EDITORIALS

Pediatric inflammatory syndrome temporally related to covid-19

Though rare, this condition warrants surveillance as well as collaborative research

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In many countries struggling with the burden of the coronavirus disease 2019 (covid-19) pandemic, a distressing and unexpected serious, delayed inflammatory syndrome has emerged among children and adolescents, a population previously thought to have been mostly spared by covid-19. Reports of an increase in the incidence of Kawasaki disease, a rare vasculitis involving the coronary arteries, in the northern provinces in Italy focused attention on this novel disorder.¹ This report was followed by an alert by UK authorities on 27 April 2020² of an influx of children in an intensive care unit in London with critical illness as well as signs of Kawasaki disease and toxic shock syndrome,³ and a study of 35 children in France and Switzerland with acute cardiac compensation after infection with severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), the virus responsible for covid-19.⁴

In a linked study, Toubiana and colleagues (doi:10.1136/bmj.m2094) have added an important layer to the growing knowledge of this disorder, strengthening the connection between SARS-CoV-2 infection and this condition.⁵ This condition is referred to variously as the pediatric multisystem inflammatory syndrome temporally associated with covid-19 (PIMS),⁶ the multisystem inflammatory syndrome in children and adolescents temporally related to covid-19,⁷ and the multisystem inflammatory syndrome in children (MIS-C) associated with covid-19.⁸

The authors describe 21 children and adolescents (≤ 18 years) admitted to a university hospital in France over about two weeks. The patients presented with Kawasaki disease and Kawasaki disease shock syndrome.⁹⁻¹¹ As in the previously reported cohorts, many of the patients were older (median age 7.9 years) than the usual age range of those with Kawasaki disease (nearly 80% younger than 5 years⁹), gastrointestinal symptoms were prominent, and over half of the patients presented in shock. As in the UK study, children of African or Caribbean ancestry were overrepresented (57%).³ Testing for SARS-CoV-2 by either reverse-transcriptase polymerase chain reaction or IgG antibodies to the virus was positive in 90% of the patients; two were negative for both. All the patients had leukocytosis and highly increased levels of inflammatory markers, including C

reactive protein and serum interleukin-6. Interestingly, two patients developed electrocardiographic changes and arrhythmias, an emerging phenomenon indicative of extensive cardiac involvement beyond coronary artery abnormalities and myocardial involvement in children and adolescents with PIMS.

All the patients received aspirin and intravenous immunoglobulin at least once, and nearly half the cohort ($n=10$, 48%) was treated with corticosteroids. Despite the highly acute illness, with 81% requiring ICU level of care, 71% needing vasoactive or inotropic agents, and 52% receiving mechanical ventilation, all the patients survived. Furthermore, no coronary artery aneurysms, as defined by a z score of 2.5 or greater of the left anterior descending or right coronary artery, or both, were found, although, as the authors correctly point out, longer term follow-up will be critical for surveillance of the coronary arteries in these patients.

The authors point to the temporal association of SARS-CoV-2 infection and the outbreak of Kawasaki-like disease as evidence of correlation. They note a pattern in which children present about one month after widespread lockdowns, as consistently reported in Italy, the UK, and now in several locations in the US, most notably the New York City area. In this cohort, children presented a median of 45 days since signs of covid-19-like illness, or a median of 36 days after contact with someone with known or presumed covid-19. Such a delay between the peak of SARS-CoV-2 infections and presentation of PIMS raises the possibility that this is a post-infectious, immunologically mediated phenomenon of covid-19. The theory that the syndrome is post-infectious is lent credence by this series, as 19 of the 21 patients had a positive IgG result to SARS-CoV-2, and by the Italian cohort, in which 8 of 10 patients were positive by serology. The immunopathology underpinning the spectrum of MIS-C remains to be elucidated.

The rapid emergence of PIMS has taught us much in an extraordinarily short period, but many questions remain. PIMS is likely a spectrum of disease that overlaps with clinically recognizable phenotypes of Kawasaki disease, macrophage activation syndrome, and toxic shock syndrome. The full range of disease and its sequelae are unknown, just as Tomisaku

Kawasaki was unaware at the time of his initial report that coronary aneurysms resulted from his eponymous disease.¹² Fortunately, to date, the absolute number of children with life threatening PIMS remains small, particularly compared with mortality from influenza: in North America, 169 influenza-related deaths occurred in children aged 14 years or younger during the 2019-20 season, with 81 of these in 2020 so far.¹³ It will only be possible to compare PIMS with other post-infectious complications, such as encephalomyelitis after measles infection,¹⁴ once thorough surveillance of both pediatric SARS CoV-2 infections and PIMS is accomplished.

It seems highly likely that more reports will appear from around the globe as recent peaks of SARS-CoV-2 infections in new regions result in waves of PIMS in children and adolescents. How many waves will come and how far will the waves extend from each affected area? Is PIMS here with us to stay in one form or another, hopefully at a lower frequency? Will epicenters already impacted be able to learn in time to provide data on optimal management strategies? Urgent issues that will be best tackled by an international, multidisciplinary pediatric community include determination of the incidence and spectrum of mild to severe PIMS through systematic surveillance; best treatment strategies; the incidence and clinical course of coronary artery dilation, aneurysms, and other cardiac complications and their association with risk factors such as severity of presenting illness; and non-cardiac long term health sequelae. The rapid release of publications about PIMS, such as that of Toubiana and colleagues⁵ is the first step in this critical process.

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The BMJ policy on financial interests is here: <https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf>.

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