CLINICAL SCIENCE

Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort

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ABSTRACT

Background Current data suggest that COVID-19 is less frequent in children, with a milder course. However, over the past weeks, an increase in the number of children presenting to hospitals in the greater Paris region with a phenotype resembling Kawasaki disease (KD) has led to an alert by the French national health authorities.

Methods Multicentre compilation of patients with KD in Paris region since April 2020, associated with the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ('Kawa-COVID-19'). A historical cohort of 'classical' KD served as a comparator.

Results Sixteen patients were included (sex ratio=1, median age 10 years IQR (4·7 to 12.5)). SARS-CoV-2 was detected in 11 cases (69%), while a further five cases had documented recent contact with a quantitative PCR-positive individual (31%). Cardiac involvement included myocarditis in 44% (n=7). Factors prognostic for the development of severe disease (ie, requiring intensive care, n=7) were age over 5 years and ferritinaemia >1400 µg/L. Only five patients (31%) were successfully treated with a single intravenous immunoglobulin (IVIg) infusion, while 10 patients (62%) required a second line of treatment. The Kawa-COVID-19 cohort differed from a comparator group of 'classical' KD by older age at onset 10 vs 2 years (p<0.0001), lower platelet count (188 vs 383 G/L (p<0.0001)), a higher rate of myocarditis 7/16 vs 3/220 (p=0.0001) and resistance to first IVIg treatment 10/16 vs 45/220 (p=0.004).

Conclusion Kawa-COVID-19 likely represents a new systemic inflammatory syndrome temporally associated with SARS-CoV-2 infection in children. Further prospective international studies are necessary to confirm these findings and better understand the pathophysiology of Kawa-COVID-19.

Trial registration number
NCT02377245

Key messages

What is already known about this subject?

- COVID-19 is less frequent in children than adults, with a milder course. However, cases of paediatric inflammatory multisystem syndrome with features resembling atypical Kawasaki disease have been recently reported in children in the UK, as well as in Italy and the USA.

What does this study add?

- We describe 16 cases of Kawasaki-like disease following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This association suggest COVID-19 is a novel cause of atypical Kawasaki disease occurring several weeks after SARS-CoV-2 infection.
- Severe disease, with the need for intensive care due to myocarditis, was seen in almost half of ascertained cases, with a higher risk of poor outcome for patients older than 5 years, particularly teenagers.
- Severe prognostic factors include age over 5 years and ferritin >1400 µg/L.

How might this impact on clinical practice or future developments?

- Rapid and aggressive treatment includes initial intravenous immunoglobulin infusion; subsequent treatment with steroid, anti-interleukin (anti-IL)-1 or IL-6 therapy should be considered according to evolution.

INTRODUCTION

Since the first reported case of pneumonia in December 2019 in Wuhan, China, coronavirus disease 2019 (COVID-19) related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a severe pandemic, with more than 200 000 deaths worldwide.[1 2] Compared with adults, children appear to be less affected and to develop milder disease.[3] Only rare cases of severe and fatal outcomes have been reported in paediatric series.[4 5] Alerts on Paediatric Multisystem

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Inflammatory Syndrome temporally associated with SARS-CoV-2 (PIMS-TS), in the UK, and Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19, in the USA, as well as observational cohorts, including Kawasaki disease and myocarditis, have been recently reported.[6–9] Yet, it is not known whether these manifestations should be considered as the same spectrum of a novel disease or as an association of different post infectious diseases.

Kawasaki disease (KD) is a medium and small-sized vessel vasculitis of unknown pathogenesis. It occurs mainly in children under the age of 5 years. Coronary dilation and aneurysms are the main complication (26% to 40% if no treatment is administered, and reduced to 3% to 6% when treated timely with immunoglobulin infusion). KD represents the primary cause of acquired heart disease in developed countries.[10] Pericarditis occurs in 18% of patients. Myocarditis is observed in 3% of cases, leading only occasionally to cardiogenic shock in the acute phase.[11 12] Seasonal variation, epidemiological clustering and a very low risk of recurrence suggest that infectious agents may be the main trigger of KD, although no unique specific microorganism has been identified yet.[13] Host genetic factors might be involved in the pathophysiology of KD, which results in strong activation of the innate immune system.[14 15]

In France, the greater Paris region has been a hot spot of COVID-19 cases between March and April 2020. Almost 6 weeks after the first French SARS-CoV-2 outbreak, we report a series of 16 patients presenting features of KD-like systemic inflammatory disease, associated with a proven or highly suspected SARS-CoV-2 infection ('Kawa-COVID-19').

PATIENTS AND METHODS

Kawa-COVID-19 cohort

Patients were included on a retrospective basis according to the initial contact with two national referral networks (RAISE and CEREMAIA) encompassing seven different Paris-region hospitals (Robert-Debré and Pitié-Salpétrière in Paris, Kremlin-Bicêtre, Argenteuil, Louis-Mourier, Pontoise and Créteil Hospitals). Inclusion criteria were: age under 18 years, complete or incomplete KD and positive testing for SARS-CoV-2 infection by reverse transcription PCR (RT-PCR) or serology and/or close contact with an individual confirmed with COVID-19. KD was defined by persistent fever over 5 days associated with at least four of the five following criteria: conjunctivitis, lymphadenopathy, skin rash, red and cracked lips, inflammation of hands and feet.[16] Severe disease course was defined by a necessity for intensive care (at least one organ failure) and/or fatal outcome. We deliberately chose to include patients displaying clinical signs of complete or incomplete KD in order to compare them to our 'historical' KD cohort, prior to SARS-CoV-2 pandemic. Kawasaki shock syndrome was defined on the basis of systolic hypotension for age, a sustained decrease in systolic blood pressure from baseline of >or=20% or clinical signs of poor perfusion.[17]

Historical KD cohort

As previously published, we recorded the number of patients diagnosed with KD according to the same validated diagnostic criteria[16] between 2005 and 2020 in one of our centres. The clinical and biological characteristics were comparable to the French national cohort.[12 18] Patients for whom another diagnosis was confirmed during the follow-up were excluded. For each patient, demographic, clinical and biological data were recorded. All data were collected anonymously. This historical cohort of 'classical' KD patients, prior to the COVID-19 pandemic, was compared with the Kawa-COVID-19 cohort described here.

Patients were registered in the national BaMaRa (centre for rare diseases) database and the JIR cohort (www.jircohort.org).

Virology and immunology investigations

Specific RT-PCR for SARS-CoV-2 in nasopharyngeal secretions, blood or stool was performed using either the Xpert Xpress SARS-CoV-2 (Cepheid) or the Abbott Real Time SARS-CoV-2 assay. SARS-CoV-2 serology was performed using Human COVID-19 IgG/IgM antibody (ELISA kit EUROIMMUN). The multiplex PCR, FilmArray Respiratory Panel 2 plus (bioMérieux), tested for the presence of the following respiratory pathogens: Adenovirus, coronavirus 229E, coronavirus HKU, coronavirus NL63, coronavirus OC43, metapneumovirus, rhinovirus/enterovirus, influenza A, influenza B, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, Respiratory Syncitial Virus (RSV), *Bordetella parapertussis*, *Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.

Statistics

First, we described patient characteristics as numbers and percentages for categorical variables, and median with IQR for quantitative ones. Second, we assessed the association between these characteristics and severe evolution using the Fisher's exact test for categorical variables, and the Mann-Whitney U test for quantitative variables. Third, quantitative variables associated with severity were transformed into binary variables using the receiver operating characteristic (ROC) curve. We then built a scoring system to predict patient severity. ROC curves were used to obtain the optimised cut-off value for the score maximising sensitivity and specificity to distinguish severe and non-severe patients. Finally, we compared the characteristics of Kawa-COVID-19 patients and the historic KD cohort using the Fisher's exact test for categorical variables, and the Mann-Whitney U test for quantitative variables. A two-sided p value <0.05 was considered statistically significant. All statistical analysis were made using R V.3.6.1 (http://www.R-project.org).

RESULTS

Kawa-COVID-19 patients are affected at all ages

Sixteen patients were included (sex ratio 1). Clinical and biological characteristics are summarised in table 1. Median age was 10 years (IQR (4.7 to 12.5)). Underlying conditions were reported in six patients (37%), specifically: overweight (n=4, all weights above 3 SD, two BMI available over 1.5 SD), asthma (n=2). Only one child was receiving chronic treatment (salbutamol) at the time of diagnosis. Median time from the onset of Kawa-COVID-19 to hospitalisation was 5 days (IQR 4 to 7).

Investigations consistent with prior SARS-CoV-2 infection

Twelve patients (75%) reported exposure to a family member with either proven COVID-19 (n=5) or highly suspected COVID-19 (n=7; at least two of the following symptoms: fever, anosmia, loss of taste, cough, respiratory signs). A median disease-free interval of 21 days (IQR 21 to 24) separated first exposure and hospitalisation (data available for 10 patients). The medical history was notable for the absence of any COVID-19 clinical signs in all patients. SARS-CoV-2 assessments in patients are summarised in online supplementary table S1. SARS-CoV-2 infection was confirmed in 11 patients by RT-PCR, in nasopharyngeal secretion and stool samples in 9 and 2 patients,

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Table 1 Clinical and biological features of the Kawa-COVID-19 cohort

Clinical and biological results	Kawa-COVID-19 cohort	Group 1 severe	Group 2 non-severe	P value
Number of patients	16	7	9	
Sex ratio	1	0.7	0.8	1
Age (median in years, (IQR))	10 (4.7 to 12.5)	12 (9.5 to 15.5)	5 (2 to 10)	0.043
Comorbidities: n (%)	6 (37%)	2 (28%)	4 (44%)	1
Asthma	2	0	2	
Overweight	4	2	2	
Family c/s COVID-19 infection n (%)	12 (75%)	6 (86%)	6 (67%)	
First infectious exposure - hospitalisation (median days, (IQR))	21 (21 to 24)	21 (21 to 25)	21 (15 to 21)	
Patient symptoms: n (%)				
Fever	16 (100%)	7 (100%)	9 (100%)	1
Respiratory signs	2 (12%)	1 (14%)	1 (11%)	**1**
Gastrointestinal signs	13 (81%)	6 (86%)	7 (78%)	**1**
Anosmia	1 (6%)	1 (14%)	0	0.438
Neurological signs	9 (56%)	5 (71%)	4 (44%)	0.431
Skin rash	13 (81%)	6 (86%)	7 (78%)	1
Hands and feet erythema/oedema	11 (68%)	5 (71%)	6 (67 %)	1
Conjunctivitis	15 (94%)	6 (86%)	9 (100%)	0.438
Dry cracked lips	14 (87%)	6 (86%)	8 (89%)	**1**
Cervical lymphadenopathy	6 (37%)	3 (43%)	3 (33%)	1
Arthritis	1 (6%)	1 (14%)	0	0.438
Haemodynamic failure	11 (69%)	7 (100%)	4 (44%)	0.034
Complete Kawasaki disease: n (%)	10 (62%)	4 (57%)	6 (67%)	1
Kawasaki disease shock syndrome n (%)	7 (44%)	6 (86%)	1 (11%)	
Biological results: median, (IQR)				
CRP (mg/L)	207 (162 to 236)	245 (182 to 299)	193 (170 to 219)	0.174
Leucocytes (G/L)	11.5 (9 to 14.4)	12.7 (11.7 to 30)	9.7 (9.7 to 11.9)	0.114
Neutrophils (G/L)	9.2 (7.6 to 10.7)	10 (9.6 to 10.7)	8 (6.4 to 9.6)	0.137
Lymphocytes (G/L)	1.15 (0.8 to 1.7)	0.93 (0.67 to 1.12)	1.6 (1 to 1.7)	**0.345**
Platelets (G/L)	188 (164 to 244)	183 (170 to 240)	193 (136 to 228)	1
Ferritinaemia (g/L)	1067 (272 to 1709)	1760 (1693 to 2500)	295 (165 to 536)	0.003
Sodium (mmol/L)	130 (127 to 134)	127 (127 to 132)	130 (129 to 136)	0.312
Urea (mmol/L)	6.3 (4.1 to 17)	24 (6.8 to 32)	4.2 (3.8 to 6.2)	0.003
Creatinine (µmol/L)	59 (44 to 124)	145 (87 to 237)	44 (44 to 61)	0.038
Troponin (ng/L)	58 (36 to 165)	64 (52 to 1023)	40 (21 to 60)	0.073
BNP (pg/mL)	4319 (2747 to 6493)	2231 (1664 to 3287)	7209 (5751 to 7339)	0.2
Albumin (g/L)	21 (19 to 23)	18.5 (18 to 20)	22 (22 to 24)	0.212
Positive SARS-CoV-2 RNA testing: n (%)				
RT-PCR all sites	11 (69%)	6 (86%)	5 (55%)	
Nasopharyngeal RT-PCR	9/16 (56%)	5/7 (71%)	4/9 (44%)	0.358
RT-PCR in stool	2/5 (40%)	1/1 (100%)	1/4 (25%)	1
RT-PCR in blood	0/4	0/2	0/2	1
Serology (IgG+)	7/8 (87%)	3/3 (100%)	4/5 (80%)	1
Abnormal chest X-ray	5 (31%)	2 (28%)	3 (33%)	1
Heart ultrasound: n (%)				
Abnormal	11 (69%)	6 (86%)	5 (55%)	0.308
Coronary dilation	3 (19%)	1 (14%)	2 (22%)	1
Median Z-score (IQR)	2.6 (1.7 to 3.7)	2.6	2.7 (1.7 to 3.7)	
Myocarditis	7 (44%)	6 (86%)	1 (11%)	0.015
Median LVEF (IQR)	35 (32 to 46)	34 (3 to 43)	50	
Pericarditis	4 (25%)	1 (14%)	3 (33%)	0.242
Treatment:				
Intravenous immunoglobulin	15 (93%)	7 (100%)	8 (89%)	1
Single infusion	10 (67%)	6 (85%)	4 (44%)	
Second infusion	5 (33%)	1 (14%)	4 (44%)	
Steroids	4 (25%)	3 (43%)	1 (11%)	0.262
Anti-IL-1 treatment	1 (6%)	1 (14%)	0	
Anti-IL-6 treatment	1 (6%)	1 (14%)	0	
Hydroxychloroquine	1 (6%)	1 (14%)	0	

Continued

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Table 1 Continued

Clinical and biological results	Kawa-COVID-19 cohort	Group 1 severe	Group 2 non-severe	P value
Acetylsalicylique acide	15 (93%)	7 (100%)	8 (89%)	
Anti-inflammatory dose (30 to 50 mg/kg)	7 (52%)	3 (43%)	3 (37%)	
Anti-aggregant dose	8 (50%)	4 (57%)	5 (62%)	
Delay treatment - end of fever (median days, (IQR))	2 (1 to 9)	6 (4 to 8)	2 (1 to 5)	0.458
Delay between onset and end of fever (median days, (IQR))	9 (8 to 13)	9 (9 to 12)	8 (8 to 12)	0.346

BNP, brain natriuretic peptide; c, confirmed; CRP, C-reactive protein; IL, interleukin; LVEF, left ventricular ejection fraction; RT-PCR, reverse transcription PCR; s, suspected; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

respectively, and by serology in 7 patients. When available, PCR cycle threshold (Ct) was above 35 in six out of seven patients (86%), reflecting a low viral load. SARS-CoV-2 viraemia performed for four patients was negative. Two patients remained negative by all tests, but had close exposure to confirmed SARS-CoV-2 individuals (positive RT-PCR by nasopharyngeal testing). Chest X-Rays and CT scans were performed in respectively, 15 and 8 patients. Two patients had typical COVID-19 radiological CT features (figure 1A). No other viral agents were identified on respiratory screening (11 patients tested).

Clinical description at onset of Kawa-COVID-19 patients

Ten patients (62%) fulfilled the American Heart Association (AHA) definition of complete KD. Fever above 39°C was present in all patients, and over 40°C in severe patients (n=7). Main associated features were mucocutaneous involvement (n=15, 94%) such as diffuse skin rash (n=13, 81%), rash/oedema of hands and feet (n=11, 68%), conjunctivitis (n=15, 93%), dry cracked lips (n=14, 87%), cervical lymphadenopathy (n=6, 37%) and arthritis (n=1, 6%) (table 1, figure 1B–E). In addition to classical manifestations of KD,[8] other features were frequent, such as gastrointestinal symptoms (n=13, 81%) and haemodynamic failure (ie, tachycardia and one of the following signs: arterial systemic hypotension, cold extremities, decreased peripheral pulse, capillary refill time >3 s, oliguria or blood lactate >2 mmol/L) 11/16 (69%). Two patients experienced orchitis. Less typical features, including neurological signs (ie, headaches (n=6, 37%), aseptic meningitis (n=3, 18%)), respiratory signs (cough or dyspnoea (n=2, 12%), Raynaud syndrome (n=2, 12%) and anosmia (n=1, 6%), were observed and may be linked to COVID-19.[4 19 20]

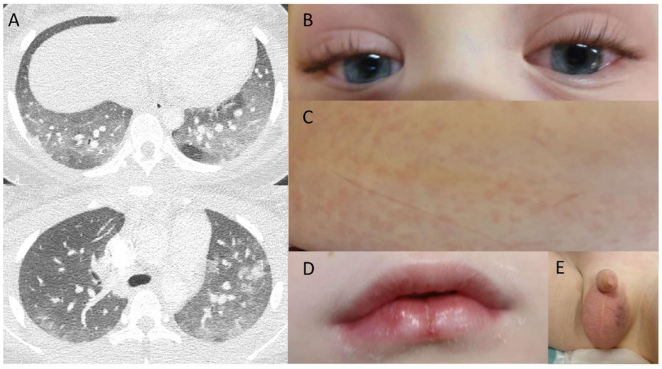

Figure 1 Clinical features of Kawa-COVID-19 patients. (1A) Chest CT scan (lung window) of a 12-year-old girl with Kawasaki disease and SARS-CoV-2 infection showing diffuse peripheral ground-glass opacities in both lungs. (1B-1E) Mucocutaneous lesions in a 4.5-year-old boy with Kawasaki disease and SARS-CoV-2 infection: Non-purulent conjunctivitis (1B), maculo-papular rash (1C), dry cracked lips (1D) and orchitis (1E).

Neither pulmonary embolism nor acute respiratory distress syndrome was reported.

Inflammatory storm with features of macrophagic activation syndrome

Biological signs are summarised in table 1. Inflammatory biomarkers were highly elevated in all patients with median C-reactive protein (CRP) 207 mg/L (IQR 162 to 236), and median procalcitonin (PCT) 12.6 ng/L (IQR 6 to 110). Median leucocyte count was 11.5 G/L (IQR 9 to 14.4) with median neutrophil count 9.2 G/L (IQR 7.5 to 10.7) and median lymphocyte count 1.15 G/L, (IQR 0.8 to 1.7). Ferritin (median 1067 µg/L (IQR 272 to 1709)) was abnormal in 12 of 14 tested patients, and highly elevated (>500 µg/L) in 50% of cases. Two patients (12%) met the biological criteria for macrophagicactivation syndrome (MAS) using the 2016 classification in systemic juvenile idiopathic arthritis.[21] Nevertheless, none of the patient fulfilled hemophagocytic lymphohistiocytosis (HLH) MAS criteria.[22] Acute renal failure was observed in nine cases (56%), with elevated urea (median urea 6.3 mmol/L (IQR 4.1 to 17)) and creatinine (median creatinine 59 µmol/L (IQR 44 to 124)). Seven patients (43%) had hypoalbuminaemia (median 21 g/L (IQR 19 to 23)) and two of them had high uricaemia. Liver enzymes were abnormal in five cases (31%). Serum cytokines were elevated in tested patients, especially tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6) (online supplementary table S2).

Kawa-COVID-19 is associated with severe vascular and cardiac involvement

Myocardial enzymes were elevated in 11 patients (100% of patients with available data): median troponin was 58 ng/L (IQR 36 to 165)) (n<20) and median N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was 4319 pg/mL (IQR 2747 to 6493) (n<100). Cardiac ultrasound was abnormal in 11 patients (68%): coronary dilation in three cases (18%) with median Z-score of 2.6 (1.7 to 3.7) without any aneurysm, pericarditis in four patients (25%) and myocarditis in seven patients (43%), with a median left ventricular ejection fraction at diagnosis of 35% (32% to 46%).

Therapeutic management and intensive care unit requirement

Fifteen patients (94%) received a first infusion of 2 g/Kg of intravenous immunoglobulin (IVIg). Among these patients and as a second line of treatment: four received a second IVIg infusion, one received a second IVIg infusion associated with steroids, two received steroids and finally, two received other biologics. Aspirin was added to IVIg either at anti-inflammatory doses (30 to 80 mg/kg/day) in seven (47%) patients or as an anti-aggregant in eight (53%) patients. One patient received IL-1 receptor antagonist (anakinra 4 mg/kg) for respiratory

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distress and another received IL-6 receptor antagonist (tocilizumab 8 mg/kg) for persistent systemic inflammation. One patient received hydroxychloroquine for initial suspicion of systemic lupus erythematosus. None of the patients received antiviral treatment.

Seven patients were admitted to intensive care unit (ICU) for either heart failure due to myocarditis (ie, abnormal troponin and/or NT-proBNP levels and cardiogenic shock or acute left ventricular dysfunction (left ventricular ejection fraction <50%) for six out of seven patients or respiratory distress without cardiac involvement (one out of seven patients). Seven patients met the criteria for Kawasaki disease shock syndrome (44%), among whom six were admitted to the ICU. All these patients required fluid rescuscitation and six required inotropic supports. Respiratory assistance for ICU patients included oxygen therapy (n=4, 57%) for a median time of 2 days, non-invasive ventilation (n=3, 42%) or invasive ventilation (n=2, 28%).

Outcome

Overall median follow-up after inclusion was 14 days (IQR 10 to 20). Median duration of Kawa-COVID-19 disease from onset until abatement of fever was 9 days (IQR 8 to 13) in 10 patients. Median time between initiated treatments and clinical remission was 2 days (IQR 1 to 8). All patients are in remission (ie, absence of fever, disappearance of clinical signs, complete regression of inflammatory biomarkers) after treatment and have been discharged on anti-aggregant aspirin treatment. No patients died. Severe patients, that is, those requiring ICU, represented 44% of the cohort (n=7). All of them have achieved inflammatory remission. However, two of them still present with mild cardiac dysfunction secondary to myocarditis. One patient is still undergoing steroid treatment for autoimmune haemolytic anaemia, after the second IVIg infusion. Nine patients have been examined during follow-up (7 to 15 days after discharge): all were asymptomatic, with negative inflammatory biomarkers, seven with normal heart ultrasounds and two with mild persistant cardiac dysfunction. One patient achieved remission without treatment. This patient presented all signs in favour of complete KD, with normal cardiac ultrasound at day 8. No other infectious agent was diagnosed, beside a positive SARS-CoV-2 nasal PCR. No other diagnosis was confirmed. All clinical signs and inflammatory biomarkers spontaneously resolved at day 8. At 30 days of follow-up, the patient's clinical examination was normal, with history of skin peeling of the hands and feet at day 15. The CRP level remained negative, without any other inflammatory marker, and the heart ultrasound was also normal.

Factors associated with severe Kawa-COVID-19

We compared severe and non-severe patients (table 1). Severe patients included significantly older patients (median age 12 vs 5 years, p=0.043) and displayed higher ferritin levels (median 1760 µg/L vs 295 µg/L (p=0.003)). Based on ROC curve analysis, a threshold of ferritin >1400 µg/L and age >5 years provided the best discriminators. By combining these two parameters (one point for each of them) a highly discriminant score was obtained (area under the curve 0.957, sensitivity=80%, specificity=100% for a threshold ≥2) (table 1, online supplementary figure S1).

Finally, we compared the Kawa-COVID-19 patients with our historic cohort from the same region (ascertained before the onset of the SARS-CoV-2 pandemic). The results are shown in table 2. Major differences in our cohort were: older age (median 10 vs 2 years, p<0.0001), lower platelet counts (p<0.0001) and lower lymphocyte counts (p<0.0001). Importantly, a higher frequency of cardiac involvement, particularly myocarditis (1% vs 44%, p=0.0001) and pericarditis (7% vs 25%, p=0.029), was observed in Kawa-COVID-19 patients. Moreover, a greater number of these patients required a second line of treatment after one IVIg infusion (10/16 vs 45/220, p=0.004).

Table 2 Comparison between Kawa-COVID-19 cohort and historical cohort in the Paris region

	Historical cohort (n=220)	Kawa-COVID-19 cohort (n=16)	P value
Median age (IQR)	2 (1.2 to 3.6)	10 (4.7 to 12.5)	<0.0001
Male gender	128/220 (58%)	8/16 (50%)	0.63
Clinical features: n (%)			
Skin rash	187/220 (85%)	13/16 (81%)	0.718
Hands and feet erythema/ oedema	120/220 (54%)	11/16 (68%)	0.099
Conjunctivitis	176/220 (80%)	15/16 (94%)	0.342
Dry cracked lips	189/220 (85%)	14/16 (87%)	1
Cervical lymphadenopathy	114/220 (52%)	6/16 (37%)	0.309
Complete Kawasaki disease: n (%)	142/220 (64%)	10/16 (62%)	1
Biological results: median (IQR)			
CRP (mg/L)	142 (95 to 197)	207 (162 to 236)	0.006
Platelets (G/L)	383 (289 to 491)	188 (164 to 244)	<0.0001
Lymphocytes (G/L)	3.08 (1.86 to 4.77)	1.15 (0.8 to 1.7)	<0.0001
Natraemia (mmol/L)	135 (134 to 137)	130 (127 to 134)	0.0003
Albumin (g/L)	25 (22 to 28)	21 (19 to 23)	0.024
Echocardiography abnormalities: n (%)	54/220 (26%)	11/16 (69%)	0.0004
Myocarditis	3/220 (1%)	7/16 (44%)	0.0001
Coronary dilations	42/220 (19%)	3/16 (19%)	1
Pericarditis	15/220 (7%)	4/16 (25%)	0.029
Resistance to single IVIg	45/220 (20%)	10/16 (62%)	0.004
Origin:			164
Afro-Caribbean	67/187 (36%)	10/16 (62%)	56
Middle East	44/187 (23%)	2/16 (12%)	532
European	48/187 (27%)	4/16 (25%)	1
Asia	28/187 (15%)	0/16	136

CRP, C-reactive protein; IVIg, intravenous immunoglobulin.

DISCUSSION

Until recently, COVID-19 has been considered as a benign disease in children.[1] Herein, we report 16 patients presenting a systemic inflammatory syndrome mimicking KD, temporally associated with SARS-CoV-2 infection (Kawa-COVID-19). Severe disease, requiring intensive care, was observed in 44% of cases. Although classical signs of KD, complete or not, were present in all patients, we could identify fairly clear differences from typical KD that should draw attention to this syndrome, and suggest that it represents a novel entity (figure 2), consistent with the series of Verdoni *et al*.[7] First, the median age at presentation is greater than in classical KD, with older age (>5 years) as an indicator of possible ICU support. Second, both the frequency and severity of myocarditis is strikingly different from classical KD. Third, abdominal pain and/or diarrhoea were more frequently (81%) reported than in classical KD (approximately one out of three patients).[16] Finally, the cytokine storm, reflected clinically by heart failure, pneumonia, gastrointestinal, neurological and renal features, associated with elevated CRP levels, ferritin and cytokines (IL-1, TNFα and IL-6 especially), was more common in the syndrome that we describe. These

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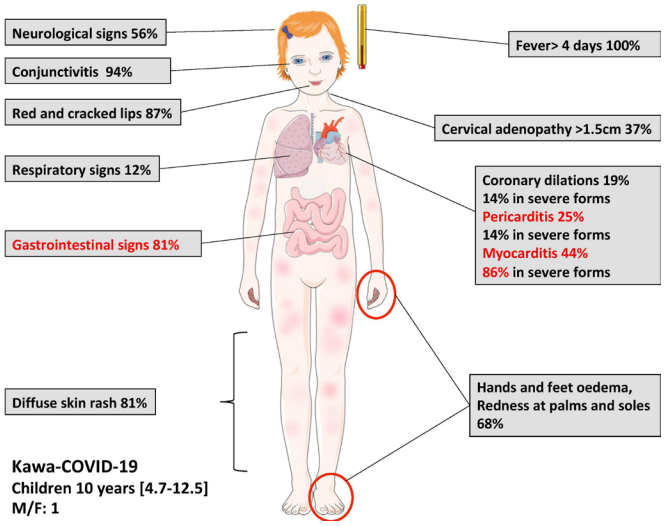

Figure 2 Main clinical features of Kawa-COVID-19 from the Paris region cohort, n=16 patients. In red: higher frequencies than classical Kawasaki disease.

signs, heart failure apart, are also common in adults with severe COVID-19.[23] However, in contrast to severe adult COVID-19, our patients rarely demonstrated respiratory features, suggesting a different underlying host immune response in children.

Our data suggests that clinicians should suspect Kawa-COVID-19 in any child presenting with unexplained high fever and an elevation of CRP in the context of the SARS-CoV-2 pandemic, especially if mild signs of COVID-19 or confirmed exposure to SARS-CoV-2 were reported in the past 4 weeks. In such cases, classical clinical signs of KD should be carefully searched for, as well as digestive symptoms and respiratory features. Some investigations should be systematically performed on an urgent basis, in order to diagnose life-threatening complications. These include a search for myocarditis (troponin, NT-proBNP, ECG), features of MAS (white blood cells, fibrinogen, ferritin, albuminaemia) and renal impairment (creatinine, urea, proteinuria). Clinicians should be particularly cautious with patients over 5 years demonstrating elevated ferritin levels (above 1400 µg/L) because of the risk of rapidly progressive Kawa-COVID-19 and heart failure. Patients should undergo SARS-CoV-2 testing by RT-PCR, at least in nasopharyngeal secretions and stool, and SARS-CoV-2 serology should also be undertaken, since RT-PCR may be negative, related to the late onset of this syndrome after initial COVID-19 signs or exposure, along with other viral investigations in order to exclude alternative diagnoses.

Our descriptive study does not demonstrate a direct link between KD and SARS-CoV-2 so far. Interestingly, all these cases occurred between 7th April and 30th April 2020, 1 week after the peak of the epidemic in the greater Paris region (occurring between 31st March and 1st April 2020). Moreover, such an increase in the incidence of KD has been noted in several other European countries and the USA. The Royal College of Paediatrics and Child Health, UK, and the New York City Health Department issued guidelines related to a paediatric multisystem inflammatory syndrome temporally associated with COVID-19 at the end of April 2020 and beginning of May 2020, respectively. In addition, a case report of such an association and a few paediatric series of hyperinflammatory shock during COVID-19 pandemic have been recently published.[6–8 24]

Pathophysiology has yet to be elucidated. However, a post-infectious process with delayed immune activation leading to a cytokine burst, responsible for fever, skin rash, cardiac failure and a major inflammatory syndrome, seems likely, similar to the presumed pathophysiology of 'classical' KD.[25 26] Onset of the disease appears to occur 2 to 4 weeks after acute SARS-CoV-2 infection or exposure. Thus, in the majority of patients, nasal SARS-CoV-2 viral load was low (Ct >35 in 86%) or negative, with some residual stool excretion. Where antibodies could be assessed, all patients were IgG positive (n=7), suggesting SARS-CoV-2 infection in the previous 2 weeks or more.[27] No concomitant viraemia was observed, in contrast to severe adult COVID-19, where high viral loads are reported.[28] Moreover, no other viral pathogens were identified, as assessed by multiplex PCR array. These findings suggest that SARS-COV-2 might act as a trigger of a post-infectious inflammatory disease. Viral elements have been found in endothelial cells infected by SARS-CoV-2, as well as an accumulation of inflammatory cells, apoptosis and pyroptosis.[29] SARS-CoV-2-epithelial damage at an early stage may induce secondary local endothelitis, which may explain a delayed auto-inflammatory vasculitic phenotype with upregulation of IL-1β or IL-6, such as in KD models.[30 31] The question remains if Kawa-COVID-19 paediatric patients display a specific cytokine imbalance and immune disregulation in comparison to adult COVID-19 individuals, and if underlying genetic factors of susceptibility may predispose some children more than others to such inflammatory disease. Indeed, a trend of over-representation of Afro-Caribbean descent was observed in our cohort.

Because of the rapidly progressive evolution, patients should receive thorough monitoring and prompt therapeutic management. Indeed, 44% and 19% of patients, respectively, presented either with myocarditis or dilated coronary arteries. Treatment with IVIg 2 g/kg should rapidly be administered and appeared to be effective in a majority of cases, as in classic KD.[12 18] Nevertheless, associated anti-inflammatory treatment, such as steroids or biologics, was necessary in 31% of patients and should be considered if a severe course is observed or in the presence of factors prognostic for a severe course—particularly, age over 5 years and elevated ferritin levels (>1400 µg/L). According to KD literature data, several additional treatment approaches may be considered. Thus, steroids have been successfully used in KD for several years. Anakinra, an IL-1 receptor antagonist, has been reported as promising in refractory cases,[32] and its strong anti-inflammatory effect is still being investigated in clinical trials[33] (KAWAKINRA, ClinicalTrials.gov: NCT02390596). Tocilizumab, an anti-IL-6 receptor monoclonal antibody, is used in systemic onset juvenile idiopathic arthritis, which shares some features with Kawa-COVID-19, such as skin rash, fever, arthritis, major inflammatory syndrome and elevated ferritin and MAS features. Moreover, series including adult patients with severe COVID-19 demonstrate elevated IL-6 levels, as well as patients tested in our cohort and tocilizumab has shown promising results in such patients (CORIMUNO-19, ClinicalTrials.gov: NCT04331808).[34 35] Further clinical studies and international collaborations are now required to evaluate these treatment options.

CONCLUSION

The present series suggests that an auto-inflammatory disease resembling KD is linked to a SARS-CoV-2 infection (Kawa-COVID-19). However, this disease differs from classical KD as it occurs at an older age, and presents with a higher frequency of severe myocarditis and/or pericarditis. Features prognostic of a severe course include age greater than 5 years and elevated ferritin

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(>1400 µg/L). Single IVIg resulted in a remission of inflammatory manifestations in only 5 out of 16 patients (31%), and 10 patients (62%) required a second line of treatment. Further prospective international collections of Kawa-COVID-19, including the assessment of immunological and host genetic factors, are necessary to better understand this novel disease entity.

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