

Kawasaki disease or Kawasaki syndrome?

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In the first months of COVID-19 pandemic, paediatricians were not much involved in the management of the illness. Reports from China had shown that relatively few children and adolescents were affected, and that most of those who were infected had experienced milder disease compared with adults.^{1,2} The same trend was initially seen after the spread of COVID-19 to Western countries.^{3,4}

However, between April and May 2020, a rise in the number of children and adolescents with an acute multisystem hyperinflammatory state fulfilling full or partial criteria for Kawasaki disease (KD),⁵ although frequently accompanied by unusual or less common symptoms, such

as abdominal pain, diarrhoea and myocardial failure, was noticed in European and North American countries or regions mostly hit by the COVID-19 pandemic.⁶⁻⁹ A number of these children needed urgent intensive care treatment due to the development of toxic shock syndrome, leading to multiorgan failure and circulatory shock, usually of myocardial origin, and some of them had signs of macrophage activation syndrome (MAS). Markers of inflammation were elevated, with neutrophilia, prominently increased C-reactive protein, interleukin (IL)-6, D-dimer and ferritin levels, and hypoalbuminaemia. Lymphopenia and relative thrombocytopenia were often present. Management was based on the administration of anti-inflammatory treatment, which included intravenous immunoglobulin (IVIG) and glucocorticoids. In some instances, IL-1, IL-6 or tumour necrosis factor inhibitors were given. Some, but not all, of these patients tested positive on swabs or serology for SARS-CoV-2 or were exposed to potential contact with a household member affected with COVID-19.

Alerts have been issued by national health authorities and paediatric scientific societies to raise awareness of this

emerging syndrome in the medical community.¹⁰⁻¹⁴ This condition, which has been named 'Paediatric inflammatory multisystem syndrome temporarily associated to SARS-CoV-2 infection' (PIMS-TS) in the UK, 'Multisystem inflammatory syndrome in children' in the USA and 'Multisystem inflammatory syndrome in children and adolescents with COVID-19' by the WHO, has encountered an increasing interest within the media. National and international collaborative efforts are currently ongoing, with the aim to characterise its features and risk factors, to understand causality and to examine treatment interventions, clinical presentations, severity, outcomes and epidemiology.

The suspicion of a possible association between COVID-19 and KD was first put forward by Jones *et al*,¹⁵ who reported in Hospital Pediatrics on 7 April 2020 that a girl aged 6 months diagnosed and treated for classic KD tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR). One month later, Riphagen *et al*⁶ described the features of eight children with the aforementioned hyperinflammatory syndrome, which presented with clinical manifestations similar to atypical KD, together with prominent gastrointestinal symptoms, and progressed towards multiorgan involvement and severe shock, requiring admission to the Intensive Care Unit (ICU) and haemodynamic support. All children were given IVIG and four of them received methylprednisolone. One patient developed a giant coronary aneurysm. Despite

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family exposure to COVID-19 in four children, all tested negative for SARS-CoV-2 on bronchoalveolar lavage or nasopharyngeal aspirates. Six out of eight children were of Afro-Caribbean descent and one of them died.

Shortly afterwards, the characteristics of 10 children diagnosed with a KD-like disease (five with classic KD and five with incomplete features) seen in Bergamo, Italy were detailed by Verdoni *et al.*⁷ These patients were aged 2.9 to 16 years (mean 7.5) and eight of them tested positive for SARS-CoV-2 either by nasal swab or serology. Five exhibited evidence of MAS and five of KD shock syndrome. Ten were administered IVIG and eight methylprednisolone. All 10 patients recovered without sequelae, although coronary aneurysms >4mm were detected in two patients. The monthly incidence of these KD-like cases was at least 30 times greater than that observed for KD in the same region across the previous 5 years. As compared with 19 children with KD diagnosed before the start of COVID-19 epidemic, these patients were older and had higher rates of cardiac involvement, and features of MAS.

After these earlier experiences, several other case series with similar characteristics seen in various countries have been published.^{8,9,16–18} The larger sample was reported by Whittaker *et al.*,¹⁷ who described the features of 58 children (median age 9 years, 69% of black or Asian race) meeting the criteria for PIMS-TS admitted in eight UK hospitals between 23 March and 16 May 2020. In total, 78% of the patients had evidence of prior or current SARS-CoV-2 infection. Three clinical patterns were identified by examining the clinical course: (1) 23 children had persistent fever and elevated acute phase reactants, but no signs of organ failure or features suggestive of KD or toxic shock syndrome; (2) 29 children developed shock, often associated with clinical, echocardiographic and laboratory evidence of myocardial injury; (3) seven children fulfilled the American Heart Association (AHA) diagnostic criteria for KD⁵; one of them progressed to shock. When coronary artery aneurysms were considered, a total of 13 children met the criteria for KD. Treatment included IVIG in 71% of the patients, glucocorticoids in 64% and inotropic support in 47%. Eight patients received infliximab and three anakinra; 22% of the patients recovered with supportive care alone. Comparison of patients with PIMS-TS to pre-COVID-19 patients with KD and KD shock syndrome revealed differences in

clinical and laboratory features, namely older age, greater elevation of inflammatory parameters and lower lymphocyte counts and haemoglobin.

In this issue of the journal, Pouletty *et al.*¹⁹ describe the features of a further cluster of 16 patients seen in the Paris area between March and April 2020. Ten (71%) patients met the AHA criteria for complete KD,⁵ 13 (81%) had gastrointestinal symptoms, 7 (44%) had myocarditis and 7 (44%) and 2 (28%) met the criteria for toxic shock syndrome²⁰ and MAS,²¹ respectively. Eleven (69%) patients tested positive for SARS-CoV-2, and the remaining five had a recent contact with a family member with proven or suspected COVID-19. Ten (63%) patients were successfully treated with IVIG, whereas five required second-line treatment, including a second infusion of IVIG, glucocorticoids, anakinra and tocilizumab. Around two-third of the patients were of Afro-Caribbean origin and no fatalities were recorded. An age older than 5 years and a ferritin level greater than 1400ng/mL were associated with a higher risk for ICU admission. This cohort differed from a comparator sample of 'classic' KD for an older age at onset, a lower platelet count and a higher rate of myocarditis and of resistance to the first IVIG course.

Pouletty *et al.*¹⁹ as well as other authors^{9,17,18} wondered whether this hyperinflammatory syndrome represents a novel entity with respect to KD. The vast majority of patients so far reported exhibited, in a complete or incomplete form, the classical features of KD. The main differences were an older age at onset, a higher incidence of severe myocarditis and toxic shock syndrome and a higher percentage of patients requiring further therapy after the initial IVIG infusion. Myocardial failure, toxic shock syndrome and MAS have all been reported in KD, but are usually observed in only about 5% of patients.^{5,22} They are often associated with more severe laboratory markers of inflammation, and are more likely to be resistant to IVIG therapy and to require additional anti-inflammatory treatment. So, what seems to characterise SARS-CoV-2-associated Kawasaki-like disease is mainly the higher frequency of severe symptoms, rather than specific clinical features.

The aetiology of KD is unknown, but it is generally considered the consequence of an abnormal immune response, in genetically predisposed children, to infectious triggers entering through the upper respiratory tract. Multiple infectious agents have been suspected over the years,

including respiratory RNA virus, but none has been confirmed in subsequent studies.⁵ In the case of SARS-CoV-2-associated Kawasaki-like disease, the onset of the disease appears to occur a few weeks after acute infection or exposure, suggesting that SARS-CoV-2 might act as a trigger of a postinfectious inflammatory disease.

Autoinflammatory diseases have taught us that many rheumatic conditions may well represent syndromes rather than diseases. A monogenic illness can, indeed, mimic the clinical features of polyarteritis nodosa,^{23,24} Behcet disease,²⁵ rheumatoid factor positive polyarthritis,²⁶ systemic juvenile idiopathic arthritis²⁷ and systemic lupus erythematosus.²⁸ Thus, many of what we have called diseases are in fact syndromes presumably representing a sort of funnel, a stereotyped way of reaction of our body to multiple different aetiological factors. The recognition of the aetiology may be of utmost importance for treatment, as exemplified by the dramatic therapeutic effect of anti-tumour necrosis factor agents in case of polyarteritis nodosa associated with adenosine deaminase 2 (ADA2) mutation.²⁹

Henoch-Schoenlein purpura, the most common form of vasculitis in children, is also a syndrome. It is often preceded by a respiratory tract infection and multiple case studies have suggested a correlation with virtually all respiratory pathogens.³⁰ Although usually a benign disease, it can occasionally cause severe involvement of the kidney, gastrointestinal tract and central nervous system.

The occurrence of a Kawasaki-like disease in association with SARS-CoV-2 infection suggests that also KD is not a disease, but rather a syndrome, whose main features depend on the type of the immune response as well as on the characteristics of the triggering infectious agent. Recognition of the aetiological trigger is important since Kawasaki syndrome secondary to SARS-CoV-2 infection appears to be more severe and requires aggressive treatment.

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