FAST TRACK

Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study

Julie Toubiana,[1,2] Clément Poirault,[1] Alice Corsia,[3] Fanny Bajolle,[4] Jacques Fourgeaud,[5] François Angoulvant,[6] Agathe Debray,[1] Romain Basmaci,[7] Elodie Salvador,[3] Sandra Biscardi,[8] Pierre Frange,[9] Martin Chalumeau,[1,10] Jean-Laurent Casanova,[11,12] Jérémie F Cohen,[1,10] Slimane Allali[1]

For numbered affiliations see end of the article.

Correspondence to:
M Chalumeau
martin.chalumeau@aphp.fr
(ORCID 0000-0001-8175-3706)

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ABSTRACT

OBJECTIVES

To describe the characteristics of children and adolescents affected by an outbreak of Kawasaki-like multisystem inflammatory syndrome and to evaluate a potential temporal association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

DESIGN

Prospective observational study.

SETTING

General paediatric department of a university hospital in Paris, France.

PARTICIPANTS

21 children and adolescents (aged ≤18 years) with features of Kawasaki disease who were admitted to hospital between 27 April and 11 May 2020 and followed up until discharge by 15 May 2020.

MAIN OUTCOME MEASURES

The primary outcomes were clinical and biological data, imaging and echocardiographic findings, treatment, and outcomes. Nasopharyngeal swabs were prospectively tested for SARS-CoV-2 using reverse transcription-polymerase chain reaction (RT-PCR) and blood samples were tested for IgG antibodies to the virus.

RESULTS

21 children and adolescents (median age 7.9 (range 3.7-16.6) years) were admitted with features of Kawasaki disease over a 15 day period, with 12 (57%) of African ancestry. 12 (57%) presented with Kawasaki disease shock syndrome and 16 (76%) with myocarditis. 17 (81%) required intensive care support. All 21 patients had noticeable gastrointestinal symptoms during the early stage of illness and high levels of inflammatory markers. 19 (90%) had evidence of recent SARS-CoV-2 infection (positive RT-PCR result in 8/21, positive IgG antibody detection in 19/21). All 21 patients received intravenous immunoglobulin and 10 (48%) also received corticosteroids. The clinical outcome was favourable in all patients. Moderate coronary artery dilations were detected in 5 (24%) of the patients during hospital stay. By 15 May 2020, after 8 (5-17) days of hospital stay, all patients were discharged home.

CONCLUSIONS

The ongoing outbreak of Kawasaki-like multisystem inflammatory syndrome among children and adolescents in the Paris area might be related to SARS-CoV-2. In this study an unusually high proportion of the affected children and adolescents had gastrointestinal symptoms, Kawasaki disease shock syndrome, and were of African ancestry.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Acute clinical manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are less common and less severe in children than in adults

Recent observations, however, have raised concerns about a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS), with shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorders

WHAT THIS STUDY ADDS

Kawasaki-like multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection has characteristics that differ from those of classic Kawasaki disease

The characteristics comprise a higher frequency in children of African ancestry, predominant acute gastrointestinal symptoms, haemodynamic instability, and myocarditis

These clinical findings should prompt high vigilance among primary care and emergency doctors, and preparedness during the coronavirus disease 2019 pandemic in countries with a high proportion of children of African ancestry and high levels of community transmission

Introduction

In children and adolescents, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is mostly responsible for mild respiratory symptoms, in contrast with severe forms reported in adults.[1 2] An association between the disease caused by SARS-CoV-2, coronavirus disease 2019 (covid-19), and late manifestations of vasculitis has been increasingly suspected, especially in young asymptomatic patients, which might be due to post-viral immunological reactions.[3 4]

Kawasaki disease is the most common primary vasculitis in childhood, with medium and small sized arteries predominantly affected.[5] The annual incidence of the disease is highest in Japan, with more than 300 per 100 000 children aged 4 years or younger affected, compared with 25 per 100 000 children aged 5 years or younger in North America.[6 7] One of the most severe complications of Kawasaki disease is coronary artery aneurysm.[7] Kawasaki disease shock syndrome, a rare

form of Kawasaki disease, is often associated with myocarditis and requires critical care support during the acute phase of illness.[8 9] Although the cause of Kawasaki disease remains unclear, the role of a viral trigger in some genetically predisposed children has been hypothesised, as several viral respiratory agents have been associated with Kawasaki disease,[10-12] including seasonal coronavirus in some studies,[13 14] although not all studies.[15 16]

Recently, 17 children with signs and symptoms consistent with Kawasaki disease and laboratory evidence of recent SARS-CoV-2 infection were reported in the United States (n=1), England (n=8), and Italy (n=8).[17-19] These reports included cases with hyperinflammatory syndrome and multiorgan involvement, provisionally named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) in Europe[20] and multisystem inflammatory syndrome in children (MIS-C) in the United States.[21] Given the highly variable prevalence of SARS-CoV-2 infection in Europe, the possibility of an association between Kawasaki disease and positive testing for SARS-CoV-2 needs confirmation.

We evaluated a potential temporal association with SARS-CoV-2 infection in a cluster of 21 children and adolescents with features of Kawasaki disease who were admitted to the general paediatric department of a university hospital in Paris, France between 27 April and 11 May 2020 and followed up until discharge by 15 May.

Methods

We included all children and adolescents (aged ≤18 years) who were admitted to the general paediatric department of Necker Hospital for Sick Children in Paris, France between 27 April and 11 May 2020 and met the criteria for Kawasaki disease.[7] Patients were followed up until discharge by 15 May 2020. This university hospital serves as the regional reference centre for emerging infectious diseases in children. All parents provided written informed consent.

We reviewed the medical files of all the patients to collect personal and clinical data, laboratory test results, and imaging and echocardiographic findings using a standardised study specific form. For the purposes of this study, we used the criteria of the American Heart Association to define the presence of complete and incomplete Kawasaki disease,[7] and the criteria proposed by Kanegaye et al to define Kawasaki disease shock syndrome.[8] From each patient we obtained at least two nasopharyngeal swabs to test for SARS-CoV-2 using reverse transcription-polymerase chain reaction (RT-PCR; SARS-CoV-2 R-GENE, Argene; bioMerieux, Marcy l'Étoile, France). To exclude hospital acquired SARS-CoV-2 infection, we collected samples from the patients for RT-PCR testing within the first three days of hospital admission. We also took blood samples to test for IgG antibodies against SARS-CoV-2 (Architect SARS-CoV-2 chemiluminescent microparticle immunoassay -CMIA-; Abbott Core Laboratory, IL),[22] and other laboratory tests, such as for inflammatory and cardiac markers. Standard cardiology investigations included regular electrocardiography and echocardiography. We defined a coronary artery dilation to be present if the coronary artery diameter z score was between 2.0 and <2.5 and an aneurysm to be present if the z score was 2.5 or greater.[7] Resistance to intravenous immunoglobulin treatment was defined as persistent or recrudescent fever at least 36 hours and less than seven days after completion of the first immunoglobulin infusion.[7]

We described patients' characteristics using medians and percentages. Differences between groups were assessed by the Mann-Whitney U test. Statistical analysis was carried out using SPSS v25 (SPSS, Chicago, IL).

Patient and public involvement

We acknowledge the importance of public involvement. For this study, limited staff resources and absence of dedicated funding, short delays, and lockdown challenges made involving patients and members of the public, and especially children and adolescents, not possible at this time. We did make sure our participants remained aware of the progress of the ongoing study and its aims.

Results

Evidence of SARS-CoV-2 infection

Between 27 April and 11 May 2020, a total of 21 children and adolescents were admitted with features of Kawasaki disease (table 1). In response to the covid-19 pandemic, France closed schools and began its lockdown on 17 March 2020. According to the parents, all 21 patients reported here had not left home for school, social gatherings, or travel since lockdown was implemented. A recent history of viral-like symptoms was reported in nine of the patients: headache, cough, coryza, fever for less than 48 hours, and, for one patient, anosmia. The median duration between these symptoms and the onset of signs and symptoms of Kawasaki disease was 45 (range 18-79) days. A history of recent contact with family members displaying viral-like symptoms was reported in 10 households: parents or grandparents (n=11) and siblings (n=3). Symptoms in five of these family contacts were highly suspicious of covid-19 (ageusia, anosmia, suggestive findings on thoracic computed tomography). One contact had a positive RT-PCR test result for SARS-CoV-2 while symptoms were still present. The median interval between the reported contact and Kawasaki disease was 36 (range 18-45) days. The result of RT-PCR testing for SARS-CoV-2 was positive in eight (38%) of the 21 patients presented here (table 2). All but one of them had no symptoms suggestive of covid-19; one had anosmia that started 24 hours before the symptoms of Kawasaki disease. IgG antibodies against SARS-CoV-2 were detected in 19 of the 21 (90%) patients, with a median IgG index of 5.4 (range 2-9). The two patients with negative IgG results also tested negative

Table 1 | Clinical characteristics of children and adolescents presenting with symptoms and signs of Kawasaki disease during the coronavirus disease 2019 pandemic. Values are numbers (percentages) unless stated otherwise

Characteristics	Total (n=21)
Personal:	
Median (range) age (years)	7.9 (3.7-16.6)
Girls	12 (57)
Parents country of birth (n=42):	
Sub-Saharan Africa/Caribbean islands	24 (57)
Asia	4 (10)
Europe	12 (29)
Middle East	2 (5)
Kawasaki disease principal clinical criteria:	
Complete presentation (fever >4 days and ≥4 principal criteria)	11 (52)
Lips and oral cavity changes	16 (76)
Bilateral bulbar conjunctival injection	17 (81)
Rash	16 (76)
Changes to extremities	10 (48)
Cervical lymphadenopathy	12 (57)
Median (range) days of fever before intravenous immunoglobulin	5 (0-12)
Kawasaki disease associated clinical features:	
Gastrointestinal symptoms	21 (100)
Perineal or face desquamation	4 (19)
Arthralgia	2 (10)
Irritability	12 (57)
Other neurological features	6 (29)
Myocarditis	16 (76)
Median (range) left ventricular ejection fraction rate	42 (10-57)
Serous effusion	12 (57)

for SARS-CoV-2 by RT-PCR. These two patients with complete and incomplete Kawasaki disease according to the American Heart Association criteria[7] had no myocarditis and did not require intensive care support. Their procalcitonin levels were less than 1µg/L, and coronary artery dilation was detected in one patient. Multiplex PCR targeting human respiratory syncytial viruses, seasonal coronaviruses, parainfluenza and influenza viruses, metapneumovirus, and rhinovirus/enterovirus in nasopharyngeal swabs, was negative in 19 patients tested; serum PCR results for adenovirus, Epstein Barr virus, cytomegalovirus, human herpesvirus 6, and parvovirus B19 were negative in nine patients tested, and one patient with positive anti-SARS-CoV-2 IgG also had a serology suggestive of recent Epstein Barr virus infection.

Clinical features

Table 1 presents the clinical features of the 21 patients admitted with a diagnosis of Kawasaki disease. The ratio of male patients to female patients was 0.75. The median age at presentation was 7.9 (range 3.7-16.6) years. Twelve (57%) patients had at least one parent originating from sub-Saharan Africa or a Caribbean island, and three (14%) from Asia (two from China, one from Sri Lanka). The 21 patients had no relevant personal or family medical history, and none reported living in unhealthy environments or social housing. Sixteen (76%) patients had a body mass index below the 97th centile.

Eleven (52%) of the patients fulfilled the complete criteria for Kawasaki disease, whereas the remaining 10 had incomplete Kawasaki disease. Among the principal criteria for Kawasaki disease, polymorphous skin rash (76%), changes to the lips and oral cavity (76%), and bilateral bulbar conjunctival injection (81%) were the most common signs. All the patients had gastrointestinal symptoms, which occurred early in the course of illness before the onset of the principal manifestations of Kawasaki disease and consisting of acute abdominal pain, often associated with vomiting and diarrhoea (95%). Four patients had peritoneal effusion, with acute surgical abdomen in two of the four. One of them underwent abdominal surgery for suspected appendicitis, but had aseptic peritonitis. Irritability was common (57%), and six (29%) patients presented with headaches, confusion, or meningeal irritation. One of the three patients who underwent lumbar puncture had cerebrospinal fluid pleocytosis. Among other acute manifestations of Kawasaki disease, pericardial effusions occurred in 10 (48%) patients and pleural effusion in three (14%) patients. Myocarditis was diagnosed in 16 (76%) patients, with left ventricular ejection fraction ranging between 10% and 57%. Two of these 16 patients displayed important electrocardiographic changes (increased QT interval and occasional ventricular arrhythmias or diffuse ST-segment elevation) not attributable to any drug for QTc prolongation.

Imaging and laboratory findings

Of the 18 patients who underwent chest imaging (radiography or computed tomography), ground glass opacities, local patchy shadowing, and interstitial abnormalities were present in eight (44%) patients (table 2). Echocardiography detected coronary artery abnormalities in eight (38%) patients after a median of 7.5 (range 5-11) days of fever, which consisted of dilations (z score between 2.0 and 2.5) in five (24%) patients and increased coronary visibility in three (14%) patients. No coronary aneurysms were identified.

All patients had high levels of inflammatory markers, including leucocytosis with a predominance of neutrophils, and high levels of C reactive protein, procalcitonin, and serum interleukin 6 (IL-6; table 2). Seventeen (81%) patients had lymphopaenia, and anaemia was common, with a median haemoglobin level of 86 (range 53-122) g/L. Hyponatraemia (<135 mmol/L) and hypoalbuminaemia (<32 g/L) were observed in 20 (95%) patients. Transient kidney failure was observed in 11 (52%) patients. Moderate increases in serum alanine transaminases and γ-glutamyltransferase levels occurred in 62% and 76% of patients, respectively, and increases in γ-glutamyltransferase occurred after a median of 6.5 (range 5-16) days after disease onset. Lipase was increased in 10/16 (63%) patients tested. D-dimer levels were increased (>500 µg/L) in 19/20 (95%) patients. Increased levels of high sensitivity cardiac troponin I (>26 pg/mL) and B-type natriuretic peptide (>100 ng/L) were found in 17/21 (81%) and 14/18 (78%) patients, respectively.

Table 2 | Imaging and laboratory findings of children and adolescents presenting with symptoms and signs of Kawasaki disease during the coronavirus disease 2019 pandemic. Values are medians (ranges) unless stated otherwise

Characteristics	Total (n=21)
Ultrasound findings on coronary arteries during hospital admission (No (%)):	
Increased visibility	3 (14)
Dilation (z score 2 to <2.5)	5 (24)
Aneurysm (z score ≥2.5)	0
Chest radiography or computed tomography abnormalities (No (%)):	
Ground glass opacity, local patchy shadowing, interstitial abnormalities	8/18 (44)
Biochemistry findings:	
White cell count ($\times 10^9$/L)	17.4 (5.4-42.8)
Neutrophil count ($\times 10^9$/L)	13.6 (3.3-36.4)
Lymphocyte count ($\times 10^9$/L)	1.1 (0.4-5.6)
Haemoglobin (g/L)	86 (53-122)
Platelet count ($\times 10^9$/L)	499 (78-838)
C reactive protein (mg/L)	253 (89-363)
Procalcitonin (µg/L)	22.5 (0.1-448)
Interleukin 6 (pg/mL)*	170 (4-1366)
Sterile pyuria (No (%))†	10/16 (63)
Albumin (g/L)	21 (16-37)
Natrium (mmol/L)	130 (116-135)
Creatinine (µmol/L)	63 (27-417)
Alanine aminotransferase (IU/L)	70 (6-257)
γ-glutamyl transferase (IU/L)	59 (10-205)
Lipase (IU/L)†	108 (19-537)
Lactates (mmol/L)*	2.8 (1.6-9)
D-dimers (µg/L)‡	4025 (350-19330)
High sensitivity cardiac troponin I (ng/L)	282 (10-6900)
B-type natriuretic peptide (ng/L)§	3354 (16-16017)
Positive microbiological findings:	
Nasopharyngeal SARS-CoV-2 RT-PCR	8 (38)
Positive SARS-CoV-2 serum serology (IgG)‡	19 (90)
Positive nasopharyngeal PCR for other viruses	0/19

RT-PCR=reverse transcription-polymerase chain reaction; PCR=polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; IgG=immunoglobulin G.
*Missing data for four patients.
†Missing data for five patients.
‡Missing data for one patients.
§Missing data for three patients.

Treatment and outcomes

All 21 patients received high dose intravenous immunoglobulin (2 g/kg) after fever for a median duration of 5 (range 0-12) days and low dose aspirin (3-5 mg/kg/day) (table 3), and seven patients received concomitant corticosteroids (2-10 mg/kg/day). Five (24%) patients showed resistance to intravenous immunoglobulin and were treated with a second infusion (2 g/kg), with corticosteroids (2 mg/kg/day) in four of these patients. Eighteen (86%) patients received empirical broad spectrum antibiotic treatment, which always included a third generation cephalosporin. Median duration of antibiotic treatment was 6.5 (range 2-13) days. All test results for bacteria (urine, cerebrospinal fluid, and blood culture) were negative.

Seventeen (81%) patients were admitted to an intensive care unit (ICU) for management of haemodynamic instability. After hospital admission for a median 2 (range 1-5) days, 10 of these patients were admitted to the ICU. All presented with the criteria for Kawasaki disease on admission to the ICU. Twelve (57%) patients were considered to have Kawasaki disease shock syndrome: 11 received intravenous fluid resuscitation, and eight received vasoactive agents because of sustained hypotensive shock. Fourteen (67%) patients received inotropic agents for myocarditis with cardiac dysfunction. Median duration of vasoactive or inotropic agents was 3 (range 1-7) days. Eleven (52%) patients needed mechanical ventilation for cardiovascular compromise. Patients admitted to the ICU had higher levels of systemic inflammation markers, with a higher peak procalcitonin level (26 µg/L, range 1.7-448 µg/L), compared with those who did not require admission to the ICU (1 µg/L, range 0.13-4.17 µg/L; P=0.001). Median ICU length of stay was 5 (range 3-15) days. By 15 May 2020, after 8 (range 5-17) days of hospital stay, all patients were discharged home. No deaths were recorded.

Discussion

In this study, the temporal association between the onset of the covid-19 pandemic in France and the results of tests (RT-PCR and IgG antibodies) for SARS-CoV-2 in our patients with Kawasaki-like disease suggests a causal link. Furthermore, only one patient had symptoms suggestive of acute covid-19 and most had positive serum test results for IgG antibodies, suggesting that the development of Kawasaki disease in these patients is more likely to be the result of a post-viral immunological reaction. An association between Kawasaki disease and viral respiratory infections has been suspected,[10 14 23] especially rhinovirus and enterovirus, and various viral agents, including human coronaviruses.[10 13 14] However, no difference has been reported in clinical presentation between patients with Kawasaki disease with and without documented respiratory viral infection.[10]

In our series, we describe a Kawasaki-like multisystem inflammatory syndrome with an over-representation of myocarditis and Kawasaki disease shock syndrome, consistent with recent findings.[18 19] Mild myocarditis is common in the early phase of Kawasaki disease, as shown by cardiac biopsies and scintigraphy,[24 25] and generally improves quickly as inflammation resolves.[24 26] More severe myocarditis with decreased left ventricular contractility can sometimes occur, however, especially in the context of Kawasaki disease shock syndrome. This syndrome is a rare complication that affects 1.5% to 7.0% of patients with Kawasaki disease, and it has a higher incidence in Western countries compared with Asian countries.[9] It results from both myocardial dysfunction and decreased peripheral vascular resistance, usually requiring intravenous fluid resuscitation together with inotropic and vasoactive agent infusion in ICU.[8 27] Kawasaki disease shock syndrome might mimick toxic shock syndrome,[8] justifying systematic antibiotic use in our series. The pathophysiology of Kawasaki disease shock syndrome remains unclear. A high level of circulating pro-inflammatory cytokines might contribute to the distributive component of shock. Indeed, Kawasaki disease shock syndrome has been found associated with high levels of IL-6, C reactive protein, and procalicitonin.[9] In our series, we observed high levels of procalcitonin; 10-fold higher than those recently reported in 27 patients with Kawasaki disease

Table 3 | Treatment and outcomes of children and adolescents presenting with symptoms and signs of Kawasaki disease during the coronavirus disease 2019 pandemic. Values are numbers (percentages) unless stated otherwise

Variables	Total
Treatment:	
Intravenous immunoglobulin (2g/kg) infusion	21 (100)
Intravenous immunoglobulin (2g/kg) retreatment	5 (24)
Steroids (2-10 mg/kg/day)	10 (48)
Aspirin (3-5 mg/kg/day)	21 (100)
Broad spectrum antibiotics	18 (86)
Outcome and serious complications:	
Persistent fever 36 hours after end of initial intravenous infusion	5 (24)
Median (range) length of hospital stay (days)	8 (5-17)
Admitted to intensive care unit	17 (81)
Fluid resuscitation	11 (52)
Vasoactive and inotropic agents*	15 (71)
Mechanical ventilation	11 (52)
Death	0

*Adrenaline, dobutamine, milrinone and/or noradrenaline.

shock syndrome.[9] C reactive protein and IL-6 levels were also high. This major pro-inflammatory state, together with multiorgan dysfunction, recently named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS),[20] might reflect a particularly strong post-viral immunological reaction to SARS-CoV-2 compared with other viral agents.[28] Of note, a cytokine storm syndrome with increased levels of inflammatory markers such as IL-6 was described in adults with covid-19,[29] and it has been associated with fatality.[30]

Besides inflammatory markers, clinical and biological features of our patients were often consistent with the diagnosis of Kawasaki disease shock syndrome. Indeed, older age, higher D-dimer levels, lower haemoglobin and albumin levels, and more severe hyponatraemia were previously found to be associated with Kawasaki disease shock syndrome.[9] In contrast with a recent series,[18] only 24% of our patients had a body mass index above the 75th centile, which does not support the hypothesis of overweight as a risk factor for Kawasaki-like multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection. Resistance to intravenous immunoglobulin treatment and coronary artery abnormalities were less common in our series than in previous series of Kawasaki disease shock syndrome.[8 9] However, these results should be treated with caution as coronary artery abnormalities might appear later during follow-up. Gastrointestinal symptoms were also unusually common, affecting all of our 21 patients. A previous study reported intestinal pseudo-obstruction in only 2% of 310 patients with Kawasaki disease.[31] As previously described, other symptoms of Kawasaki disease appeared after the intestinal ones in all patients, which could have led to diagnostic and therapeutic delays in some children.[32] Suspected mechanisms involve intestinal ischaemia secondary to bowel vessel vasculitis. Rapid resolution of symptoms in all patients after treatment with intravenous immunoglobulin supports this hypothesis.

The observation of a higher proportion of patients of African ancestry is consistent with recent findings,[18] suggesting an effect of either social and living conditions or genetic susceptibility. Kawasaki disease is rarely reported in sub-Saharan Africa, but it might be more common than previously thought.[33] In the United Kingdom and the United States, a 2.5-fold higher incidence was reported in children of Asian ancestry than of European ancestry, with an intermediary 1.5-fold risk for children of African ancestry.[34 35] Besides, African-Americans have been disproportionately affected by the covid-19 pandemic, also suggesting an increased susceptibility to severe SARS-CoV-2 infection.[36 37] Therefore, African countries where the SARS-CoV-2 pandemic has spread might face a potentially large number of children with Kawasaki disease, and supply shortages of intravenous immunoglobulin should be anticipated in such settings. The absence of reported cases of Kawasaki-like multisystem inflammatory syndrome associated with SARS-CoV-2 infection in Asian countries where the covid-19 pandemic started, and where the incidence of Kawasaki disease is the highest, is noteworthy.[38] Ethnic differences in the development of Kawasaki disease shock syndrome were previously reported, with a lower incidence in Asian countries than in Western countries.[89] This warrants future studies investigating underlying genetic and immunological mechanisms.

Table 4 | Main features of classic Kawasaki disease and Kawasaki-like multisystem inflammatory syndrome. Numbers are percentages of people affected unless stated otherwise

Characteristics	Classic Kawasaki disease*	Kawasaki-like syndrome series
High risk population	Asian	African
Age	6 months-5 years	4-17 years
Incomplete form of Kawasaki disease†	5-20	48
Gastrointestinal symptoms	Uncommon	100
Kawasaki disease shock syndrome	2-7	57
Myocarditis with ventricular dysfunction	<1	76
Intensive care support	4	81
Levels of inflammatory markers	Increased	Noticeably increased
Lymphopaenia	Rare	81
Coronary artery dilations/aneurysm	4-13	24
Intravenous immunoglobulin resistance	10-20	24

*Supported by Li et al,[9] Saundankar et al,[40] Makino et al,[6] and McCrindle et al.[7]
†Incomplete form according to American Heart Association criteria[7]: fever ≥5 days, 2 or 3 principal clinical criteria of Kawasaki disease, and echocardiographic or laboratory features of Kawasaki disease.

Limitations of this study

Our study has limitations. Firstly, potential recruitment bias might have contributed to the high number of patients with Kawasaki-like multisystem inflammatory syndrome admitted to the general paediatric department in our hospital. This hospital is the referral centre for paediatric patients with severe covid-19 in the Paris area. Secondly, the low number of patients precluded indepth comparisons of phenotypes with adequate statistical power. Thirdly, a causal link with SARS-CoV-2 infection has not been established, despite a strong suspicion of exposure to SARS-CoV-2. Household members were not systematically tested for SARS-CoV-2 ongoing infection. Besides, a new released kit for antibody testing has been used and false positive results for SARS-CoV-2 IgG assay might occur as a result of cross reactivity from pre-existing antibodies.[39] However, a study recently reported 99.9% specificity and 100% sensitivity for this assay.[22] Also, since Kawasaki-like multisystem inflammatory syndrome might induce immune reactions with multiple antibody production, patients may show transient cross reactive IgG leading to false positive serology results for SARS-CoV-2. IgG antibody levels against SARS-CoV-2 should therefore be monitored.

Conclusions and policy implications

Our study documents an outbreak of Kawasaki-like multisystem inflammatory syndrome in children and adolescents in the Paris area and its association with recent SARS-CoV-2 infection. Further studies are needed to explore potential causality. The patients reported here had characteristics that differ from those of patients with classic Kawasaki disease (table 4): this present form seems to be more common among children of African ancestry, with predominant acute gastrointestinal symptoms, haemodynamic instability, and myocarditis. These clinical findings should prompt high vigilance among primary care and emergency doctors, and preparedness during the covid-19 pandemic in countries with a high proportion of children of African ancestry.

AUTHOR AFFILIATIONS

[1]Department of General Paediatrics and Paediatric Infectious Diseases, Necker-Enfants Malades University Hospital, Assistance Publique – Hôpitaux de Paris (AP-HP), Université de Paris, 149 rue de Sèvres, 75015 Paris, France

[2]Institut Pasteur, Biodiversity and Epidemiology of Bacterial Pathogens, Paris, France

[3]Paediatric Intensive Care Unit, Necker-Enfants Malades University Hospital, AP-HP, Université de Paris. Paris, France

[4]M3C-Necker-Enfants Malades University Hospital, Université de Paris, Paris, France

[5]Virology Laboratory, Necker-Enfants Malades University Hospital, AP-HP, Université de Paris, Paris, France

[6]Pediatric Emergency Department, Necker-Enfants Malades University Hospital, AP-HP; INSERM, Centre de Recherche des Cordeliers, UMRS 1138, Université de Paris, Paris, France

[7]Pediatric and Emergency Unit, Louis Mourier Hospital, Université de Paris, Paris, France

[8]Pediatric Emergency Unit, Hôpital Intercommunal, Créteil, France

[9]Department of Clinical Microbiology, Necker-Enfants Malades University Hospital, AP-HP; EHU 7328 PACT, Imagine Institute, Université de Paris, Paris, France

[10]Obstetrical, Perinatal and Pediatric Epidemiology Research Team, Centre of Research in Epidemiology and Statistics, INSERM, Université de Paris, Paris, France

[11]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Imagine Institute, Pediatric Hematology and Immunology Unit, Necker-Enfants Malades Hospital, AP-HP, Université de Paris, Paris, France

[12]St Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller Unversity, Howard Hughes Medical Institute, New York, NY, USA

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Ethical approval: The study protocol, questionnaires, procedures, and informed consent forms were approved by the ethical committee (Comité de Protection des Personnes Ouest IV, No DC-2017-2987).

Data sharing: Code for all the analyses as well as the anonymised database will be made available on reasonable request.

Dissemination to participants and related patient and public communities: We immediately disseminated the work by prepublishing in MedRxiv. We sent the manuscript to some members of the French public health authorities, and The BMJ editorial team sent our findings to the World Health Organization during the reviewing process. WHO and the French public health authorities might, at their discretion, share this further with population groups.

The manuscript's guarantor (MC) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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