



Distinctive Features of Kawasaki Disease Following SARS-CoV-2 Infection: a Controlled Study in Paris, France

Julie Toubiana^{1,2} · Jérémie F. Cohen^{1,3} · Joséphine Brice¹ · Clément Poirault¹ · Fanny Bajolle⁴ · William Curtis⁵ · Florence Moulin⁶ · Soraya Matczak^{1,2} · Marianne Leruez⁷ · Jean-Laurent Casanova^{8,9} · Martin Chalumeau^{1,3} · Melissa Taylor¹ · Slimane Allali¹

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Abstract

Background An outbreak of multisystem inflammatory syndrome in children, including Kawasaki disease (KD), emerged during COVID-19 pandemic. We explored whether Kawasaki-like disease (KD), when associated with confirmed SARS-CoV-2 infection, has specific characteristics.

Methods We included children and adolescents with KD criteria admitted in the department of general pediatrics of a university hospital in Paris, France, between January 1, 2018, and May 26, 2020. The incidence of KD was compared between the outbreak and a pre-outbreak control period (January 1, 2018, to April 25). Characteristics of patients with positive SARS-CoV-2 testing (KD-SARS-CoV-2) were compared to those of the pre-outbreak period (classic KD).

Results A total of 30 and 59 children with KD were admitted during the outbreak and pre-outbreak periods, respectively (incidence ratio 13.2 [8.3–21.0]). During the outbreak, 23/30 (77%) children were diagnosed as KD-SARS-CoV-2. When compared with patients with classic KD, those with KD-SARS-CoV-2 were more frequently of sub-Saharan African ancestry (OR 4.4 [1.6–12.6]) and older (median 8.2 vs. 4.0 years, $p < 0.001$), had more often initial gastrointestinal (OR 84 [4.9–1456]) and neurological (OR 7.3 [1.9–27.7]) manifestations, and shock syndrome (OR 13.7 [4.2–45.1]). They had significantly higher CRP and ferritin levels. Noticeably, they had more frequently myocarditis (OR 387 [38–3933]).

Conclusions Children and adolescents with KD-SARS-CoV-2 have specific features when compared with those with classic KD. These findings should raise awareness and facilitate the study of their pathogenesis.

Keywords Kawasaki disease · PIMS-TS · MIS-C · SARS-CoV-2 · COVID-19

✉ Julie Toubiana
julie.toubiana@aphp.fr

¹ Department of General Pediatrics and Pediatric Infectious Diseases, Necker-Enfants Malades University Hospital, Assistance Publique – Hôpitaux de Paris (AP-HP), Necker Hospital for Sick Children, Université de Paris, 75015 Paris, France

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

³ Centre of Research in Epidemiology and Statistics - CRESS, INSERM, Université de Paris, F-75004 Paris, France

⁴ M3C-Necker Enfants Malades, AP-HP, Paris, France

⁵ Pediatric Emergency Department, Necker-Enfants Malades University Hospital, AP-HP, Université de Paris, Paris, France

⁶ Pediatric Intensive Care Unit, Necker-Enfants Malades University Hospital, AP-HP, Université de Paris, Paris, France

⁷ Virology Laboratory, Necker-Enfants Malades University Hospital, AP-HP, Université de Paris, Paris, France

⁸ Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Imagine Institute, Pediatric Hematology and Immunology Unit, Necker-Enfants Malades University Hospital, AP-HP, Université de Paris, Paris, France

⁹ St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Howard Hughes Medical Institute, The Rockefeller University, New York, NY, USA

Introduction

As of August 2, 2020, more than 17,000,000 confirmed cases and 680,000 deaths due to coronavirus disease 2019 (COVID-19) have been reported [1]. Based on serological data and modelization studies, 10% of Western Europe population has been exposed to SARS-CoV-2 [2, 3]. In adults, severe forms of COVID-19 are typically characterized by severe pneumonia and acute respiratory distress syndrome. In children, COVID-19 seems less frequent and milder than in adults, with almost no fatalities reported in this age group [4–8]. However, an outbreak of severe Kawasaki-like disease in children and adolescents emerged during the COVID-19 pandemic, leading to a first alert by the UK National Health Service, on April 25, 2020.

Several case studies, in regions with high rates of SARS-CoV-2 community transmission, reported children with signs and symptoms consistent with Kawasaki disease (KD) and laboratory evidence of recent SARS-CoV-2 infection [9]. These reports described a hyperinflammatory syndrome with multiorgan involvement, provisionally named “paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection” (PIMS-TS) in Europe and “multisystem inflammatory syndrome in children” (MIS-C) in the USA [10, 11]. MIS-C covers a broad spectrum of inflammatory diseases, including KD with confirmed (or not confirmed) SARS-CoV-2 infection.

Several teams including ours reported that patients with this multisystem inflammatory syndrome might have specific characteristics compared to classic KD [12–15]. However, only two studies specifically analyzed patients fulfilling KD criteria and compared features between patients with KD who tested positive for SARS-CoV-2 (KD-SARS-CoV-2) and classic KD. These preliminary studies only included 8 and 11 patients with KD-SARS-CoV-2 [12, 14]. We aimed at further investigating the characteristics of patients with KD-SARS-CoV-2, compared with patients of the pre-outbreak period with classic KD, in a larger controlled study in Paris area, France.

Methods

Study Design and Setting

We retrospectively reviewed the health records of children and adolescents (aged ≤ 18 years) with a diagnosis of KD admitted to the general pediatric department of Necker Hospital for Sick Children (Paris, France) between January 1, 2018, and May 26, 2020. This 600-bed university hospital hosts a large intensive care capacity and houses referral centers for pediatric cardiovascular diseases and emerging infectious diseases such as COVID-19.

Definitions

We used the criteria of the American Heart Association to define complete and incomplete KD [16], and the criteria proposed by Kanegaye et al. to define KD shock syndrome [17]. Macrophage activation syndrome (MAS) was defined using the Paediatric Rheumatology International Trials Organisation (PRINTO) criteria [18]. Low left ventricular ejection fraction ($< 50\%$) and high concentrations of high-sensitivity cardiac troponin I (> 26 ng/mL) were considered as markers of heart failure and myocarditis, respectively. Coronary artery dilation was defined as a coronary artery diameter z -score on echocardiography between 2.0 and 2.5, and aneurysm as a z -score ≥ 2.5 [16]. Resistance to intravenous immunoglobulin (IVIG) treatment was defined as persistent or recrudescence fever at least 36 h and less than 7 days after completion of the first IVIG infusion [16].

For each included patient, we extracted demographic data, prior medical history, presenting signs and symptoms, contact with confirmed or suspected cases of COVID-19, results of laboratory tests (the most abnormal value before treatment or within 24 h of treatment onset), electrocardiograms and echocardiograms, and treatments. The introduction of corticosteroids was decided by the clinician in charge, mostly because of IVIG resistance or a high risk of IVIG resistance [19].

Investigation of SARS-CoV-2 Infection

For each patient included after the alert related to MIS-C (i.e., April 26, 2020, to May 26, 2020), 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; bioMérieux, Marcy l'Étoile, France). Nasopharyngeal swabs were also tested for other viruses (R-GENE, Argene). We also systematically collected blood samples to test for IgG antibodies against SARS-CoV-2 (Architect SARS-CoV-2 chemiluminescent microparticle immunoassay; Abbott Core Laboratory, IL, USA) [20]. Positivity for RT-PCR was considered consistent with recent or ongoing SARS-CoV-2 infection, while positive IgG was deemed consistent with past infection with SARS-CoV-2 [21]. All patients with negative initial serology testing were retested after an interval of at least 3 weeks.

Statistical Analysis

First, the number of patients with KD admitted in the department of general pediatrics per two-week periods was compared between the outbreak (April 26 to May 26, 2020), and the pre-outbreak control period (January 1, 2018, to April 25, 2020) using Poisson regression modeling. Second, we defined three groups of patients, according to their date of admission in the department of general pediatrics and their results of

SARS-CoV-2 testing. The “classic KD group” included children with KD admitted during the pre-outbreak period; the “KD-SARS-CoV-2 group,” children admitted during the ongoing outbreak with positive SARS-CoV-2 results (RT-PCR, serology, or both); and the “KD-non-SARS-CoV-2 group,” children admitted during the ongoing outbreak with negative SARS-CoV-2 PCR and serology results. Characteristics of patients with KD-SARS-CoV-2 were compared to those of patients with classic KD using univariate analyses. Patients from the KD-non-SARS-CoV-2 group were excluded from this comparison to maximize clinical contrast. We also conducted a sensitivity analysis excluding patients diagnosed with “classic KD” in 2020 in the pre-outbreak period (from January 1, 2020, to April 25, 2020). Differences between groups were assessed by the Mann-Whitney *U* test, the Student *t* test, the χ^2 method, and the Fisher exact test when appropriate. For categorical variables, associations were expressed as odds ratios (OR) with their 95% confidence interval (CI). Statistical analysis was carried out using SPSS v25 (SPSS, Chicago, IL).

Ethical Approval

The study protocol, data extraction forms, and procedures were reviewed and approved by the Necker Hospital Institutional Review Board (No. 2020 0618174239) and by the ethical committee (Comité de Protection des Personnes Ouest IV, No DC-2017-2987).

Results

Descriptive Data

A total of 30 and 59 children with KD were admitted during the outbreak and pre-outbreak periods, respectively, for a Poisson incidence rate ratio of 13.2 (95%CI 8.3–21.0; Fig. 1). Among the 59 children of the pre-outbreak period, 4 were admitted between February 1, 2020, and April 25, 2020; all of them had a negative SARS-CoV-2 serology. Among the 30 children admitted after the April 25 alert, 23 (77%) were diagnosed as KD-SARS-CoV-2 (23/23 had positive SARS-CoV-2 IgG antibodies, and 9/23 had positive RT-PCR testing for SARS-CoV-2 in at least one nasopharyngeal swab; Supplemental Fig. S1). Seven (KD non-SARS-CoV-2) had a negative SARS-CoV-2 RT-PCR and serology, as well as nasopharyngeal testing for respiratory syncytial virus; human metapneumovirus; parainfluenza viruses 1, 2, and 3; rhinovirus and enterovirus; seasonal coronavirus; and influenzae A and B. Among the 23 KD-SARS-CoV-2 patients, 19 were already described in a previous case series [13]. A recent history of viral illness such as flu-like symptoms or coryza was reported in 8/23 (35%) patients. The median time interval

between viral-like symptoms and the onset of signs of KD was 48 (range, 18–123) days. A history of recent contact with family members displaying viral-like symptoms was reported in 12/23 (52%) patients, with a median time interval between the contact and the onset of KD symptoms of 35 (range, 6–65) days. None of these patients had comorbidities. No deaths were recorded.

Comparison of Patients with KD-SARS-CoV-2 and Patients with Classic KD

The 23 patients with KD-SARS-CoV-2 were more frequently of Sub-Saharan African/Caribbean ancestry (OR 4.4 [1.6–12.6]) and older (median 8.2 vs. 4.0 years, $p < 0.001$; Fig. 2) compared to the 59 patients with classic KD (Table 1). No difference was observed between the two groups in terms of KD principal criteria (Table 1). Patients with KD-SARS-CoV-2 differed from patients with classic KD, with more frequent gastrointestinal symptoms (i.e., acute abdominal pain, vomiting, and diarrhea; OR 84 [4.9–1456]) and neurological manifestations (i.e., meningeal irritation and clinical signs of encephalitis; OR 7.3 [1.9–27.7]) at onset, myocarditis (OR 387 [38–3933]), and serous effusions (OR 11.6 [3.7–36.5]). KD-SARS-CoV-2 patients also fulfilled more frequently criteria of KD shock syndrome (OR 13.7 [4.2–45.1]) and more often needed admission in the intensive care unit (OR 196 [31–1257]). These associations were robust in the sensitivity analysis, except that patients with KD-SARS-CoV-2 had more often an incomplete form of KD (OR 3.3 [1.3–9.1]).

Patients with KD-SARS-CoV-2 had higher CRP and procalcitonin levels than patients with classic KD (Fig. 2), and they had significantly more profound lymphopenia and anemia (Fig. 2). Levels of platelets and fibrinogen were comparable between the two groups, but patients with KD-SARS-CoV-2 had significantly lower levels of sodium, and higher levels of ferritin. No patient met the biological criteria for MAS. Patients with KD-SARS-CoV-2 also presented significantly higher levels of alanine aminotransferase (ALT), lipase, and creatinine. The observed associations were robust in sensitivity analysis, except there was no more significant difference in ALT ($p = 0.06$) (Supplemental Table S1).

All patients were treated with IVIG (2 g/kg), and no difference was observed between KD-SARS-CoV-2 and classic KD for the median number of days of fever before IVIG treatment (Fig. 2). All patients responded to a first-line or second-line therapy of IVIG, combined in some cases with corticosteroids. Corticosteroids were more frequently used in patients with KD-SARS-CoV-2 (Table 1), and as a first-line therapy together with IVIG in most of the cases ($n = 11/14$, 79%). No anti-interleukin (IL)-1 or anti-IL-6 was administered. No statistically significant difference was observed in terms of IVIG resistance and coronary artery dilations/aneurysms between patients with KD-SARS-CoV-2 and

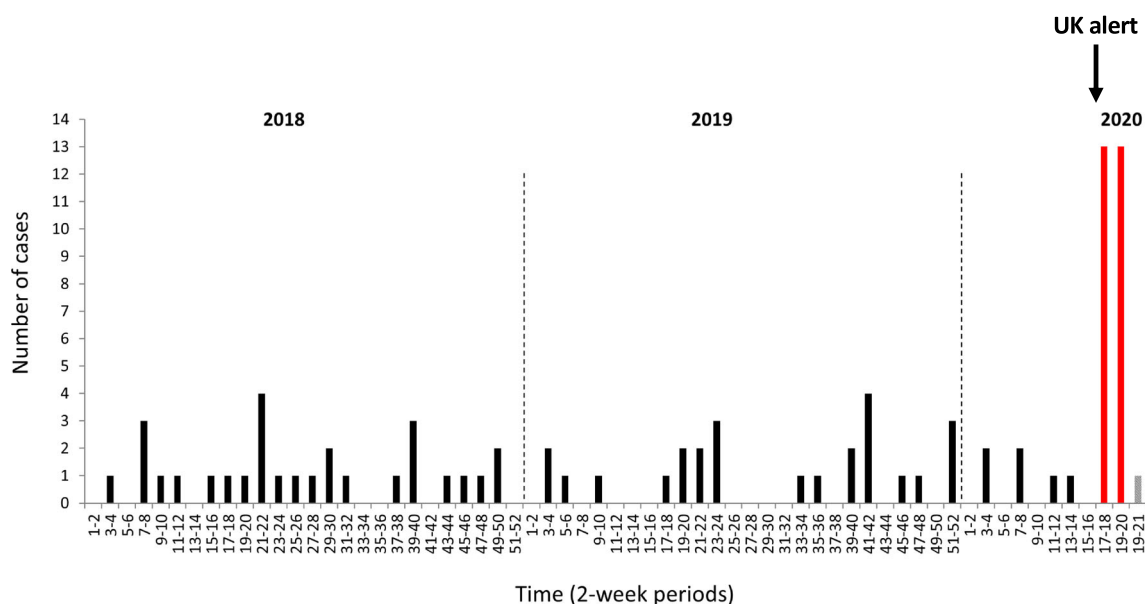


Fig. 1 Frequency of Kawasaki disease at the general pediatric department of Necker Hospital for Sick Children, Paris, France, between January 1, 2018, and May 26, 2020 (2-week periods)

classic KD (Table 1). At an outpatient visit between day 7 and day 28 after discharge, we observed that all patients had a favorable outcome in terms of clinical KD features, cardiac function, and biological markers. Two patients with classic KD developed coronary artery aneurysms, and none was observed in the KD-SARS-CoV-2 group.

Discussion

Main Findings

This study provides evidence of a temporal association between the outbreak of Kawasaki-like disease and COVID-19 pandemic, with a 13-fold increase in the incidence of patients admitted with KD during the COVID-19 pandemic. This study also confirms that children with KD-SARS-CoV-2 have specific characteristics compared to children from a control cohort of classic KD. Patients with KD-SARS-CoV-2 were more frequently of Sub-Saharan African ancestry, were older, and presented more frequently with gastrointestinal and neurological symptoms, and manifestations consistent with myocarditis. Biochemical investigations revealed higher levels of inflammatory markers, more frequent lymphopenia and increased ferritin levels. These patients also had a more severe disease course, with more frequent KD shock syndrome and admission in the intensive care unit. Still, patients with KD-SARS-CoV-2 did not develop more coronary artery dilation/aneurysm. We found no significant difference in IVIG resistance, but this finding is difficult to interpret because children in the KD-SARS-CoV-2 group received more frequently steroids in association with IVIG.

Interpretation

Several series of patients with MIS-C have recently been reported, especially in countries with a high incidence of COVID-19 [12–15, 22–38]. The extent to which these patients fulfilled KD criteria has not been assessed in all studies. Among these studies, patients fulfilling KD criteria [16] represented 22 to 100% of MIS-C patients. Differences in inclusion criteria may explain this variability, notably whether incomplete forms of KD were considered. Of note, almost all series of MIS-C or PIMS-TS reported similar rates of coronary artery dilation or aneurysm than those observed in classic KD, and IVIG was the most commonly used treatment, which may reflect a high degree of suspicion for KD among physicians in charge of these patients.

In line with three other studies in which patients with multisystem inflammatory syndrome were compared with a control group of classic KD [12, 14, 15], KD-SARS-CoV-2 patients reported here were older and had more frequently myocarditis and cardiogenic-vasoplegic shock requiring intensive care support than classic KD patients. Levels of inflammatory markers (notably CRP and procalcitonin) were higher, and patients with KD-SARS-CoV-2 had more profound lymphopenia, anemia, hyponatremia, and hypoalbuminemia. These characteristics are commonly observed in patients with KD shock syndrome, a severe form of KD similar to toxic shock syndrome, which affects up to 7% of classic KD patients [39]. By analogy with toxic shock syndrome, the multiorgan involvement and hyperinflammatory state observed in MIS-C patients, with particularly high levels of CRP, PCT, and IL-6, may reflect a strong immunological response to a pathogenic SARS-CoV-2 superantigen [40, 41]. The role of

Table 1 Comparison of patients with classic Kawasaki disease (KD) and patients with KD associated with confirmed SARS-CoV-2 infection (KD-SARS-CoV-2)

| Characteristics (%) [#] | n | MIS-C outbreak | | Comparison between classic KD and KD-SARS-CoV-2 Odds ratio [95% CI]* | P* | |
|---|----|---------------------|------------------------|---|-----------------|---------------------------|
| | | Classic KD (n = 59) | KD-SARS-CoV-2 (n = 23) | | | KD-non-SARS-CoV-2 (n = 7) |
| General | | | | | | |
| Sex | | | | | | |
| Girls | 37 | 23 (39) | 11 (48) | 3 (43) | 1.4 [0.5–3.8] | 0.47 |
| Boys | 52 | 36 (61) | 12 (52) | 4 (57) | Reference | |
| Parents born in Sub-Saharan Africa/Caribbean islands^S | | | | | | |
| Yes | 32 | 16 (30) | 15 (65) | 1 (14) | 4.4 [1.6–12.6] | 0.004 |
| No | 52 | 38 (70) | 8 (35) | 6 (86) | Reference | |
| Kawasaki disease principal criteria | | | | | | |
| KD presentation | | | | | | |
| Incomplete | 36 | 20 (34) | 13 (57) | 3 (43) | 2.5 [0.9–6.8] | 0.06 |
| Complete | 53 | 39 (66) | 10 (43) | 4 (57) | Reference | |
| Lips and oral cavity changes | | | | | | |
| Yes | 73 | 51 (86) | 17 (74) | 5 (71) | 0.4 [0.1–1.5] | 0.18 |
| No | 16 | 8 (14) | 6 (26) | 2 (29) | Reference | |
| Bilateral bulbar conjunctival injection | | | | | | |
| Yes | 67 | 43 (73) | 19 (83) | 5 (71) | 1.8 [0.5–6.0] | 0.27 |
| No | 22 | 16 (27) | 4 (17) | 2 (29) | Reference | |
| Rash | | | | | | |
| Yes | 69 | 48 (81) | 16 (70) | 5 (71) | 0.5 [0.2–1.6] | 0.25 |
| No | 20 | 11 (19) | 7 (30) | 2 (29) | Reference | |
| Extremity changes | | | | | | |
| Yes | 51 | 34 (58) | 12 (52) | 5 (71) | 0.8 [0.3–2.1] | 0.66 |
| No | 38 | 25 (42) | 11 (48) | 2 (29) | Reference | |
| Cervical lymphadenopathy | | | | | | |
| Yes | 63 | 46 (78) | 14 (61) | 3 (43) | 0.4 [0.2–1.2] | 0.12 |
| No | 26 | 13 (22) | 9 (39) | 4 (57) | Reference | |
| Other Kawasaki associated features | | | | | | |
| Gastrointestinal symptoms | | | | | | |
| Yes | 48 | 21 (36) | 23 (100) | 4 (57) | 84 [4.9–1456] | 0.002 |
| No | 41 | 38 (64) | 0 | 3 (43) | Reference | |
| Arthralgia/arthritis | | | | | | |
| Yes | 7 | 5 (9) | 1 (4) | 1 (14) | 0.5 [0.05–4.4] | 0.46 |
| No | 82 | 54 (91) | 22 (96) | 6 (86) | Reference | |
| Desquamation in groin | | | | | | |
| Yes | 14 | 8 (14) | 6 (26) | 0 | 2.3 [0.7–7.4] | 0.18 |
| No | 75 | 51 (86) | 17 (74) | 7 (100) | Reference | |
| Myocarditis | | | | | | |
| Yes | 22 | 1 (2) | 20 (87) | 1 (14) | 387 [38–3933] | < 0.001 |
| No | 67 | 58 (98) | 3 (13) | 6 (86) | Reference | |
| Serous effusion | | | | | | |
| Yes | 21 | 7 (12) | 14 (61) | 0 | 11.6 [3.7–36.5] | < 0.001 |
| No | 68 | 52 (88) | 9 (39) | 7 (100) | Reference | |
| Neurological signs (apart from irritability) | | | | | | |
| Yes | 12 | 4 (7) | 8 (35) | 0 | 7.3 [1.9–27.7] | 0.003 |
| No | 77 | 55 (93) | 15 (65) | 7 (100) | Reference | |
| Outcome and serious complications | | | | | | |
| Admitted to the intensive care unit | | | | | | |
| Yes | 26 | 3 (5) | 21 (91) | 2 (29) | 196 [31–1257] | < 0.001 |
| No | 63 | 56 (95) | 2 (9) | 5 (71) | Reference | |

Table 1 (continued)

| Characteristics (%) [#] | n | Pre-outbreak | MIS-C outbreak | | Comparison between classic KD and KD-SARS-CoV-2 Odds ratio [95% CI]* | P* |
|---------------------------------------|----|------------------------|---------------------------|------------------------------|---|---------|
| | | Classic KD (n = 59) | KD-SARS-CoV-2 (n = 23) | KD-non-SARS-CoV-2 (n = 7) | | |
| Kawasaki disease shock syndrome | | | | | | |
| Yes | 23 | 6 (10) | 14 (61) | 3 (43) | 13.7 [4.2–45.1] | < 0.001 |
| No | 66 | 53 (90) | 9 (39) | 4 (57) | Reference | |
| Coronary artery dilation or aneurysm | | | | | | |
| Yes | 12 | 6 (10) | 5 (22) | 1 (14) | 2.5 [0.7–9.0] | 0.17 |
| No | 77 | 53 (90) | 18 (78) | 6 (86) | Reference | |
| Treatment | | | | | | |
| Intravenous immunoglobulin resistance | | | | | | |
| Yes | 23 | 19 (32) | 5 (22) | 1 (14) | 0.6 [0.2–1.8] | 0.35 |
| No | 63 | 40 (68) | 18 (78) | 6 (86) | Reference | |
| Steroid treatment | | | | | | |
| Yes | 39 | 20 (34) | 14 (61) | 5 (71) | 3.0 [1.1–8.2] | 0.03 |
| No | 50 | 39 (66) | 9 (39) | 2 (29) | Reference | |

Classic KD: children with KD admitted between January 1, 2018, and April 25, 2020; KD-SARS-CoV-2: children admitted between April 26, 2020, and May 26, 2020, with positive SARS-CoV-2 testing; KD-non-SARS-CoV-2: children admitted between April 26, 2020, and May 26, 2020, with negative SARS-CoV-2 testing

[#] Values are numbers (percentages) unless stated otherwise

[§] Missing data

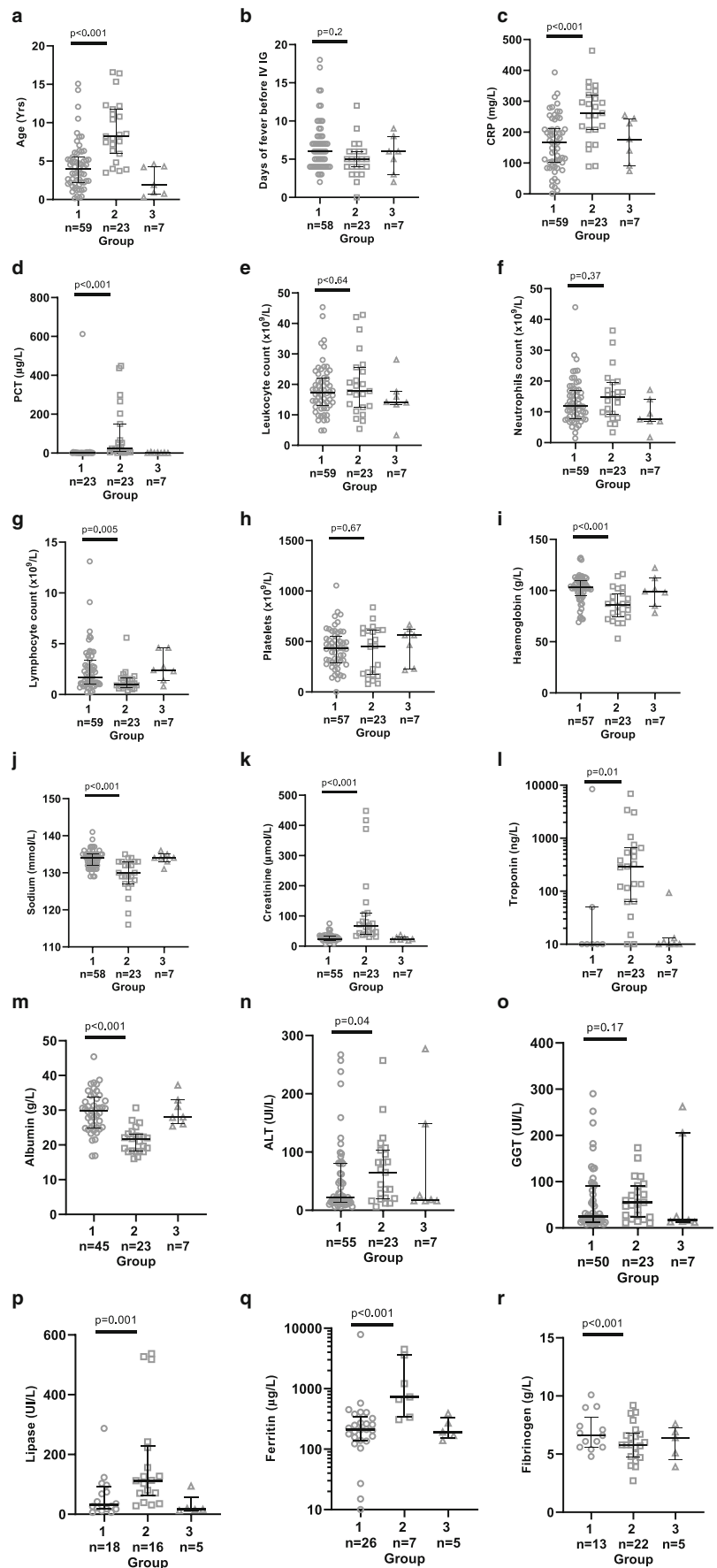
*Classic KD and KD-SARS-CoV-2 groups were compared using univariate analysis

superantigens in the pathophysiology of classic KD has been previously suggested [42]. In adults with COVID-19, a cytokine storm syndrome with multiorgan dysfunction correlates with poor outcomes [43, 44]. However, unlike adult patients, children and adolescents with MIS-C have no significant respiratory involvement. The cytokine storm observed in our series of patients with KD-SARS-CoV-2 was associated with several criteria of MAS (e.g., cytopenia, profound hyponatremia and hypoalbuminemia, and hyperferritinemia), though not fulfilling all criteria for MAS according to the PRINTO criteria, such as hypofibrinogenemia or low platelet count [18]. This might be due to early treatment with corticosteroids suppressing MAS features, and inadequate performance of the PRINTO criteria for KD, which were originally designed for systemic juvenile idiopathic arthritis-associated MAS [45]. Further studies investigating the role of viral load, cytokine balance, antibodies, and immune cell response are needed to better understand the reasons for such differences in the course of SARS-CoV-2 infection between adults and children.

In our series, gastrointestinal and neurological symptoms were also more frequent in KD-SARS-CoV-2 than in classic KD, which likely reflects intestinal and neurological vasculitis, as symptoms quickly resolved after IVIG perfusion. These symptoms were also often observed in MIS-C or PIMS-TS series. In our KD-SARS-CoV-2 series, all children had

marked gastrointestinal symptoms at the early stage of illness. Some authors have hypothesized that SARS-CoV-2 may be directly involved in MIS-C digestive manifestations by primarily infecting the gastrointestinal tract [46, 47]. However, in classic KD, gastrointestinal symptoms also usually appear before all other KD manifestations [48]. Regarding the patients' ethnic origins, we observed a higher proportion of children of Sub-Saharan African and Caribbean ancestry in the KD-SARS-CoV-2 group, when compared with classic KD, which is consistent with previous findings [12, 28]. Although the incidence of KD is usually 10- to 30-fold higher in Asia than in North America and Europe, no significant increase of KD incidence was observed in Korean children during the COVID-19 pandemic, despite high exposure to the virus [49]. Reports of PIMS-TS in the UK described a substantial rate of patients of Asian ancestry, but mainly from South Asia (India, Pakistan, Bangladesh) [15, 27]. Also, KD shock syndrome has a higher incidence in Western countries than in Asia [50]. Therefore, susceptibility to KD might involve a combination of environmental factors, infectious triggers, and genetic background that predisposes to hyperinflammation [51–53]. Whether children and adolescents of Sub-Saharan African ancestry were more exposed to SARS-CoV-2 in France deserves further investigations. Overall, these findings confirm that KD-SARS-CoV-2 has specific characteristics compared to classic KD; this is

Fig. 2 Comparison of biological features between patients with KD-SARS-CoV-2 and patients with classic KD. Group 1 corresponded to “classic KD,” i.e., children with KD admitted between January 1, 2018, and April 25, 2020. Group 2 corresponded to “KD-SARS-CoV-2,” i.e., children admitted between April 26, 2020, and May 26, 2020, with positive SARS-CoV-2 (PCR and/or serology) testing. Group 3 corresponded to “KD-non-SARS-CoV-2,” i.e., children admitted between April 26, 2020, and May 26, 2020, with negative SARS-CoV-2 (PCR and serology) testing



emphasized by the observation that the KD-non-SARS-CoV-2 group was similar in all measured parameters to pre-pandemic classic KD.

This study has several limitations. First, it is a relatively small case series conducted in a unique clinical center. Our findings require confirmation in larger multicenter studies. Second, our results suggest a temporal association between SARS-CoV-2 infection and an outbreak of Kawasaki-like syndrome, but we were not able to formally investigate this association. Other similar series were described in regions severely hit by COVID-19, like the North of Italy, and other large cities with high levels of SARS-CoV-2 community transmission, London and New York especially. In France, the geographical distribution of cases was similar to the one of all-ages COVID-19 hospitalizations [23]. A study including a control population allowing to estimate the seroprevalence of SARS-CoV-2 in children from the Paris area is needed to reinforce causal interpretation. Third, because KD cases in the pre-outbreak era were less severe, early screening for myocarditis and heart failure was not routinely done in our center, which impeded comparisons because of missing data. Also, two patients who presented with KD in January 2020 were not tested for anti-SARS-CoV-2 antibodies, because the test was not yet available in routine care in Necker Hospital. This might have led to misclassification bias, with reduced statistical power.

As long as SARS-CoV-2 circulates, primary care physicians and emergency practitioners should be aware of this outbreak of KD-SARS-CoV-2. Raising awareness may contribute to improving diagnostic delays, which in turn may improve access to appropriate treatments, including IVIG, corticosteroids, and anti-IL-1 treatments such as anakinra [54, 55]. Public health implications are also important. Indeed, even if this outbreak of severe KD-SARS-CoV-2 concerns a relatively small number of children, the fact that it affects more frequently children of Sub-Saharan African ancestry should raise specific concern in areas with a high proportion of children of these origins.

Conclusions

This controlled study confirms that KD-SARS-CoV-2 has specific characteristics compared to classic KD, including more common Sub-Saharan African ancestry, older age, more frequent gastrointestinal involvement, KD shock syndrome and admission in intensive care unit, myocarditis, and higher levels of inflammatory markers. As long as the COVID-19 pandemic continues, clinicians should keep a high degree of suspicion for this severe form of KD.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10875-020-00941-0>.

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Authorship Contributions JT, SA, and MC conceived the study. JT, SA, MC, and JFC designed the study. JT and CP collected and were responsible for the data. MT and SM participated to data analysis. JT, MT, WC, FM, FB, JB, and JLC participated in patient care, investigation, and data collection. JT and JFC performed the statistical analysis. ML performed the microbiology analyses. JT, SA, MC, and JFC wrote the first draft of the manuscript. All authors drafted the manuscript for important intellectual content, contributed to the revision of the final version of the manuscript, and approved the final version submitted.

Data Availability Data are available upon reasonable request.

Compliance with Ethical Standards

Ethics Approval and Consents The study protocol, data extraction forms, and procedures were reviewed and approved by the Necker Hospital Institutional Review Board (No. 2020 0618174239) and by the ethical committee (Comité de Protection des Personnes Ouest IV, No DC-2017-2987). All parents provided written informed consent. This study was conducted in accordance with the Helsinki Declaration, with informed consent obtained from each patient's guardians.

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