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Multisystemic Inflammatory Syndrome in COVID-19 in Children; A Narrative Review

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Introduction

In 2020, an unexpected pandemic occurred after the detection of certain pneumonia cases of unknown etiology in Wuhan city, Hubei province, China. On January 7, 2020, the etiological agent was detected and found to be a novel coronaviridae, named COVID-19 later termed SARS-CoV-2. Further analyses indicated that SARS-CoV-2 is the seventh member of the coronaviridae family, which includes SARS-CoV and MERS-CoV as highly pathogenic members. To contain the outbreak and halt the subsequent human-to-human transmission, surgical mask use and symptom monitoring were implemented in Wuhan. The WHO declared a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and on March 11, 2020, upgraded it to a pandemic [1].

According to the WHO, more than 748 million cumulative cases and approximately 6.9 million confirmed deaths have been reported worldwide regarding COVID-19, with a mortality rate of ~0.9%. Although SARS-CoV-2 infects all age groups, children are less susceptible than adults. Many studies have suggested that there is a significant but weaker infection risk of SARS-CoV-2 in children compared to adults, as well as a mild disease severity and better prognosis in infected children. Globally, pediatric cases ~~have~~ represented 0.9%-3% of cumulative cases. As of December 2020, 43 reported deaths in children due to COVID-19 had been confirmed by the CDC [2].

In April-May 2020, health authorities in London, North Italy, and New York reported a few clusters of children under 16 years of age (median 8 years) characterized by fever, abdominal pain, gastrointestinal symptoms, skin rash, conjunctivitis, and myocarditis after COVID-19 infection. None of the children tested positive for SARS-CoV-2 in RT-PCR but were found to carry SARS-CoV-2 IgM/IgG or other unrelated viruses. Some developed shock or respiratory failure and required intensive care. On May 2020, WHO coined the term multisystem inflammatory syndrome in children (MIS-C) to identify this condition of unknown etiology. In May 2020, the Centers for Disease Control and Prevention (CDC) also acknowledged MIS-C [3].

2. Epidemiology of Multisystemic Inflammatory Syndrome in COVID-19

Multisystemic Inflammatory Syndrome (MIS) has emerged in children following the COVID-19 pandemic, raising several concerns regarding its epidemiology and impact on the pediatric population. The presence of the virus in the intestines has been hypothesized to be a contributor to the resulting hyper-inflammatory response. The manifestation of MIS strongly resembles classic Kawasaki disease (KD). However, classic KD has a drastically

different epidemiology, with infants and children younger than 5 years being primarily affected [4], in addition to the geographical/ethnic distribution of the disease with a higher incidence in East Asia and in children with Asian ancestry [5]. Meanwhile the epidemiology of MIS-C polarizes that of KD, with the highest incidence being in children older than 5 years of age (median age of 8-9 years) [6-8], and Black and Hispanic children facing a harsher and more frequent incidence than other ethnic groups [9]. A critical risk factor for MIS-C appears to be genetic diversity, as 60% to 70% of cases occur in populations with African, Afro-Caribbean, and Latin American ancestry, with further supportive evidence in the literature, with a curiously scarce number of cases reported from East Asia, from which KD is reported at a striking rate [10, 11]. Although the incidence of SARS-CoV-2 infection in children varies throughout the world, MIS-C incidence is far lower and appears to be relatively constant [12]. There seems to be an association between MIS-C and childhood obesity, but this remains an area in need of further research [reference Dufort and Feldstein]. Concerning gender, KD tends to affect male children more than females, whereas no significant difference was noted regarding the incidence of MIS-C [13]. The fatality rate of MIS-C is much higher than that of KD, reaching up to 2% of affected children [13, 14]. Cases of MIS occurred following the beginning of humanitarian efforts to control the pandemic. After the emergence of MIS-C and its reports by several laboratory and other establishments, the WHO finally included it in the list of post-COVID-19 conditions in June 2022 [15].

The extent of MIS-C and its global impact depends upon the extent of the COVID-19 outbreak and viral seroprevalence. Although numbers of SARS-CoV-2 seroprevalence varied between countries and regions, Brazil, UK, and

US had reported the worst outbreaks in the continent disproportionately affecting children. Outbreaks in these locations preceded reported cases of MIS-C. The discordance in the timing of COVID-19 and MIS-C reflects differences in vulnerability to the two inflammatory conditions. Peak pediatric COVID-19 viral positivity in each country preceded significant increases in MIS-C cases. Overall, an increase of pediatric MIS-C was observed along with an increase of pediatric COVID-19 cases and an increase of adult COVID-19 cases. Furthermore, there is an elevated risk of developing MIS-C among children from lower socio-economic backgrounds and Black children. The emergence of MIS-C during the COVID-19 pandemic is therefore a consequence of a rarer response to the more common respiratory illness [16, 17].

3. Clinical Features and Diagnosis

Multisystemic inflammatory syndrome in children (MIS-C) presents atypically at the initial evaluation with a lack of respiratory signs or symptoms and/or gastrointestinal (GI) illness. Traditional clinical manifestations associated with respiratory disease and GI disturbance are rarely seen together within the same cohort of patients. Initially following respiratory outbreaks, public health agencies should seek to broaden the recognition of atypical presentations including signs of needing inotropic support and rapid clinical deterioration before 5 days from hospitalization. Increasing awareness of these atypical presentations may improve detection and response to future outbreaks [18].

Most patients had fever for at least 3 days prior to initial evaluation, similar to initial observations from Europe. Fever is an expected result found within hyper-inflammatory protocols for sicker pediatric patients and was not

reported on case definitions by other public health agencies. The incorporation of a febrile cohort in public health messaging may help to enrich and refine the search for more cases [19].

Over a quarter of patients described presented with neurologic symptoms including headaches, altered mental status, encephalopathy, and seizures, consistent with similar findings by the pediatric emergency medicine investigation in New York, Italy, and other regions. Also, data in this small series of patients with neurologic exclusionary testing show the absence of neuroinvasive coinfecting pathogens. Neurologic illness may be a prominent clinical feature of MIS-C, diverting attention from more nonspecific signs such as fever, gastrointestinal symptoms, and rash [20].

Clinical laboratory tests suggest a broad hyper-inflammatory and immune response likely involving both innate and adaptive immune branches. On admission, all patients had either elevated C-reactive protein or interleukin-6 levels, and all except one had markedly elevated D-dimer levels. IL-6 is a key proinflammatory cytokine found to be elevated in critically ill COVID-19 patients. Day 1 D-dimer levels correspond to values associated with poor outcomes in adult COVID-19 and appear deserving of further investigation as a risk stratification marker. Although ferritin levels were not available until day 3, early reports from Italy noted elevated ferritin levels in MIS-C patients. Pediatric literature connects hyper-ferritinemia with a variety of pathologies including macrophage activation syndrome, Type II diabetes, and hemophagocytic lymphohistiocytosis (HLH). Standardized laboratory tests for HLH diagnosis should also be assessed in MIS-C patients. Other laboratory findings highlight the possibility of GI disease and coagulopathy in some patients, complementing findings of myocarditis and findings

hypoinflammatory variants of Kawasaki-like disease. On review, laboratory tests from pediatric patients with other serious COVID-19 complications were lower in some of these groups compared to MIS-C [21].

4. Pathophysiology and Immunological Mechanisms

The temporality of symptoms in MIS-C appears to differ from that of the acute presentation of COVID-19 in children. The systemic inflammatory phenomenon is postulated to result from a dysregulated inflammatory and immune response to SARS-CoV-2; however, the pathophysiology of MIS-C remains poorly understood. Evidence suggests that both humoral and cell-mediated immune responses may play critical roles in the development of MIS-C. As SARS-CoV-2 is now an endemic virus, it is likely that the incidence of MIS-C will continue to wax and wane in tandem with the epidemiology of COVID-19. A greater understanding of the underlying immunopathological mechanisms and long-term consequences of MIS-C will be critical to informing the development of effective therapeutics for this condition [22, 23].

An exaggerated cytokine release and systemic inflammatory response can occur in some children and adolescents after infection with SARS-CoV-2. The clinical entity was termed MIS-C, for multisystem inflammatory syndrome in children, as part of a broader spectrum of postinfection inflammatory syndromes in children and adults. The proposed term "COVID-19-related MIS-C" (multisystem inflammatory syndrome in children due to SARS-CoV-2 infection) takes into consideration the full pathogenic chain. While the clinical picture is suggestive of Kawasaki disease (KD) or secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome

(sHLH/MAS), specific differences and unique features can be seen, indicative of a unique disease entity [24].

Public health interventions to reduce viral transmission significantly impact MIS-C case counts, further reinforcing the causal relationship. A wide age range is observed for MIS-C (involving neonates, toddlers, older children, and adolescents). Co-infection with other viruses (respiratory syncytial virus, cytomegalovirus, human adenoviruses, and several others) may elevate the risk of developing MIS-C after infection with SARS-CoV-2. There is an increased risk of MIS-C following recovery from COVID-19 compared with children with SARS-CoV-2 infection but no prior exposure [12].

5. Management and Treatment Strategies

Timely recognition of the syndrome is essential to minimize morbidity and mortality. Most cases described had a relatively good clinical outcome, recovered without respiratory and cardiac sequelae, even though a few may have relapsed during the first 3 months of the monitoring period. Recurrences, however, tend to be less severe than the primary episode. Medical treatment is critical for successful control of the excessive inflammatory response, hemodynamic stabilization, and the recovery of cardiac function. Several therapies have been reported to be successful, most of them derived from protocols for patients with Kawasaki disease (KD), such as the use of immunomodulatory medications (IVIG, corticosteroids), with recalcitrant disease requiring biologics such as anakinra, tocilizumab, or infliximab [25]. The use of full-dose anticoagulation may result in a better outcome. Although it is impossible to compare these studies due to patient heterogeneity and different treatments, they provide fundamental knowledge.

6. Conclusion and Future Directions

Despite numerous studies analyzing the characteristics of MISC and its inflammatory process associated with COVID-19, there is still a need for more exploration regarding this novel and potentially lethal hyper-inflammatory process of childhood. This discipline requires greater awareness due to its detectability in areas lacking therapeutic approaches and advanced healthcare systems [26].

Over the past 3 years, numerous publications have contributed to the diagnostic criteria for MIS-C cases, initially derived from septic shock recommendations and later refined through reported cases. Nevertheless, further research is necessary to reach a comprehensive understanding of COVID-19-associated hyperinflammation. Attention was paid to viral load quantification, but little has been done to target sequelae and potential vulnerabilities connected with individual predispositions.

Children in MISC are mostly asymptomatic, and scarce experimental evidence is available on the impact of SARS-CoV-2 in childhood. This may imply a need to examine candidates that aggravate COVID-19's infection or progression, distinct from other coronavirus strains.

Children with MISC display a dysregulated complex phenotype of adaptive innate and humoral immunity that resembles childhood macrophage activation syndrome. There is a knowledge gap concerning the underlying physiology of the immune disruption involved in MISC. Exploring candidate mechanisms that could explain the unique features of MISC compared to other hyperinflammatory scenarios would be beneficial. These include the potential role of Angiotensin-converting enzyme 2 (ACE2)/Ang (1–7)/MasR axis

machinery, impaired virus clearance, SARS-CoV-2 escape strategies regarding spike protein neutralizing antibodies, excessive complement activation, and the impact of environmental factors on childhood immunity.

Although the acute clinical manifestations of COVID-19 in children are milder than those in adults, the unknown long-term sequelae associated with active illness raise concerns. Children represent a sizable virally exposed cohort, with critical outcomes in most cases. Research into the sustainability of immunity and long-term effects on growth and development is warranted.

Although the occurrence of MISC with SARS-CoV-2 is rare, cases being reported underline the need for early recognition and treatment as COVID-19 in adults has severe long-term physiological and health implications. Integrating contributions from many disciplines with an interest in childhood immune response to COVID-19 would be beneficial to advance understanding of this novel post-infectious inflammatory disease.

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