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Children Multisystem Inflammatory Syndrome Associated with COVID: Updates of the Literature

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Abstract **Review Article**

The current investigation was carried out because of the realization that although though the effects of COVID-19 in children are milder in comparison to those in adults, severe symptoms can still be seen in children. This realization led to the decision to carry out the study. Multiple nations have reported cases of children exhibiting symptoms of a multisystem inflammatory syndrome that has been linked to COVID-19. The primary purpose of this investigation was to conduct a literature search focusing on this syndrome and the effects it has on children. According to the findings of this work, a severe acute infection with COVID-19 can put children at risk for developing a multisystem inflammatory syndrome that can be fatal. Several organs, including the kidneys and lungs, are susceptible to damage from this. The treatment of this syndrome was another topic of conversation. When considered together, a severe acute infection with COVID-19 or an infection with MIS-C can result in illnesses that have the potential to be fatal in children. This is especially true when the infections are combined.

Keywords: COVID-19, multisystem inflammatory syndrome, children, lung, kidney.

1. INTRODUCTION

The current study was carried out because of the considerations that COVID-19 has several impacts on children, including multisystem inflammatory syndrome. These considerations led to the decision to carry out the investigation. The decision to carry out the study was influenced by the criteria. In the following sections, which will come after this one, a more in-depth investigation into the effects of COVID-19 on the progression of children's multisystem inflammatory syndrome is going to take place.

2. An overview of Children multisystem inflammatory syndrome COVID

It is possible for numerous organs and bodily systems in a child's body to become inflamed at the same time, which is referred to as the illness known as "multisystem inflammatory syndrome in children" (MIS-C) (Waseem *et al*., 2022). The heart, lungs, kidneys, brain, skin, eyes, and gastrointestinal organs are all examples of systems that fall under this category (Yuki *et al*., 2020). At this time, we do not have any clue as to what causes MIS-C in persons. On the other hand, we are aware that a sizeable number of children who tested positive for MIS-C were in contact with an individual who had COVID-19 or had the virus that causes COVID-19 (Waseem *et al*., 2022). After getting medical therapy, most children who have been diagnosed with this condition have seen signs of improvement. The MIS-C is a dangerous condition that even has a chance of causing death (Russell *et al*., 2020).

MIS-C was discovered early in the pandemic. This suggests SARSCoV-2. Hyperinflammation and multiple organ system involvement are indications of MIS-C, which affects children and adolescents. Half of these individuals have cardiovascular issues, which can be fatal. These two illnesses have similar diagnostic criteria, which can make it difficult to distinguish them (Levin *et al*., 2020).

3. The impacts of MIS-C on immunological impairment

Researchers are working hard to understand out how MIS-C triggers immunological dysregulation, although the exact mechanism is not yet completely understood. The fact that there was a latent period between the peak of initial COVID-19 infection and the onset of MIS-C, as well as the observation that the majority of children diagnosed with MIS-C have a

positive SARS-CoV-2 IgG test but a negative polymerase chain reaction (PCR) test, both point to a post-infectious etiology being the most likely explanation (Dufort *et al*., 2020; Whittaker *et al*., 2020). A mechanism for the development of MIS-C has been hypothesized, and it involves either an uncontrolled cytokine storm involving hyperinflammatory markers such as tumor necrosis factor- (TNF-), interleukin (IL)-1b, and IL-6 and interferon-alfa, or a superantigen-like motif in the "spike" protein. Both of these possibilities involve a superantigen-like motif in the "spike" protein (Molloy and Bearer, 2020; Pang *et al*., 2020; Tezer and Demirdağ, 2020).

4. Epidemiology of MIS-C

Europe, North America, Asia, and Latin America report more children and adolescents with COVID-19-associated multisystem inflammatory diseases. The severe acute respiratory syndrome-causing coronavirus is spreading worldwide. COVID-19's link to children's multisystem inflammatory illness is uncertain. This study examines the epidemiology, etiology, clinical characteristics, and therapy of COVID-19-associated multisystem inflammatory disease in children and adolescents. The researchers also studied COVID-19-induced inflammatory pathways. These processes can damage organs in severely ill children. These findings illuminate future therapeutic methods, the possibility of a vaccination, and the need for a precise case definition and treatment procedure for this rare disease (Jiang *et al*., 2022).

Since December 2019, the COVID-19 pandemic, caused by SARS-CoV-2, has spread worldwide. Wuhan reported the first unidentified pneumonia cluster. As of August 5, 2020, COVID-19 has caused over 18 million cases and 690,000 deaths (WHO, 2020). Laboratory testing has shown COVID-19 infection in a small percentage of this age group (Jiang *et al*., 2022). National statistics from Asia, Europe, and North America showed 2.1–7.8% of COVID-19 cases were among children and adolescents (Epidemiology Working Group for NCIP Epidemic Response, 2020; European Centre for Disease Prevention and Control, 2022; Government of Canada Coronavirus disease 2019; Government of Pakistan, 2022).

The disease burden of children and teens is still unknown. Asymptomatic infections, underdiagnosis of clinically silent or mild cases (typically in younger people), and the availability, validity, and targeted strategies of current testing methods contribute to this. Patient-asymptomatic infections Clinically silent or mild cases require no treatment (such as testing for viruses rather than serological testing). Even though the symptoms are less severe in children than in adults, a minority of children will need to be hospitalized and treated in intensive care to recover (Sanna *et al*., 2020).

5. Pathogenesis of MIS-C

Over the past three months, Europe, North America, Asia, and Latin America have reported more children and adolescents with COVID-19-associated multisystem inflammatory conditions. These conditions appear to develop after COVID-19 infection, affecting multiple body systems. These conditions are unexplained. Some inflammatory syndromes in children have been well-described. Kawasaki disease, toxic shock syndrome, and shock syndrome are examples. These illnesses and these pediatric cases have comparable and different symptoms (Jones *et al*., 2020; Jiang *et al*., 2022). Multisystem inflammatory syndrome COVID is also known as pediatric inflammatory multisystem syndrome temporally linked with SARS-CoV-2 (PIMS-TS) (Jiang *et al*., 2022). Multiple organ failure and shock from MIS-C require intensive care unit therapy. As a response to MIS-C, the European and US Centers for Disease Prevention and Control (CDC), the Australian Department of Health, and WHO have issued scientific briefs or advisories (Jiang *et al*., 2022).

6. Biology of COVID-19

Positive-sense single-stranded RNA coronavirus family is large. Herpesviruses, coronaviruses, and polioviruses are known (Woo *et al*., 2010). The six human coronavirus species has two strains. Beta coronaviruses include SARS-CoV, SARS-CoV-2, and MERS. SARS-CoV-2, like other coronaviruses, can be spread by close contact with contaminated surfaces. Lung, alveolar, cardiac, endothelial, and some immune cells express angiotensin-converting enzyme (Government of Canada Coronavirus disease 2019, 2022). Angiotensin-converting enzyme 2, which is abundant in these cells, binds the virus (Huang *et al*., 2020). COVID-19 pathophysiology is being studied. Dysregulated innate immune response, cytokine storm, endothelial damage, and may cause severe COVID-19, which can cause acute lung injury, acute respiratory distress syndrome, and multiple organ failure (Varga *et al*., 2020). The innate immune system needs neutrophils. Neutrophil extracellular traps result (NETs) (Fuchs *et al*., 2020). NETs are lattice-shaped and made of cell-free DNA, histones, and neutrophil granules, which contain bacteria-killing proteins and enzymes. NETs cause sepsis, thrombosis, and respiratory failure. Many viruses increase neutrophil NETosis (Jiang *et al*., 2022). Uncontrolled inflammatory and immunological reactions can cause MIS-hyperinflammation-like systemic inflammation. Virus-induced NETs capture viruses. C's Zuo *et al*., (2020) found higher plasma NET levels in SARS-CoV-2 respiratory failure patients. COVID-19 can cause thrombosis. MIS-C often has abnormal coagulopathy (e.g., increased D-dimer or fibrinogen). NETs may cause MIS-C because NETosis promotes thrombosis (Zuo *et al*., 2020).

7. The impacts of COVID-19 on children

COVID-19 affects few children. Most kids and teens have mild SARS-CoV-2 symptoms (Jiang *et al*., 2022). Pediatric acute respiratory distress syndrome is rare. MIS-C, a new pediatric COVID-19 issue, may cause severe clinical signs. MIS-C infections begin one month after COVID-19 peaks. Public Health England reported more MIS-C cases on April 16, 2020. Four weeks after the UK COVID-19 pandemic (Jiang *et al*., 2022). Comparable findings were found in the US (n = 89), France (n = 68), and elsewhere. Second, children often have SARS-CoV-2 infections. RT-PCR only detects 30% of MIS-C cases with SARS-CoV-2 antibodies. SARS-CoV-2-induced immune responses may cause this inflammatory state (Jiang *et al*., 2022).

Selva *et al*., (2020) found significant differences between children's and adults' antibodies against coronavirus proteins in COVID-19 patients. Fc receptor binding and antibody subgroup concentrations affected responses. These findings suggest that antibody response may contribute to adult COVID-19-related inflammation. MIS-C investigations are required. Due to their similarities, MIS-C and adult hyperinflammatory response may involve antibodies. Gruber and colleagues91 found that SARS-CoV-2-neutralizing antibodies in MIS-C patients activated IL-18, IL-6, myeloid chemotaxis, lymphocytes, monocytes, and natural killer cells. Initial analysis revealed this. Fc-receptor 1 and intercellular adhesion molecule 1 upregulation on neutrophils and macrophages increased antigen presentation and Fc-mediated responses. Gruber *et al*., (2020) found endothelium, stomach, and immune cell autoantibodies in MIS-C patients.

Like dengue, SARS-CoV antibodies may cause inflammation or help the virus enter and multiply. SARS-CoV-2 inflammation may use similar pathways. MIS-C patients rarely contract SARS-CoV-2, so antibody-dependent inflammation is likely caused by an acquired immune response. Anti-SARS-CoV spike antibodies cause inflammation in primates and human macrophages95. Anti-SARS-CoV-2 antibodies may cause inflammation like other antibodies (Jiang *et al*., 2022). Hoepel *et al*., (2020) found that patient anti-spike antibodies activate macrophages, supporting SARS-CoV-2.

Both the Kawasaki illness and the inflammatory diseases that can be caused by SARS-CoV-2 can develop to cardiac aneurysms. Kawasaki illness resembles SARS-CoV-2 disorders. According to these findings, the virus might be functioning as the immunological trigger and causing immune-mediated damage to the heart and coronary arteries, just way it is seen in Kawasaki illness. Like Kawasaki disease. This condition causes an injury that is comparable to the one observed in Kawasaki illness. Immune complexes are abundant in Kawasaki illness patients (Menikou *et al*., 2019). These immune complexes may damage blood vessels by activating the Fc receptor or complement.

8. MIS-C management

Several organizations have released MIS-C management guidelines, however there are no mainstream recommendations. Medical practitioners in some centers developed COVID-19 treatment procedures based on the adult guidelines. Based on symptoms, prior Kawasaki disease treatments, etc., these procedures were created. Multidisciplinary teams should treat MIS-C. This plan should include a pediatric infectious diseases unit, cardiology, immunology, rheumatology, and critical care teams. If the PCR test shows SARS-CoV-2, this strategy should consider immunotherapy, antivirals, or both. General supportive care, including vital signs, hydration, electrolytes, and metabolic status, is essential. Hypoxia and respiratory impairment are rare in children, but they must be always monitored (Jiang *et al*., 2020).

Two-thirds of MIS-C patients require intensive care after diagnosis. Multiple US-based studies led to these conclusions (Delahoy *et al*., 2021). Due to the global epidemic and the rarity of MIS-C, data on the best treatment is scarce and primarily comes from observational research. Because the pandemic is global. The consensus-based therapy guidelines emphasize immunomodulation like KD. IVIG and corticosteroids are often administered for immunomodulation. Corticosteroids usually start intravenously. The patient is then shifted to an oral regimen and the dosage is gradually lowered using physiologic principles until they are discharged. On the first day of treatment, extremely severely ill patients in the Overcoming COVID-19 US Network were given intravenous immunoglobulin mixed with steroids. 47% of patients were taking vasopressors, and 41% had a reduced ejection fraction (Abrams *et al*., 2020). After the initial treatment day, fewer patients needed immunomodulatory treatments. They received additional treatment. The international Best Available Treatment Study (BATS) found no difference in MIS-C recovery rates between IVIG alone, corticosteroids alone, or combined IVIG and corticosteroids. IVIG, corticosteroids, or both were compared for recovery rates (McArdle *et al*., 2021). Despite employing a broader definition of MIS-C than the US sample, BATS patients were healthier. To resolve cardiovascular difficulties faster, critically unwell individuals should be treated aggressively early. Anakinra, an IL-1 inhibitor, and tocilizumab, an IL-6 inhibitor, have been studied, although their efficacy is unknown. Some hospitals treat refractory MIS-C with anakinra. IVIG with infliximab helped children recover faster in a single-site study (a TNF-a inhibitor) (Cole *et al*., 2012). Hypercoagulable patients often undergo immunomodulatory and anticoagulant treatments. Common practice. CAA and thrombosis risk drive this practice. After hospital admission to the intensive care unit, low-molecular-weight heparin is commonly started. In

some settings, KD treatment includes low-dose aspirin. Long-term benefits of anticoagulation are unknown. If the patient has a CAA, anticoagulants are usually continued after hospital release and follow-up echocardiogram for severe COVID-19 and MIS-C in children (Allison *et al*., 2022). Even when the patient has CAA. Depending on their state, the patient receives vasoactive support and hydration management. Provided always. Multiple echocardiograms are needed to track heart function decline. Antibiotics are often continued until blood and other cultures are negative to rule out sepsis (Allison *et al*., 2022).

Most children with MIS-C make a full recovery. Death rates for MIS-C patients in the US range from 1% to 2% (Feldstein *et al*., 2021). In a UK case study, the hyperinflammation of most individuals resolved between six and twelve months after the diagnosis (Farooqi *et al*., 2021). Four percent to seventeen and a half percent of hospitalized patients have coronary aneurysms, but the vast majority recover within three months (McMurray *et al*., 2020; Feldstein *et al*., 2021). Although the prognosis for these children's long-term health is not yet known, there is a high likelihood that they will make a full recovery if they receive prompt treatment at presentation. Long-term effects on the heart are now being investigated. After they have been discharged, MIS-C children are followed by specialists in rheumatology, cardiology, and infectious illness (Allison *et al*., 2022).

CONCLUSIONS

Both a severe acute infection with COVID-19 or an infection with MIS-C can result in illnesses that have the potential to be deadly in children and adolescents. We are extremely fortunate that the clinical prognosis for severe COVID-19 in children is considerably better than those in adults, and that death is a rather uncommon event among these patients. Due to the rarity of COVID-19 and MIS-C, conducting research on the most effective treatment choices for severe and acute cases of these diseases is challenging. Furthermore, there is a dearth of reliable data pertaining to the treatment of children and adolescents. Because of this, it is difficult to determine which treatment options are the most effective. Most hospitals and medical institutes have successfully treated critically ill children suffering from acute COVID-19 illnesses by applying the knowledge they gained from studies carried out on adults. In order to facilitate the diagnosis and treatment of MIS-C, consensus recommendations have been made, and treatment algorithms that are analogous to those utilized for KD have been developed.

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