RMD Open
Rheumatic & Musculoskeletal Diseases

VIEWPOINT

Is it Kawasaki shock syndrome, Kawasaki-like disease or pediatric inflammatory multisystem disease? The importance of semantic in the era of COVID-19 pandemic

Isabelle Koné-Paut [1], Rolando Cimaz [2]

To cite: Koné-Paut I, Cimaz R. Is it Kawasaki shock syndrome, Kawasaki-like disease or pediatric inflammatory multisystem disease? The importance of semantic in the era of COVID-19 pandemic. *RMD Open* 2020;**6**:e001333. doi:10.1136/rmdopen-2020-001333

Received 20 May 2020
Revised 4 June 2020
Accepted 12 June 2020

[1]Service De Rhumatologie Pédiatrique, Centre De Référence Des Maladies Auto-Inflammatoires et de l'amylose inflammatoire, Hospital Bicetre, APHP and University of Paris Sud Saclay, Le Kremlin-Bicetre, France
[2]Department of Clinical Sciences and Community Health, University of Milan, and ASST G. Pini, Milan, Italy

Correspondence to
Isabelle Kone-Paut; isabelle.kone-paut@aphp.fr

ABSTRACT

A few weeks after the peak of the global 2019novel coronavirus disease pandemic, cases of shock, multisystem inflammation and severe myocarditis have occurred in children and adolescents, generating some concerns and above all many questions. An almost immediate association raised with shock syndrome related to Kawasaki disease (KD). However, in light of bo/th experience and literature have taught us about severeacute respiratory syndrome coronavirus 2 (SARS-COV-2) infection, and what already known on the epidemiology of KD, we suggest here the hypothesis of a new 'post-viral' systemic inflammatory disease related to excessive adaptive immune response rather than a form of KD caused by SARS-COV-2. We discuss analogies and differences between the two forms.

INTRODUCTION

Since the last few weeks, there have been cases in the pediatric age characterised by shock, myocarditis and variable signs of multisystem inflammation. Cases occurred more frequently in some areas, such as Europe and Eastern US, where the 2019novel coronavirus disease (COVID-19) pandemic has hit the most. Precise epidemiological data are not yet available, but several countries including Italy, France, Spain and UK have started national registries, and media attention has risen so much that there have been concerns even in the general population, previously rarely aware of Kawasaki disease (KD), that severeacute respiratory syndrome coronavirus 2 (SARS-COV-2) could cause a vasculitis in their children. Moreover, there have been multiple calls to physicians and hospitals from parents of children previously affected with KD that they might be at higher risks. Aim of this review is, therefore, to try to clarify what the current situation stands with regard to KD during the pandemic, in particular to its relation with to this multisystemic inflammatory syndrome.

COVID-19 IN THE PEDIATRIC AGE

The global pandemic of COVID-19 initially seemed to affect children only mildly. Indeed, in March 2020, the Chinese Center for Disease Control and Prevention reported that the pediatric population represented only 1% of the 72 314 cases compiled in Wuhan, the focus of the pandemic.[1] One study evaluating 1391 children systematically tested retrieved 171 (12.3%), confirmed with SARS-COV-2 infection, and in whom 27 (15.8%) had neither clinical nor radiologic symptoms. Their median age was 6.7 years with a slight male predominance (60.8%); pneumonia (bilateral ground-glass opacity) and upper respiratory tract infection were the most common features, and only one death occurred. Later, a Chinese epidemiologic survey among 2135 SARS-COV-2-exposed children gave approximately the same findings.[2] Recently, a systematic review detailed all the published pediatric cases of COVID-19.[3] Eight hundred and fifteen articles including 18 studies with 1065 participants (444 patients younger than 10 years and 553 aged 10–19 years) with confirmed SARS-COV-2 infection were included in the final analysis. Children at any age had mild respiratory symptoms, namely fever, dry cough and fatigue, or were even asymptomatic. Bronchial thickening and ground-glass opacities were the main radiologic features. Among the included articles, there was only one case of severe COVID-19 infection, which occurred in a 13-month-old infant.

As the pandemic progresses in Europe and still in line with a benign outcome, several SARS-COV-2 related cutaneous features were reported in children with peculiar attention on chilblains.[4 5] This is of particular interest, as we will discuss later, in the context of possible association with vasculitis and considering that chilblains are one of the hallmarks of monogenic lupus and of interferonopathies, which often enters the differential diagnosis with viral infections (eg, Aicardi-Goutieres syndrome).

ALERT OF A NEW MULTISYSTEM DISEASE POSSIBLY RELATED TO SARS-COV-2 INFECTION

At the end of April 2020 and coming from the UK, a first alert of severe pediatric cases referred in intensive care unit for a feature possibly related to SARS-COV-2 and overlapping with myocarditis and toxic shock syndrome changed the initial idea of a favourable outcome of COVID-19 in childhood as one of the eight patients died. It also generated some confusion as some of the patients presented clinical signs of KD, a medium-sized vasculitis of young children. Since then there have been multiple reports of similar cases, even though up to the writing of the present review (May 15, 2020) only two series have been published in peer-reviewed journals.[6 7] The definitions of this condition now include 'hyper-inflammatory shock', 'hyper-inflammatory syndrome with multiorgan involvement', 'pediatric inflammatory multisystem syndrome (PIMS)' (with or without the suffix—TS, that is, temporally associated with SARS-COV-2), 'Kawasaki-like syndrome', 'Kawasaki-like disease'. Regardless of the name given, we think it more important to understand what could be its pathophysiology, its exact clinical characteristics and best treatment options. In light of the first published cases and the growing experience of European and American pediatric centers, it looks that different clinical scenarios can be described, as follows.

KAWASAKI DISEASE DURING THE PANDEMIC

The first case of concurrent COVID-19 and KD was published by Jones *et al*,[8] and was just the first description of a child with classic KD, who also screened positive for COVID-19 in the setting of fever and minimal respiratory symptoms. There are clear-cut cases of KD (complete, incomplete and atypical), but without shock syndrome, that as every year are continuing to appear in all countries. Whether these cases are more prevalent during the SARS-COV-2 pandemic is still unclear, but preliminary unpublished data do not, in general, seem to support this hypothesis. In fact, there are hints that the contrary might be the case, and the fear of contracting hospital-acquired infections might contribute to less emergency department consultations. Indeed, an international panel that include member of the American HeartAssociation (AHA) guidelines Committee for KD gave recommendations in this regard.[9] In Japan, where the incidence of this disorder is higher than in any other country, they surveyed members of the Japanese Society for Kawasaki Disease. In just 2 days, 31 medical institution in 17 prefectures replied, and compared to the average year the number of patients were mostly unchanged, or even decreased (C. Shimizu and Takahashi, personal communication). The majority answered that there was no change in severity compared to the average year, and there were no reports of severe cases of KD or KD-like cases that could lead to ICU management. Due to the relative rarity of this disease, analyses of data collected in Europe will occur only at the end of the year, or at least when sufficient numbers will be available.

With regard to possible links with SARS-COV-2 infection, the pathogenesis of KD is still unclear,[10 11] but is the result of an excessive immune response to unidentified triggering agents, which could stimulate the innate immune system with strong systemic inflammatory response then engaging adaptive immunity leading to organ damage.

Epidemiologic evidence of a viral role in triggering KD is suggested by seasonal epidemics,[12] and a number of viruses such as adenovirus, rhinovirus, influenza, Boca virus and enterovirus have been implicated.[13 14] Of note, coronaviruses are included in the list of viruses known to trigger KD, and a high suspicion for the two species HCoV-NH and HCoV-NL63 raised, but studies eventually gave conflicting results.[15 16] The possible role of SARS-COV-2 in 'classic' KD pathogenesis has yet to be determined but in view of what previously discussed current evidence does not seem to support this hypothesis.

SPECTRUM OF SYSTEMIC HYPER-INFLAMMATORY FEATURES ASSOCIATED TO SARS-COV-2 IN CHILDREN

Unusual cases of acute myocarditis with features of toxic shock and heart failure requiring hemodynamic stabilisation in the context of marked systemic inflammation raised first alert. Most of these children had fever, skin rash, conjunctivitis, painful oedema at the extremities and significant gastrointestinal symptoms. Another somewhat milder phenotype has also appeared including children of all age groups, again with prominent gastrointestinal symptoms but with more subtle myocardial involvement. Features of macrophage activation syndrome with elevated ferritinaemia were seen in many cases.

The only two published series relate to English and Italian cases. The English case series recently been published showed a cluster of eight patients with shock, high inflammatory indices and different types of cardiologic involvement.[6] Six out of eight were of Afro-Caribbean origin. The clinical features were similar: continuous fever, rash, conjunctivitis, peripheral oedema, pain in the extremities and significant gastrointestinal involvement. Most of them did not experience significant respiratory involvement, unlike typical COVID-19. The Italian series[7] comprised 10 patients, 8 of which were

positive for SARS-COV-2 either by swab or by serology, aged 2.9–16 years (mean 7.5). Myocardial involvement and features of macrophage activation syndrome were common in this cohort. Although patients met criteria for typical and atypical KD, their clinical and biochemical features differed from the historical cohort of KD patients seen in the previous years, hence the name of Kawasaki-like disease. Notably, all 10 patients recovered without sequelae.

SEMANTIC CONTROVERSY AROUND CASES DEFINITION

Contrasting with classical KD, systemic inflammation following SARS-COV-2 infection affects older children and teenagers. Other intriguing findings are that patients with severe forms are less commonly Caucasians than the expected frequency in their general population (many of African-American or Afro-Caribbean ethnicity). In addition, such cases were not reported in Korea and Japan; these populations have the highest incidence of KD and SARS-COV-2 pandemic has been present in these areas as well; hence, a genetic background for these severe cases is likely. Regarding the clinical feature, most reported cases do not meet the AHA's case definition for KD or in a minority of cases present only as incomplete forms. [17 18] Myocardial involvement is a hallmark of this hyper-inflammatory state, whereas coronary aneurysms are the hallmark of KD. Intravenous immunoglobulins (IVIG), which are also given frequently in other causes of myocarditis anyway, were apparently effective in those patients. Indeed, the immunomodulatory properties IVIG are not specific but result in strong anti-inflammatory effect. Therefore, we think that despite some similarities, there are epidemiological, clinical and laboratory evidences that support the concept of a new syndrome separated from KD. We find it quite important at least in the present time since the name Kawasaki has generated confusion in the media and the public, and patients and families who have suffered from this condition in the past require reassurance. Moreover, the general population is now aware that SARS-COV-2 can cause damage to the vessels of children, and it is crucial to emphasise that up to now the virus has minimal morbidity and exceptional mortality in the pediatric age. For cases with inflammatory multisystem syndrome, the European Centers for Disease Prevention and Control has stated that overall risk in the EU/EEA and the UK is considered low, based on a very low probability of PIMS in children and a high impact of such condition.[19]

Many of these cases occurred after several weeks of quarantine, and it is possible that these subjects suffered from a mild form of COVID-19 after intrafamilial transmission and severe complications appeared weeks later, likely related to a dysregulated immune response. The temporal relationship between infection curves and reported cases would also be consistent with this hypothesis.

The presence of shock has led to analogies with KD shock syndrome. Toxic shock is a rare presentation of KD (1–2%),[20] often inaugural and without the typical mucocutaneous symptoms, but toxic shock has also been associated for years with bacterial toxins, especially from streptococcus and staphylococcus, playing a role of superantigen with subsequent immunologic reaction similar to anaphylaxis. At present, little is known on the link between viral infection and shock syndrome. Of interest, a retrospective cohort of 1099 SARS-COV-2 confirmed patients in China reported 12 (1.1%) with shock syndrome, the direct role of the virus may, however, be only speculative, as these patients may have had coinfections suffered from treatment-related anaphylactic reactions.[21]

Moreover, we would like to stress some important points for clinicians. Patients with fever, systemic inflammation and presenting with extreme fatigue, pallor, difficulty breathing, blood pressure instability, hepatomegaly and significant digestive signs (diarrhoea, ileus) may require early referral to intensive care units for hemodynamic assistance and close monitoring. Elevated serum ferritin and ProBNP, elevation of D-dimers, together with hypoalbuminaemia, thrombocytopenia and strikingly elevated acute phase reactants are in line with an intense cytokine storm. PCR assay of SARS-COV-2 requires either nasopharyngeal, oropharyngeal swab or stool sampling, but search of specific antibodies may be necessary in case PCR tests are negative. Prompt treatment with IVIG 2 g/kg may be effective, but as it implies infusion of large fluid volumes, it may be preferable to infuse them divided into two separate doses and to use preferably highly concentrated products. In case of obesity (BMI >30), reducing 20% of therapeutic dose may avoid renal complications linked to the increase in oncotic pressure and blood viscosity. Treatment with corticosteroids and in some cases anti-IL-1 agents may be advisable even if trials cannot justify it. Of note, in adults with severe COVID-severe infections trials with anakinra are ongoing, and the drug worked satisfactorily in cases of resistant KD.[22] The outcome of reported cases of KD does not seem to be any different from in the past, and outcome of the cases with multisystem involvement seems generally quite good with early recognition and treatment, even if few deaths occurred.

Finally, great uncertainty exists with regard to the exact classification, pathogenesis, phenotypes and best treatment choices for patients with a multisystem inflammatory disorder possibly related to SARS-COV-2 infection. However, science is likely to advance since many of these cases share common features and mechanistic studies may also be helpful to better define etiopathogenesis, improve early recognition and identify more precise targets for treatment.

Contributors IK-P and RC contributed equally to the writing of the manuscript. Both revised the manuscript critically for intellectual content, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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 IK-P has received consulting fees from AbbVie, Pfizer, Roche, CHUGAI, Novartis, SOBI and Novimmune. RC has no competing interests.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no data in this work.

ORCID iDs

Isabelle Koné-Paut http://orcid.org/0000-0001-8939-5763

REFERENCES

1 Lu X, Zhang L, Du H, *et al.* SARS-CoV-2 infection in children. *N Engl J Med* 2020;382:1663–5.
2 Dong Y, Mo X, Hu Y, *et al.* Epidemiology of COVID-19 among children in China. *Pediatrics* 2020;145:e20200702.
3 Castagnoli R, Votto M, Licari A, *et al.* Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr* 2020.
4 Piccolo V, Neri I, Filippeschi C, *et al.* Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. *JEADV* 2020;10:1111.
5 de Masson A, Bouaziz JD, Sulimovic L, *et al.* Chilblains are a common cutaneous finding during the COVID-19. Pandemic: a retrospective nationwide study from France. *J Am Acad Dermatol*, 2020.
6 Riphagen S, Gomez X, Gonzalez-Martinez C, *et al.* Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet (Lond, Engl)* 2020;395:1607–8.
7 Verdoni L, Mazza A, Gervasoni A, *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet (Lond, Engl)* 2020;395:1771–8.
8 Jones VG, Mills M, Suarez D, *et al.* COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr* 2020;10:537–40.
9 Harahsheh AS, Dahdah N, Newburger JW, *et al.* Missed or delayed diagnosis of Kawasaki disease during the 2019 novel coronavirus disease (COVID-19) pandemic. *J Pediatr* 2020.
10 Marrani E, Burns JC, Cimaz R. How should we classify Kawasaki disease? *Front Immunol* 2018;9:2974.
11 Noval Rivas M, Wakita D, Franklin MK, *et al.* Intestinal permeability and IgA provoke immune vasculitis linked to cardiovascular inflammation. *Immunity* 2019;51:508–21.e6.
12 Burns JC, Herzog L, Fabri O, *et al.* Seasonality of Kawasaki disease: a global perspective. *PLoS One* 2013;8:e74529.
13 Turnier JL, Anderson MS, Heizer HR, *et al.* Concurrent respiratory viruses and kawasaki disease. *Pediatrics* 2015;136:e609–14.
14 Kim GB, Park S, Kwon BS, *et al.* Evaluation of the temporal association between Kawasaki disease and viral infections in South Korea. *Korean Circ J* 2014;44:250–4.
15 Esper F, Shapiro ED, Weibel C, *et al.* Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis* 2005;191:499–502.
16 Chang L-Y, Chiang B-L, Kao C-L, *et al.* Lack of association between infection with a novel human coronavirus (HCoV), HCoV-NH, and Kawasaki disease in Taiwan. *J Infect Dis* 2006;193:283–6.
17 Licciardi F, Pruccoli G, Denina M, *et al.* SARS-CoV-2-induced Kawasaki-like. Hyperinflammatory syndrome: a novel COVID phenotype in children. *Pediatrics* 2020:e20201711.
18 Dallan C, Romano F, Siebert J, *et al.* Septic shock presentation in adolescents with COVID-19. *Lancet Child Adolesc Health* 2020; S2352–4642:30164–4.
19 Available https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-risk-assessment-paediatric-inflammatory-multisystem-syndrome-15-May-2020.pdf (accessed 15 may 2020)
20 Taddio A, Rossi ED, Monasta L, *et al.* Describing Kawasaki shock syndrome: Results from a retrospective study and literature review. *Clin Rheumatol* 2017;36:223–8.
21 Guan W-J, Ni Z-Y, Hu Y, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
22 Kone-Paut I, Cimaz R, Herberg J, *et al.* The use of interleukin 1 receptor antagonist (anakinra) in Kawasaki disease: a retrospective cases series. *Autoimmun Rev* 2018;17:768–74.