Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): what does the future hold?

We read with great interest the recent article by Pouletty et al., a multicentre cohort from Paris, which reported an increased incidence of Kawasaki disease (KD) like presentation in association with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (Kawa-COVID-19) in children. It is considered as a part of Paediatric inflammatory multisystem syndrome temporally associated (PIMS-TS) with SARS-CoV-2. The varied manifestations of PIMS-TS include KD-like illness, toxic shock syndrome and multisystem failure.1–4 There is a significant difference in epidemiology and diagnostic criteria used to identify this entity compared to the usual KD (non-COVID-19 related).1–4

The annual incidence of KD in Asian populations like Japan, and Pacific Islander descent was 260 per 100 000, but in the USA, it was 25 per 100 000 children.3 Though the initial epidemic of SARS-CoV-2 infection was prevalent in Asian countries like China and South Korea, no cases of PIMS-TS or Kawa-COVID-19 were reported from these countries to date. Pouletty et al.,1 in his report of 16 children with Kawa-COVID-19 illness, found that no child was from the Asian race1 (with 1.7% of population being Asian race in France). Similarly, Whitaker et al.9 in his multicentre study of 58 children with PIMS-TS with most of the participating hospitals from London had reported a higher incidence of Kawa-COVID-19 in blacks (62%) and whites (31%) compared with Asians (no case) (with Asians comprising 18.5% of London’s population).7 These findings favour a strong genetic influence in causation of Kawa-COVID-19. Other possible reasons could be a difference in the strain of SARS-CoV-2, and possible under-reporting. Anecdotal reports from India indicate there are increasing numbers of children being diagnosed with Kawa-COVID19. However, establishment of a nationwide registry is essential to collate the cases and to estimate the actual incidence. This epidemiological evidence could indicate whether there is a clear population-specific predisposition to PIMS-TS or Kawa-COVID-19.

Kawa-COVID-19 may have the typical mucocutaneous manifestations and coronary artery abnormalities (CAA) like that of usual KD. However, Kawa-COVID-19 has an older age of presentation; levels of total leucocyte counts, lymphopenia, thrombocytopenia, C reactive protein, serum ferritin, serum troponin and pro-B type natriuretic peptide were not comparable to the usual KD cohort.6 These observations were further replicated in cohorts of PIMS-TS associated KD like illnesses reported from the USA and England.6 10 11 Incidence of myocarditis, incomplete or atypical presentation, requirement of additional immunosuppressive therapy and haemodynamic instability were also significantly high in children with Kawa-COVID-19 than usual KD cohort.1 10 11 Further, establishing the SARS-Cov-2 infection in PIMS-TS by the reverse transcriptase-PCR or serology against SARS-CoV-2 is positive in only up to 78% of PIMS-TS children.6 Hence, despite having certain clinical and laboratory differences, none of them can help the clinician delineate usual KD and Kawa-COVID-19 in a given patient during the COVID-19 era.

Anti interleukin-6 (IL6) therapy (tocilizumab) had been variably used in Kawa-COVID-19 children based on the possible role of IL-6 in the pathophysiology of this hyperinflammatory state.1 10 In his prospective pilot study, Nozawa et al.12 evaluated the efficacy of tocilizumab in intravenous immunoglobulin (Ig) resistant KD on four children. None of the intravenous Ig resistant KD children had CAA at the time of administration of tocilizumab but, two children developed CAA after administration of tocilizumab, out of which one had giant CAA and later required intervention for CA stenosis. This paradoxical result was explained by the role of IL-6 in tissue regeneration, reduction of neutrophil trafficking in arterial walls, and possible role in increasing vascular endothelial growth factor to enhance remodelling.12 Thus, it is imperative to delineate the immunopathogenesis of Kawa-COVID-19 which would further facilitate development of management and follow-up strategies.

A search of a reliable diagnostic biomarker for Kawa-COVID-19 is also essential to avoid misclassifications, especially in the COVID-19 era. Wright et al.13 proposed and validated a 13 transcript blood gene expression signature to delineate KD from other infectious and inflammatory causes of febrile illnesses with good sensitivity and specificity. Similarly, Kawa-COVID-19 may have a different mRNA signature considering differences in the epidemiology, clinical and laboratory features in Kawa-COVID-19 compared with usual KD cohort.

To conclude, detailed epidemiological and experimental research are the needs of the hour which could unravel the similarities and differences of Kawa-COVID-19 and the usual KD. This may not only have an impact on the therapeutic management of Kawa-COVID-19 but could also potentially answer the long-awaited question—what is the aetiology of KD?

Murugan Sudhakar, Pandiarajan Vignesh
Allergy Immunology Unit, Department of Pediatrics, PGIMER, Chandigarh, India

Correspondence to Dr Pandiarajan Vignesh, Allergy Immunology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India; vigimmc@gmail.com

Twitter Pandiarajan Vignesh @viginesh_pgi

Contributors MS: writing of initial draft of the manuscript, editing and revision of manuscript at all stages of its production, review of the literature. PV: inception of the manuscript’s idea and editing, critical revision of the manuscript at all stages of production and final approval.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

This article is made freely available for use in accordance with BMJ’s website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite Sudhakar M, Vignesh P. Ann Rheum Dis Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2020-218738

Received 29 July 2020
Accepted 30 July 2020

ORCID iD Murugan Sudhakar http://orcid.org/0000-0002-5348-0250
Correspondence

REFERENCES