anaemia. Recommendations from the red cell study group of the paediatric haemato-oncology Italian association. *Blood Transfus* 2017;15(3):259-67. [Crossref]
- Riphagen S, Gomez X, Gonzalez-Martinez C et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020;395(10237):1607-8. [Crossref]
- Voulgaridou A, Kalfa TA. Autoimmune hemolytic anemia in the pediatric setting. *J Clin Med* 2021;10(2):216. [Crossref]