Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

MIS-C: post-infectious syndrome or persistent infection?

Li Jiang and colleagues[1] provided an exceptional Review of multisystem inflammatory syndrome in children (MIS-C). However, the possibility that MIS-C is more consistent with a subacute infection than a post-infectious syndrome was not fully considered.

Weisberg and colleagues[2] and Jia and colleagues[3] reported reduced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody breadth, specificity, and neutralising activity in patients with MIS-C compared with patients with COVID-19 respiratory infection. Weisberg and colleagues postulated that "because younger individuals have increased number of naive T cells in different sites to respond to new pathogens, it is possible that a robust T cell response efficaciously clears infection in the lung preventing severe respiratory disease in children, and a low level, persistent infection in other sites may build up over time in some children, resulting in MIS-C."[2]

ACE-2 receptors are abundantly present in arterial and venous endothelial cells and arterial smooth muscle cells, and the vascular system is a possible sight of persistent SARS-CoV-2 infection. Colmenero and colleagues,[4] in a study of seven children with chilblains, confirmed the presence of viral particles by immunohistiochemistry and electron microscopy in dermal vascular endothelium. Similar to patients with MIS-C, these patients presented approximately 4 weeks after the peak of COVID-19 in their home region, had no personal history of acute COVID-19, and were negative by nasopharyngeal RT-PCR testing.

The report by Diorio and colleagues[5] of extensive burr cells (echinocytes) in the peripheral blood smears of patients with MIS-C provides an additional clue to the pathophysiology of this recently described and unique syndrome. Activated macrophages induce nitrosative stress, which can induce echinocyte formation. Burr cell formation has also been reported in Epstein-Barr virus-triggered secondary haemophagocytic lymphohistiocytosis,[6] and the tumour necrosis factor-α and interleukin-10 elevation described by the CHOP group[5] is primarily produced by macrophage or monocyte lineages.

In MIS-C, immune responses that have not fully controlled an ongoing infection might allow persistent activation of the intrinsic immune system. This persistent innate immune inflammatory response probably occurs because of the ability of SARS-CoV-2 to block type 1 and type 3 interferon response signalling to the adaptive immune system without disrupting cytokine production.

Thankfully, most children with MIS-C recover after treatment with aspirin, corticosteroids, and immunoglobulin. Elucidation of the pathophysiology of MIS-C will inform the treatment of children who are non-responsive to standard therapy. If MIS-C is confirmed to be caused by ongoing infection, this finding might also have important implications for antiviral treatment of adults with prolonged symptoms after SARS-CoV-2 infection.

I declare no competing interests.

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