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Original article

Delineating phenotypes of Kawasaki disease and SARS-CoV-2-related inflammatory multisystem syndrome: a French study and literature review

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Abstract

Objective. To better define the clinical distinctions between the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related paediatric inflammatory multisystem syndrome (PIMS) and Kawasaki disease (KD).

Methods. We compared three groups of patients: group 1, cases from our national historic KD database (KD-HIS), before the SARS-CoV-2 pandemic; group 2, patients with KD admitted to an intensive care unit (KD-ICU) from both our original cohort and the literature, before the SARS-CoV-2 pandemic; and group 3, patients with PIMS from the literature.

Results. KD-HIS included 425 patients [male:female ratio 1.3, mean age 2.8 years (S.D. 2.4)], KD-ICU 176 patients [male:female ratio 1.3, mean age 3.5 years (S.D. 3.1)] and PIMS 404 patients [male:female ratio 1.4, mean age 8.8 years (S.D. 3.7)]. As compared with KD-HIS patients, KD-ICU and PIMS patients had a higher proportion of cardiac failure, digestive and neurological signs. KD-ICU and PIMS patients also had a lower frequency of typical KD-mucocutaneous signs, lower platelet count, higher CRP and lower sodium level. As compared with KD-HIS and KD-ICU patients, PIMS patients were older and more frequently had myocarditis; they also had fewer coronary abnormalities and lower sodium levels. Unresponsiveness to IVIG was more frequent in KD-ICU than KD-HIS and PIMS patients.

Conclusion. On clinical grounds, KD-HIS, KD-ICU and PIMS might belong to a common spectrum of non-specific pathogen-triggered hyperinflammatory states. The causes of increasing inflammation severity within the three entities and the different effects on the heart remain to be determined.

Key words: Kawasaki disease, systemic vasculitis, intensive care unit, shock syndrome, intravenous immunoglobulins, PIMS/MIS-C, SARS-CoV-2-related inflammatory multisystem syndrome, COVID-19

CLINIAL SCIENCE

Rheumatology key messages

- SARS-CoV-2-related inflammatory multisystem syndrome more likely resembles Kawasaki disease needing intensive care.
- Regular KD, severe KD and PIMS/MIS-C might belong to a common clinical spectrum.
- Understanding host-/pathogen-dependent factors explaining heterogeneity of post-infectious childhood inflammatory syndromes would help in diagnostic/therapeutic strategies.

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Introduction

At the end of April 2020, the National Health Service of England sent an alert about a severe multisystem inflammatory state in children possibly related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and features thought to overlap with those of toxic shock syndrome and atypical Kawasaki disease (KD).

Similar cases were then reported elsewhere in Europe and in North America [1–11]. This apparently new condition, named paediatric inflammatory multisystem syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C), occurred in a limited number of children and adolescents within 4 weeks of the peak of the local epidemic [12]. Thus PIMS/MIS-C was considered to occur due to an aberrant immunologic response rather than direct viral toxicity [1, 13]. The full spectrum and pathogenesis of PIMS/MIS-C are still poorly understood, but it appears to share common features with other hyperinflammatory disorders, initiating after a strong pathogen trigger of the immune system, such as KD [14–16]. KD is an acute multisystem inflammatory disease of unknown aetiology, characterized by the involvement of medium-sized arteries and affecting mainly children <5 years of age [17]. The diagnosis is based on a constellation of suggestive albeit non-specific clinical signs and supportive laboratory tests and imaging [18,19]. During the acute phase of KD, 1–7% of children present with life-threatening complications and require admission into an intensive care unit (ICU) [21–24]. KD shock syndrome (KDSS), defined as systolic hypotension and/or clinical signs of poor perfusion, is the main cause of referral to an ICU [21–27].

We aimed to define boundaries between KD and PIMS/MIS-C by comparing their clinical and biological characteristics. We used cases from our historic KD database (KD-HIS), the largest in France, implemented before the SARS-CoV-2 pandemic [28]. We also constituted a cohort of children with severe forms of KD requiring admission to an ICU (KD-ICU), the largest reported to our knowledge. To allow for comparison between these groups, we enriched both the KD-ICU and PIMS/MIS-C groups with a literature review of cases published to date.

Patients and methods

We defined three groups of patients. Group 1 comprised cases included in our historic KD database, Kawanet, recruited outside the ICU (KD-HIS). Group 2 included a new collection of patients with KD requiring intensive care (KD-ICU), plus ICU cases from a literature review to allow comparisons that were more reliable. Group 3 included cases of PIMS/MIS-C extracted from a literature review (PIMS).

Group 1: historic French database, Kawanet (KD-HIS)

The design of the Kawanet database was detailed previously [28]. Briefly, Kawanet contains demographic, clinical, biologic and radiologic data for 425 children with KD included from 65 French paediatric departments but none in ICUs between 2011 and 2014.

Group 2: children with KD admitted to an ICU (KD-ICU)

Recruitment of the cohort of patients

The group was constituted by a retrospective chart review of children admitted from 2001 to 2018 in tertiary paediatric ICUs with a final diagnosis of KD in France and in one centre in Germany (*Universitätsklinikum* of Ulm). Physician members of two French medical societies [the French-speaking Society of Paediatric Rheumatology (*Société francophone de rhumatologie et des maladies inflammatoires pédiatriques*) and the French group of Paediatric Emergency and ICU Physicians (*Groupe français d'urgences et réanimation pédiatrique*)] were contacted by three e-mail rounds. Cases were retrieved in each centre via the French hospital information system program, based on the International Classification of Diseases or local databases.

Inclusion/exclusion criteria

We included all children 0–18 years of age with a diagnosis of KD according to the American Heart Association criteria (AHA) who required admission to an ICU for KD treatment (i.e. requiring continuous monitoring and/or resuscitation procedures such as mechanical/non-invasive ventilation and inotropic or vasodilator drugs) [18]. We excluded patients who did not fulfil the AHA criteria for KD and those admitted to the ICU for a reason other than a complication of KD. The duration of stay in the ICU was defined as the date of admission to the ICU to the date of death or discharge from the ICU. The diagnostic delay was the time from the first KD symptom to diagnosis. The IVIG treatment delay was the time from the first day of fever to the first IVIG infusion. IVIG resistance was defined as persistence or reappearance of fever within 36 h after the first IVIG infusion [18].

Data collection

We collected data on demographic characteristics, clinical manifestations, other suspected diagnoses, cardiac complications and treatments. We recorded the highest level of CRP and results of chest X-rays, electrocardiography and echocardiography.

Literature review of KD-ICU patients

In July 2020 we performed a systematic literature search for published articles in PubMed, Web of Science and Google Scholar using the terms 'Kawasaki disease AND intensive care unit' or 'Kawasaki disease AND shock'. From 21 series we selected 8 case series of at least five KD-ICU children with an extensive clinical and paraclinical description.

Overall, patients with KD-ICU, including our cohort and patients from the literature review, were combined to improve the definition of this group of patients and to improve the relevance of the comparison with PIMS patients.

Group 3: Literature review of PIMS/MIS-C

In July 2020 we performed a systematic literature search for published articles in PubMed, Web of Science and Google Scholar using the terms 'Kawasaki disease AND COVID' or 'Kawasaki disease AND SARS-CoV-2' and 'COVID AND inflammatory multisystem syndrome'. From 15 retrieved articles we selected 8 case series of at least five children with PIMS with extensive clinical and paraclinical descriptions; series with a risk of redundancies were excluded (cases recruited from the same region). Patients seen in our centre were included in one of these publications [2].

Comparisons and statistical analysis

We compared the characteristics of patients from the three groups. Continuous data are described as mean (S.D.) or median (range) and categorical variables as number (%). Comparisons were based on Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Statistical analyses were performed with Prism 5.0 (GraphPad Software, San Diego, CA, USA) and MedCalc (MedCalc Software, Ostend, Belgium). All tests were two-tailed and *P*-values <0.05 were considered statistically significant.

Ethical considerations

The study protocol complies with the Declaration of Helsinki and followed ethics guidelines (CPP no. CO-10-002) and was approved by the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (Advisory Committee on Information Processing in Research in the Field of Health, no. 10.155bis) and the *Commission Nationale de l'Informatique et des Libertés* (National Commission of Informatics and Freedom, no. DR-2010-032). Written informed consent was obtained from the parents or guardians of the children who served as subjects.

Results

Subgroups of patients

Group 1: KD-HIS

Among the 425 patients with KD (Table 1 and Supplementary Table S1, available at *Rheumatology* online), 242 were boys (male:female ratio 1.3) with mean age at diagnosis of 2.8 years (S.D. 2.4; range 0.1–14.4). The mean delay to KD diagnosis was 6.0 days (S.D. 3.1). All of them were diagnosed before the SARS-CoV-2 pandemic.

Group 2: KD-ICU

Our cohort of KD-ICU Eight of 34 tertiary paediatric French ICU units and 1 ICU in Germany (Ulm) responded to our survey and provided 52 cases. Four cases did not meet inclusion criteria, thus we included 48 cases (Supplementary Table S1, available at *Rheumatology* online): 21 boys (male:female ratio 0.7) with a mean age at diagnosis of 2.8 years (S.D. 2.8; range 1 month–10.6 years) and a mean delay to diagnosis of KD of 6.4 days (S.D. 3.4). Admission to the ICU occurred at a mean of 5.3 days (S.D. 3.5; range 1–21) after fever onset. The duration of stay in the ICU was 7.9 days (S.D. 12; range 1–73), the same as the duration of follow-up. Two children (a 3-month-old boy and 1.5-year-old girl) died of myocardial infarction (Supplementary Table S2, available at *Rheumatology* online).

In our cohort, the main reason for ICU referral was KDSS in 28/48 (58%) children that was associated with impaired left ventricular systolic function in 13/48 (27%). Other reasons were giant aneurysm and/or suspected myocarditis in 7/48 (15%), neurologic disorders in 6/48 (13%), multiple organ dysfunction in 4/48 (8%), cardiopulmonary arrest in 2/48 (4%) and respiratory failure in 1/48 (2%). The top initial diagnoses were toxic/septic shock in 25/48 (52%) and acute abdomen syndrome in 12/48 (25%).

Sixteen of 48 (33%) children received volume resuscitation and 22/48 (46%) received vasopressors. Overall, 22/48 (46%) children required non-invasive ventilation and 12/48 (25%) required intubation for mechanical ventilation. Thirteen of 48 (27%) received a blood transfusion, and 13/48 (27%) received albumin infusion; 17/48 (35%) required morphine/derived analgesics. All children received broad-spectrum antibiotics.

Literature review of KD-ICU We obtained reports for 176 KD children, including our series (Table 1, Supplementary Table S3, available at *Rheumatology* online). All of them were diagnosed before the SARS-CoV-2 pandemic. Indeed, our KD-ICU cohort included patients seen until 2018 and literature review patients diagnosed through 2017 (last publication in 2019). Among them, 101 (57%) were boys (male:female ratio 1.3) with a mean age at diagnosis of 3.5 years (S.D. 3.1; range 0.1–14.6). The mean delay to diagnosis was 7.5 days (S.D. 3.8) and the mean duration of stay in the ICU was 6.8 days (S.D. 2.3). Five children of 176 (3%) died. As observed in our cohort, digestive and neurologic involvement were common in the overall KD-ICU patients (83% and 46% of cases, respectively). They had relatively low platelet counts [231 (S.D. 113) $\times$ 10^9/l] compared with the high white blood cell counts [15.6 (S.D. 7) $\times$ 10^9/l] and CRP [262 mg/l (S.D. 77)].

Group 3: literature review of PIMS/MIS-C

Data for 404 patients were retrieved; 236 were boys (male:female ratio 1.4) with mean age at diagnosis of 8.8 years (S.D. 3.7; range 0.3–17) (Table 1, Supplementary Table S4, available at *Rheumatology* online). The mean delay to diagnosis was rarely reported. The duration of stay in the ICU was 5.5 days (S.D. 1.3). Eight children of 404 (2%) died. PIMS/MIS-C also had frequent digestive involvement (88%) and neurological signs (20%). The patients had relatively low platelet counts [217 (S.D. 58) $\times$ 10^9/l] compared with the high level of CRP [245 mg/l (S.D. 119)] and also had

Table 1 Characteristics of children with SARS-CoV-2-related inflammatory multisystem syndrome (PIMS/MIS-C), KD from the French historic database (KD-HIS) and KD admitted to an ICU (KD-ICU)

Characteristics	PIMS/MIS-C[a]	KD-HIS	*P*-value	KD-ICU[b]	*P*-value
Demographics					
Age, years, mean (S.D.; range)	8.8 (3.7; 0.3–17)	2.8 (2.4; 0.1–14.4)	**<0.0001**	3.5 (3.1; 0.1–14.6)	**<0.0001**
Sex (male), *n/N* (%)	236/404 (59)	242/424 (57)	0.5	101/176 (57)	0.6
Duration of stay in ICU, days, median	5.5	0	–	6.8	–
Clinical features, n/N (%)					
Modifications of the extremities	110/386 (28)	292/417 (70)	**<0.0001**	58/84 (69)	**<0.0001**
Diffuse exanthema[c]	235/404 (58)	320/399 (80)	**<0.0001**	71/84 (85)	**<0.0001**
Conjunctivitis	230/404 (57)	374/421 (89)	**<0.0001**	72/84 (86)	**<0.0001**
Buccal involvement[d]	160/396 (40)	350/413 (85)	**<0.0001**	75/84 (89)	**<0.0001**
Cervical adenopathy $\geq$1.5 cm	52/396 (13)	219/397 (55)	**<0.0001**	48/84 (57)	**<0.0001**
Complete KD (AHA criteria)	100/346 (29)	290/425 (68)	**<0.0001**	90/146 (62)	**<0.0001**
Digestive symptoms/signs	302/346 (88)	226/414 (54)	**<0.0001**	58/70 (83)	0.2
Neurologic signs	82/404 (20)	68/407 (17)	0.3	55/120 (46)	**<0.0001**
Biological data[e], mean (S.D.) (*n*)					
Lymphopenia[f], *n/N* (%)	235/312 (75)	NA	–	NA	–
Platelet count ($\times 10^9$/l)	217 (58) (218)	385.2 (152.3) (406)	**<0.0001**	231 (113) (176)	0.1
CRP level at peak (mg/l)	245 (119) (218)	155.2 (97.1) (345)	**<0.0001**	262 (77) (115)	0.2
ALT level (IU/l)	51 (124) (95)	70.9 (99) (319)	0.1	74 (50) (176)	**0.03**
Sodium level (mmol/l)	129.9 (3.6) (53)	134.5 (0.4) (356)	**<0.0001**	132.7 (2.3) (75)	**<0.0001**
Elevated troponin	231/389 (60)	NA	–	6/11 (55)	0.7
Macrophage activation syndrome[f]	6/32 (19)	NA	–	1/26 (4)	0.08
Abnormal chest X-ray	107/231 (46)	37/235 (16)	**<0.0001**	16/31 (52)	0.5
Cardiac complications (acute phase) , *n/N* (%)					
Coronary abnormalities	48/404 (12)	163/418 (39)	**<0.0001**	106/176 (60)	**<0.0001**
Impaired LVSF and/or RV dysfunction	193/338 (57)	NA	–	34/103 (33)	**<0.0001**
Pericardial effusion	98/332 (30)	75/413 (18)	**0.0001**	23/87 (26)	0.4
Myocarditis	59/136 (43)	13/405 (3)	**<0.0001**	12/59 (20)	**0.002**
Mortality	8/404 (2)	0/425	**0.003**	5/176 (3)	0.5
Treatment, *n/N* (%)					
IVIG infusion	314/404 (78)	420/425 (99)	**<0.0001**	116/121 (96)	**<0.0001**
Unresponsiveness to IVIG	55/205 (27)	94/348 (27)	NS	76/159 (48)	**<0.0001**
Corticosteroids	219/404 (54)	31/380 (8)	**<0.0001**	47/115 (41)	**0.01**
Aspirin	50/61 (82)	387/415 (93)	**0.004**	91/94 (97)	**0.001**
Inotropic drugs	213/404 (53)	0/425	–	81/133 (61)	0.1

[a]Overall PIMS defined from a systematic review of the literature [2–4, 8–11, 35]. [b]Overall severe KD defined from a systematic review of the literature, including our series [21–24, 26, 27, 29, 30]. [c]Erythema and/or oedema and/or desquamation. [d]Cheilitis and/or mucosa erythema. [e]Laboratory results were the first reported. [f]Defined according to each article criteria. NA: not available; NS: not significant; LVSF: left ventricular systolic function; RV: right ventricle; Significant results are highlighted in bold.

paradoxically low levels of white blood cells with frequent lymphopenia (75%).

Comparison of groups

Comparison of KD-HIS and our cohort of KD-ICU

We compared our 48 KD-ICU patients with the 425 patients from the Kawanet database (Supplementary Table S1, available at *Rheumatology* online). About half of patients hospitalized in an ICU had an incomplete form of the disease (48% *vs* 32%; $P = 0.02$). A large proportion of children also had digestive signs (77% *vs* 54%; $P = 0.004$). Children in an ICU had significantly more respiratory signs (52% *vs* 28%; $P = 0.001$) and neurological signs (52% *vs* 17%; $P < 0.0001$). They initially had a lower platelet count, higher CRP level and lower sodium level. Chest X-rays revealed more frequent unspecific abnormalities, that was asymmetrical and/or bilateral alveolo-interstitial syndrome [16/31 (52%) *vs* 37/235 (16%); $P = 0.001$].

All patients in an ICU received at least one IVIG infusion and aspirin. The mean delay between fever onset and the first IVIG infusion was 5 days (S.D. 2.7; range 1–19), which was shorter than in the KD-HIS group (6.6 days (S.D. 3.6); $P = 0.003$). Patients in an ICU more frequently showed unresponsiveness to IVIG (50% *vs* 27%; $P = 0.001$). All received a second IVIG infusion, which was ineffective in 16/24 (68%) patients.

Comparison of KD-HIS and PIMS/MIS-C

We compared the 425 patients from the Kawanet database with the 404 patients with PIMS (Table 1). Patients with PIMS/MIS-C were older [8.8 years (S.D. 3.7) *vs* 2.8 (2.4)] and only 29% had AHA criteria for complete KD. A large proportion of children with PIMS had digestive signs (88% *vs* 54%; $P < 0.0001$). Patients with PIMS/MIS-C had a higher CRP level, lower platelet count and lower sodium level. They had fewer coronary abnormalities (12% *vs* 39%; $P < 0.0001$) but more frequently had myocarditis (43% *vs* 3%; $P < 0.0001$) or pericardial effusion (30% *vs* 18%; $P = 0.0001$).

Comparison of KD-ICU and PIMS/MIS-C

We compared the 176 children with KD-ICU with the 404 patients with PIMS (Table 1). Patients with PIMS/MIS-C were older [8.8 years (S.D. 3.7) *vs* 3.5 (3.1)]. Both groups had a low sodium level and high alanine aminotransferase (ALT) level, but the sodium level was lower in PIMS/MIS-C patients and the ALT level was higher in KD-ICU patients. Patients with PIMS/MIS-C had fewer coronary abnormalities (12% *vs* 60%; $P < 0.0001$) but more frequently had myocarditis (43% *vs* 20%; $P = 0.002$) or ventricular impairment (57% *vs* 33%; $P < 0.0001$).

Discussion

Here we clarified the phenotype of PIMS/MIS-C as compared with KD, especially to define whether it is acceptable to combine both conditions. For this study we collected as much data as possible by using our own KD database and by an additional French survey on the most severe cases of KD, so-called KD-ICU. The literature review allowed for increasing the number of KD-ICU cases. Moreover, we compared our historic KD patients outside of an ICU, KD-ICU patients and PIMS/MIS-C patients.

KD-ICU is rarely described in Europe and we have collected the largest number of cases reported so far. Our data highlight intriguing similarities between KD-ICU described before the SARS-CoV-2 pandemic and PIMS/MIS-C. Both conditions are dominated by particular clinical features: a high frequency of digestive involvement, mimicking colitis and/or peritonitis and reported in up to 87% of KD-ICU cases (range 82–91%); a high frequency of signs of hypoperfusion, mimicking shock syndrome; a high frequency of neurological signs, remarkably similar to those observed in PIMS/MIS-C; and a low frequency of the mucocutaneous signs described in the first KD definition by T.Kawasaki [17]. This peculiar presentation explains the low rate of complete KD forms as defined by AHA criteria, reported in 38% of KD-ICU patients (range 22–48%) [21–26, 29, 30]. This atypical presentation also led to 62% of misdiagnoses on ICU admission in our series of KD-ICU, despite a mean fever duration of 5 days. One of the most puzzling findings is the frequency of myocarditis in KD-ICU (20%), which approaches that of PIMS/MIS-C (43%) and was exceptional in regular KD (3%). Of interest, shock syndrome (58%) and impaired left ventricular systolic function (27%) were prominent in KD-ICU, and are hallmarks of PIMS/MIS-C.

The main characteristics in the three groups reveal that they might belong to a common clinical spectrum, differing in intensity of inflammation, as defined in Table 2. The more intense is the inflammatory response, the lower the frequency of specific KD signs (i.e. ocular/buccal, cutaneous signs, coronary abnormalities), and the higher the frequency of multisystem involvement and cardiac impairment. In both KD-ICU and PIMS/MIS-C, the CRP level is extremely high, which contrasts with relative thrombocytopenia; and both include hyponatremia, which appears even lower in PIMS/MIS-C.

This clinical spectrum from KD-HIS to KD-ICU and PIMS/MIS-C may reflect a common underlying mechanism characterized by a cytokine storm of diverse intensity. Indeed, increased production of IL-1, IL-6, IL-10 and TNF-α is the hallmark of KD-ICU, even more intense than in regular KD, and also observed in PIMS/MIS-C. Elevated IFN-γ expression has also been described in KD-ICU and in PIMS/MIS-C [24, 31, 32]. An increased neutrophil count is usually observed in the KD and KD-ICU immunologic signature and may differentiate them from PIMS/MIS-C. Indeed, peripheral blood cell immunophenotyping of 25 children with PIMS/MIS-C compared with healthy controls revealed a transient differential T and B cell subset lymphopenia, similar neutrophil and monocyte counts, but an abnormal activated phenotype [31]. This hyperinflammatory state is associated with diffuse capillary leakage and endothelial injury, leading to multisystem involvement [23, 24, 27, 33]. As observed in another multisystem inflammatory disease, Still's disease, macrophage activation syndrome occurred as collateral damage of hyperinflammation, and it was even more frequent in PIMS/MIS-C than KD-ICU (19% *vs* 4%). Of note, CRP level, thrombocytopenia and hyponatremia are items of the Kobayashi score predicting IVIG resistance in Japanese children with KD [34]. Moreover, the intensity of the cytokine storm is associated with IVIG unresponsiveness, observed at a remarkably high rate in KD-ICU (48%) but not as high in PIMS/MIS-C (27%), but these patients more frequently received corticosteroids [35, 36]. This variability in intensity of aberrant inflammatory responses might be modulated by host specificities, depending on immune responses and genetic predispositions [14].

In addition, the hyperinflammatory pattern was associated with a much higher mortality in PIMS/MIS-C [8 (2%)] and KD-ICU [5 (3%)] than in KD patients (0.015–0.17%) [8–10, 18, 20–23, 25–27, 29, 37].

Some intriguing epidemiological characteristics distinguished KD-HIS and KD-ICU from PIMS/MIS-C. The first is the age of onset: KD occurred in 80% of cases in children <5 years of age, whereas PIMS/MIS-C affects older children and adolescents [2–11, 18]. The contrast is not well understood; however, younger children could be protected against the novel SARS-CoV-2 because of

Table 2 Main features of historical KD, KD admitted to an ICU (KD-ICU) and SARS-CoV-2-related inflammatory multisystem syndrome (PIMS/MIS-C)

Characteristics	Historical KD	KD-ICU	PIMS/MIS-C
Demographics			
Age, years, median	<5	<5	>7
Mortality, %	~0	3	2
Clinical signs			
Complete KD criteria[a], %	68	62	29
Digestive symptoms/signs	Rare	Frequent	Frequent
Neurologic signs	Rare	Frequent	Frequent
Biological signature			
White blood cell count	Increased	Increased	Decreased
Thrombocytopenia	Rare	Frequent	Frequent
CRP level at peak, mg/l	<200	>200	>200
Sodium level, mmol/l	135	132	130
Macrophage activation syndrome	Rare	Rare	Frequent
Abnormal chest X-ray	Rare	Frequent	Frequent
Cardiac complications (acute phase)			
Shock syndrome	Rare	Frequent	Frequent
Coronary abnormalities	Frequent	Frequent	Rare
Pericardial effusion, %	18	26	30
Myocarditis, %	3	20	43

[a]Associated with higher frequency of ocular/buccal and cutaneous signs.

their increased contact with other coronaviruses, with possible cross-immunity, and because of more recent exposure to vaccines containing SARS-CoV-2 shared epitopes [38, 39]. Another hypothesis could be their lower expression of angiotensin-converting enzyme receptor, a possible entry for SARS-CoV-2 [40]. Second, the incidence of KD is highest in Asian populations, whereas PIMS/MIS-C seems to affect Caucasian and Afro-Caribbean populations [3, 10, 37]. Moreover, Afro-Caribbean children showed particular clinical and biological characteristics during PIMS/MIS-C and KD, which suggests a genetic susceptibility to a more severe inflammatory response [3, 28, 33, 41, 42]. Interestingly, KD-ICU might also develop preferentially in children from Western countries rather than Asian descendants [21–24].

Viral triggering is highly probable in PIMS/MIS-C and KD [16, 43]. Particular immunogenicity of certain viruses is critical in immune-mediated disorders and might determine a specific phenotype; in the example of SARS-CoV-2, it might be related to superantigen properties [44], as observed in *Staphylococcus* sepsis [45], or to a vascular tropism [46, 47]. The ability of coronaviruses to block type I/III IFN responses might also affect the delayed cytokine storm in patients lacking control of viral replication and a severe phenotype [32, 33].

Our study has some limitations because we could not collect all cases of KD in ICUs, some biological data were missing and long-term follow-up data collection for KD-ICU patients was not possible. In addition, the PIMS/MIS-C group was restricted to cases in the literature, including PIMS/MIS-C patients seen in our centre, to allow more reliable comparison with patients referred to an ICU and others that did not require intensive care.

Conclusion

SARS-CoV-2-related PIMS/MIS-C more likely resembles KD-ICU. Like KD-ICU, PIMS/MIS-C comprises digestive and neurologic involvement, shock syndrome and a low frequency of mucocutaneous signs, related to a hyperinflammatory biological response. Myocarditis is more frequent in PIMS/MIS-C than KD-ICU, in contrast to coronary abnormalities. KD and PIMS/MIS-C might belong to a common clinical spectrum sharing nonspecific features related to an abnormal inflammatory response but differing in intensity. Our findings reinforce the hypothesis of the main role of a pathogen/viral trigger during KD pathogenesis and emphasize the need to understand host- and pathogen-dependent factors explaining the occurrence and heterogeneity of likely post-infectious childhood inflammatory syndromes.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials. Complementary data are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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