Editorial

Multisystem inflammatory syndrome associated with SARS-CoV-2 infection in children

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In April 2020, reports from the United Kingdom documented a presentation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in children, in some with features similar to incomplete Kawasaki disease (KD) or toxic shock syndrome[1]. This presentation was subsequently called Multisystem Inflammatory Syndrome in Children (MIS-C)[2]. It is defined as the presence of persistent fever, inflammation and multi-organ dysfunction, with evidence of past or recent temporarily associated SARS-CoV-2 infection, and to the exclusion of other microbial causes[3]. In some documented cases, the syndrome has presented late, around 2 to 6 weeks after the onset of the index illness.

Maternal SARS-CoV-2 may potentially cause a similar hyper-inflammatory syndrome in neonates (MIS-N) due to transplacental transfer of antibodies[4]. Pawar R, *et al*[4] reviewed the perinatal history, clinical features and outcomes of 20 neonates with features consistent with MIS-C related to maternal SARS-CoV-2 in Kolhapur, India, from 1st September 2020 to 30th April 2021. Fifteen singletons and 5 twins born to 18 mothers with a history of COVID-19 or exposure during pregnancy presented with features consistent with MIS-C during the first 5 days after birth. Nineteen were positive for anti-SARS-CoV-2 IgG and all were negative for IgM antibodies. Eighteen (90%) neonates had cardiac involvement (prolonged QTc, 2:1 AV block, cardiogenic shock, coronary dilatation), 40% had respiratory failure, 10% had fever, 30% had feeding intolerance, 10% had melaena and 5% had renal failure. All infants had elevated inflammatory biomarkers and received steroids and intravenous immunoglobulin (IVIG). Two infants died.

A systematic review by Sood M, *et al*[5] found that fever (95%) was the most common clinical manifestation of MIS-C followed by gastrointestinal (78%), cardiovascular (75.5%), and respiratory system (55.3%) involvement. Some features of MIS-C resemble KD, toxic shock syndrome, and secondary haemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS)[2]. The relationship of MIS-C to SARS-CoV-2 infection suggests that the pathogenesis involves some post-infectious immune dysregulation[2,5].

Patients with MIS-C should ideally be managed in a paediatric intensive care unit (PICU) since rapid clinical deterioration may occur[2]. Specific immunomodulatory therapy depends on the clinical presentation[2]. The systematic review by Sood M, *et al*[5] found that 49% had shock, 32% had myocarditis, 18% had coronary vessel abnormalities and 9% had congestive cardiac failure. Sixty-three percent of the patients were admitted to the PICU, 63% received IVIG, 58% received corticosteroids and 19% received alternate agents like tocilizumab[4]. However, the mortality was low (2.2%)[4].

A multicentric prospective national registry, including 47 PICUs, compared the clinical, laboratory and therapeutic features between MIS-C and non-MIS-C patients[6]. It was concluded that MIS-C was the most frequent presentation among critically ill children with SARS-CoV-2 infection, that MIS-C patients were older and usually healthy, that they showed a higher prevalence of gastrointestinal symptoms and shock and were more likely to receive vasoactive drugs and immunomodulators and less likely to need mechanical ventilation than non-MIS-C patients[6].

Available literature shows that our knowledge of MIS-C is largely incomplete[7]. It is highly likely that the criteria currently used to diagnose MIS-C are too broad, meaning that children with different diseases are included[7]. As there is some lack of clarity on the pathogenesis of MIS-C, different therapeutic approaches have been used, but no specific therapy is currently available[7]. Further studies are urgently required to better define MIS-C and its real impact on child health, and to determine the best clinical and therapeutic approach and its true prognosis,

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