

# Vasculitis in the Pediatric Patient with COVID-19: What is the Role of Perinuclear Anti-Neutrophil Cytoplasmic Antibodies in the Pathophysiology?

Keren Paola Osorio-Mendoza<sup>1</sup>, Leonardo Eduardo Dussan-Duque<sup>2</sup>, Valentina Negrete-Perez<sup>1</sup>, Diana Carolina Ortiz-Torres<sup>3</sup> and Md Moshur Rahman<sup>4\*</sup>

<sup>1</sup> School of Medicine, Universidad de Sucre, Sincelejo, Colombia.

<sup>2</sup> School of Medicine, Universidad Antonio Nariño, Bogotá, Colombia.

<sup>3</sup> School of Medicine, Universidad Metropolitana, Barranquilla, Colombia.

<sup>4</sup> Assistant Professor, Neurosurgery Department, Holy Family Red Crescent Medical College, Dhaka, Bangladesh.

**\*Corresponding Author:** Dr. Md Moshur Rahman, Assistant Professor, Neurosurgery Department, Holy Family Red Crescent Medical College, 1 Eskaton Garden Rd, Dhaka 1000, Bangladesh.

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The COVID-19 pandemic has been one of the most important public health problems of the 21st century. It has affected all age groups and all areas of human life, requiring organizational modifications and rapid updates of clinical practice guidelines. Pediatric patients may be one of the most affected groups, because the process of growth and development depends on social interaction, lifestyle, nutrition, and physical and psychological well-being [1]. Another challenge in this group is the early and appropriate management of COVID-19, multisystemic inflammatory syndromes and associated complications [2]. Keshavarz et al [2] conducted a systematic review where they evaluated 133 children who developed Kawasaki disease associated with COVID-19, finding that 55.6% of these cases should be managed in the Pediatric Intensive Care Unit, 36.8% needed respiratory support and more than 20% required intubation or mechanical ventilatory support [2]. Approximately 10% of these patients die due to severe heart failure, shock and cerebral infarction, substantially compromising the functional prognosis of those who develop these complications and do not die [2].

Another inflammatory syndrome that has become important during the acute phase of COVID-19 and post-COVID-19 syndrome is perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) vasculitis, which can be symptomatic or asymptomatic, and fatal. Fireizen et al [3] reported the case of a 17-year-old adolescent who, two months after developing COVID-19 pneumonia, presented to the emergency department with acute renal failure and diffuse alveolar hemorrhage, with positive myeloperoxidase and P-ANCA markers [3]. The patient underwent renal biopsy, showing evidence of necrotizing glomerulonephritis with immune complex deposition [3], which adversely modifies the functional renal prognosis of this adolescent throughout his life, as demonstrated in the cases of Izci Duran et al [4], where their patients were discharged with hemodialysis.

Reiff et al [5] reported a case of P-ANCA vasculitis during the acute phase of an adolescent with COVID-19, which made the management of multi-organ lesion and complications even more difficult [5]. Two other situations are the presentation of asymptomatic vasculitis and the development of post-vaccination vasculitis, both of which remain a mystery [6,7]. Unfortunately, not much is yet known about the pathophysiology of P-ANCA vasculitis not associated with COVID-19 [8]. There are several phenotypes, depending on the expression of certain proteins, such as PR3-ANCA (proteinase 3-anti-neutrophil cytoplasmic antibodies) which is associated with granulomatous vasculitis, or MPO-ANCA (myeloperoxidase-anti-neutrophil cytoplasmic antibodies) which is associated with small vessel necrotizing vasculitis [8]. In vitro studies have shown that ANCA stimulates neutrophils to produce reactive oxygen species and lytic enzymes, proinflammatory molecules, such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin (IL) 1 and IL 18, which causes dysregulation of neutrophil adhesion molecules and translocation of antigens to the membrane surface of vessels of different tissues, generating transmigration and local inflammation [8].

In the case of COVID-19, where there is a diverse, active and progressive inflammatory state, it can be presumed that depending on unknown genetic and/or risk factors, this specific hyperreactivity can generate and damage target organs such as the kidney [3-6]. However, knowing that the multisystem inflammatory state by COVID-19 can injure other organs such as brain and heart, it is a challenge to try to simultaneously manage the suppression of the inflammatory response and the evolution of SARS-Cov-2 viral activity. In this order of ideas, P-ANCA vasculitis is a question that should be debated by the pediatric clinical, scientific and social community, allowing the timely detection and classification of the disease and phenotype, adequate multidisciplinary approach and establishment of a prognosis that allows planning a rehabilitation process to ensure the recovery and maintenance of the functional capacity of the pediatric.

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