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.

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Severe refractory Kawasaki disease in seven infants in the COVID-19 era

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A cohort of seven infants (aged ≤1 year) with severe Kawasaki-like disease were diagnosed and treated at five hospitals in the UK between February and March, 2020 (appendix p 1). All of the infants received prompt intravenous immunoglobulins and steroid treatment, but none responded and all required the addition of a biological agent because of continued inflammation, recurring fever, and progressive changes on echocardiography. Six patients (86%) developed coronary artery aneurisms (Z score >2·5) and one infant died as a result of a ruptured aneurysm, despite early aggressive treatment. Five infants (71%) had negative serology for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); therefore, any correlation with the COVID-19 pandemic and paediatric inflammatory multisystemic syndrome temporally associated with SARS-CoV-2 is unclear.[1–3] Nonetheless, we would like to alert paediatricians to this new and very aggressive phenotype in infants.

The post-mortem examination of one infant (infant 2) showed markedly abnormal coronary arteries with multiple massive saccular aneurysms (appendix p 4). Histology of the affected vessels showed typical features of Kawasaki disease, with florid vasculitis, vessel wall destruction, and aneurysm formation in the absence of fibrinoid necrosis (appendix p 5). There was no thrombotic occlusion of the coronary arteries or any other myocardial changes (apart from the affected vessels), and no non-cardiac vasculitis. There was no inflammation in the upper or lower airways and no evidence of pneumonitis or myocarditis to suggest ongoing active viral infection. Post-mortem swabs from the nasopharynx and lung of infant 2 were negative for SARS-CoV-2, but respiratory PCR was positive for adenovirus in vivo.

One infant (infant 1) was treated with two doses of infliximab, with the second dose given at day 42 because of new echocardiographic changes and rising C-reactive protein. This infant remains on immunosuppressant therapy 3 months after presentation. Infant 6 did not respond to anakinra and was subsequently treated with infliximab (appendix pp 1–3).

All patients had high C-reactive protein at presentation (80–276 mg/L) and high platelets in the later stages of the disease (468–1419 × 10^9/L; appendix pp 1–3). The other inflammatory parameters that are typically elevated in paediatric inflammatory multisystemic syndrome temporally associated with SARS-CoV-2, such as ferritin, lactate dehydrogenase, and D-dimers, were only mildly elevated in these patients. Lymphocytopenia was present in one infant. One infant tested positive for SARS-CoV-2 on PCR and one infant tested positive on antibody testing (appendix pp 1–3).

Although it is well known that Kawasaki disease in children aged 1 year and younger has a worse prognosis than in older children (aged >1 year), particularly in boys with coronary artery disease, the severity of disease in this cohort is unusual compared with the literature, in which 10–20% of infants develop aneurysms.[4] We cannot link these cases to the COVID-19 pandemic, as serology and PCR results for SARS-CoV-2 were mostly negative. Nevertheless, we feel that it is important that paediatricians consider early aggressive treatment and close cardiac monitoring of Kawasaki disease in infants, in whom a severe disease course might be occurring.

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An adult presentation consistent with PIMS-TS

Following reports of paediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PIMS-TS),[1,2] a UK-born man of Somali origin, aged 21 years, was admitted to University College London Hospitals (UK) with 6 days of fever and abdominal pain associated with constipation, anorexia,

and headache. He described a transient maculopapular palmar rash 4 days into illness (appendix pp 3–4). He had non-exudative conjunctivitis, cervical lymphadenopathy, cracked lips, and prominent lingual papillae (appendix pp 3–4). A CT scan showed mesenteric adenopathy and terminal ileitis. The patient had neutrophilia, eosinophilia, lymphopenia, elevated inflammatory markers, and elevated troponin T with normal electrocardiogram, transthoracic echocardiogram, and CT coronary angiogram (appendix pp 2–3).

The patient had no previous history of COVID-19 symptoms or contact with known COVID-19 cases. Nasopharyngeal and stool samples were negative for SARS-CoV-2 by PCR. Other infective and inflammatory conditions were excluded (appendix p 2). Adult and paediatric specialists conferred and concluded that the most likely diagnosis was Kawasaki-like disease on the PIMS-TS spectrum. The patient was treated with intravenous immunoglobulin and methylprednisolone, which resulted in rapid resolution of symptoms and normalisation of blood parameters (appendix p 3); he was discharged on low-dose aspirin 8 days after admission to hospital.

SARS-CoV-2 serology[3] (checked before treatment with intravenous immunoglobulin) was strongly positive, suggesting recent exposure to SARS-CoV-2 (appendix p 2). Kawasaki disease has been described in adults in association with viral infection.[4,5] To the best of our knowledge, this is the first reported case of adult Kawasaki-like disease related to SARS-CoV-2 infection. There is an urgent need to recognise and fully characterise PIMS-TS in young adults to improve our understanding of pathogenesis, guide treatment decisions, and prevent sequelae in these patients.

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Intravenous anakinra for cytokine storm syndromes

In their Viewpoint on cytokine storm syndromes, Puja Mehta and colleagues[1] stated that "there is a critical need and growing call for unified nomenclature (such as cytokine storm syndromes)". Although we agree that a multidisciplinary effort is needed to analyse and classify these conditions, we have concerns about unifying them all under a single umbrella. Indeed, cytokine storm syndromes currently encompass several different conditions with extremely varied causes, pathophysiological processes, or prominant cytokines. Although they manifest with similar symptoms, they might have only one truly common feature: hypercytokinaemia.

For instance, haemophagocytic lymphohistiocytosis might be the consequence of deficient cytotoxic cells (primary and some virally-induced haemophagocytic lymphohistiocytosis),[2] hyperactivation of the inflammasome pathway (NLRC4-associated macrophage activation syndrome),[3] or a yet-to-be-defined combination of these factors (eg, Still's disease spectrum). All of these conditions are characterised by elevated plasma concentrations of IL-1 family cytokines (IL-1β and IL-18) and tissue haemophagocytosis. Alternatively, cytokine release syndrome secondary to chimeric antigen receptor T-cell therapy has been linked to high IFN-γ release, whereas the involvement of the IL-1 family cytokines seemed less prominent.[4] Lastly, it is noteworthy that cytokine storm has attracted great interest, as a result of its description as a major determinant of COVID-19 outcomes. Yet, despite there being no definitive understanding of its immunopathology, a hallmark of COVID-19-associated cytokine storms seems to be prominent IL-6 elevation, with only 25% of patients showing evidence for IL-1-driven macrophage activation or haemophagocytosis.[5] In the remaining 75% of patients, the disease has been compared with complex immune dysregulation seen in patients with sepsis (ie, prominent role for IL-6, low HLA-DR expression, and lymphopenia).

These considerations are important because the clinicians' armamentarium is now large enough to offer the best targeted therapies in these different contexts (ie, inhibitors of IL-1, IFN-γ, or IL-6). Defining criteria for choosing one treatment over the other, or instead of a less-targeted therapy (eg, corticosteroids or Janus kinase inhibitors) will certainly be one of the challenges of clinical trials in the near future.

Overall, we suggest that if an international, multidisciplinary effort is mounted to unify cytokine storm syndromes within one spectrum, this nomenclature will have to be subdivided on the basis of the cause, the supposed pathophysiology, and

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