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RESEARCH LETTER

PEDIATRIC INFLAMMATORY MULTISYSTEM SYNDROME DUE TO SARS-COV-2 INFECTION OR RECENT VACCINATION

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Given the hypothesis that Pediatric Inflammatory Multisystem Syndrome (PIMS) is associated with immune dysregulation precipitated by SARS-CoV-2 infection[1,2,3,4], similar vaccine-related immunological effects in children could be of concern.[5] PIMS temporally associated with COVID-19 vaccines may pose substantial diagnostic and therapeutic challenges.[9] Nonetheless, a lower incidence of PIMS has been observed in vaccinated children when compared to unvaccinated children with COVID-19, with very few case reports, although some needing intensive care treatment.[3,4,5,6,7,8] A study evaluating vaccine effectiveness in 24 hospitals of 20 different states in the United States (US) showed that 95% patients aged 12-18 years hospitalized with PIMS were unvaccinated, and only unvaccinated children with PIMS required intensive care.[6] Similarly, other studies demonstrated that vaccination in children and adolescents confers a high level of protection against COVID-19 hospitalization.[4,7]

Surveillance in the US, using results from Centers for Disease Control and Prevention´s (CDC) National Surveillance System, Vaccine Adverse Event Reporting System and CDC's Clinical Immunization Safety Assessment Project, also suggested that PIMS after COVID-19 vaccination is a rare event, when accessing children and young adults aged 12 to 20 years, between December 2020 and August 2021. There were only 21 PIMS reported cases after immunization, of which six had no previous SARS-CoV-2 infection [negative Polymerase chain reaction (PCR) results and negative anti nucleocapsid (anti-NP) antibodies], raising awareness of a possible causal event. Overall, this surveillance showed that vaccination was associated with a high level of protection against PIMS, highlighting its importance among eligible children.[3]

A similar pharmacovigilance surveillance study in France, conducted between June 2021 and January 2022, showed that only eight out of 4 079 234 vaccinated adolescents (12-17 years) presented with PIMS without evidence of previous SARS-CoV-2 infection. This rare adverse event should be weighed against the rate of post-SARS-CoV-2 multisystemic inflammatory syndrome in the same age group, which was much higher.[8] These studies on vaccine effectiveness show that, in large vaccinated populations, the occurrence of events after vaccination does not necessarily imply causation.[3,4,5,6,7,8]

SARS-CoV-2 infection antibody response leads to the development of both anti spike protein (anti-SP) and anti-NP specific antibodies, but vaccination is only capable of producing anti-SP vaccine antibodies.[5,6] IgG anti-NP and IgG anti-SP antibodies after natural COVID-19 infection can generally be detected within approximately one to three weeks after the onset of symptoms. A similar interval can be seen for IgG anti-spike antibodies following COVID-19 immunization. The longevity of measurable antibody responses to natural SARS-CoV-2 infection can vary among individuals, ranging from several months to more than a year. The level and duration of these antibody responses may decline over time, and can be influenced by factors such as severity of infection and each person's immune system. Long-term immunity may also involve memory B cells and T cells, even if antibody levels wane. Regarding vaccination, generally measurable antibody responses can persist for at least several months, but the exact duration of protection also differs from person to person.[5,6]

The management of PIMS is still controversial. According to the American Academy of Pediatrics, the American College of Rheumatology and the National Institute of Health in the US, initial therapy usually starts with intravenous immunoglobulin (IVIG) alone in patients with mild disease, especially if the patient has a preexisting condition that may warrant avoidance of glucocorticoids (for example, diabetes mellitus, hypertension, obesity). A stepwise progression adding low to moderate dose glucocorticoids also may be part of the initial approach or may be given if, despite treatment with IVIG, persistent fevers or rising inflammatory markers are seen. High dose glucocorticoids or biologics should be used as

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intensification therapy in patients with refractory disease. Notwithstanding, if IVIG is not available, treating patients with systemic glucocorticoids alone is also acceptable.[10,11,12] On the other hand, observational cohort studies in the United Kingdom, when evaluating IVIG as a reference, compared this procedure with using IVIG plus glucocorticoids or glucocorticoids alone.[13,14,15] They found no substantial differences, among children with suspected PIMS, when accounting for the need of inotropic support or mechanical ventilation, reduction in disease severity and death. Even more, when restricting the analyses to patients who met the World Health Organization (WHO) criteria for PIMS, there was modest evidence of benefit of using glucocorticoids alone over IVIG alone for the outcomes described above.

Vaccination of children and adolescents has been shown to be protective against PIMS. The measure of anti-SP and anti-NP antibodies is important in differentiating a post vaccine from post SARS-CoV-2 infection, since SARS-CoV-2 infection antibody response leads to the formation of both anti-SP and anti-NP antibodies, but vaccination is only capable of producing anti-SP antibodies.

Even though it is rare, PIMS can still occur after immunization, however, it is almost always a post-infectious event not related to vaccination. The development of PIMS after SARS-CoV-2 immunization is currently considered an uncertain event, and further research is needed to establish a clear causal relationship. Therefore, the occurrence of events after vaccination does not necessarily imply causation.

Compliance with Ethical Standards

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Conflict of Interest None

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