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Changes in Kawasaki disease incidence and phenotype during the COVID-19 pandemic

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ABSTRACT

INTRODUCTION. The aetiology of Kawasaki disease (KD) remains unknown. Changes in infectious exposure during the COVID-19 pandemic owing to infection prevention measures may have affected the incidence of KD, supporting the pathogenic role of an infectious trigger. The purpose of this study was to evaluate the incidence, phenotype and outcome of KD before and during the COVID-19 pandemic in Denmark.

METHODS. This was a retrospective cohort study based on patients diagnosed with KD at a Danish paediatric tertiary referral centre from 1 January 2008 to 1 September 2021.

RESULTS. A total of 74 patients met the KD criteria of whom ten were observed during the COVID-19 pandemic in Denmark. All of these patients were negative for SARS-CoV-2 DNA and antibodies. A high KD incidence was observed during the first six months of the pandemic, but no patients were diagnosed during the following 12 months. Clinical KD criteria were equally met in both groups. The fraction of intravenous immunoglobulin (IVIG) non-responders was higher in the pandemic group (60%) than in the in the pre-pandemic group (28.3%), although the rate of timely administered IVIG treatment was the same in both groups (≥ 80%). Coronary artery dilation was observed in 21.9% in the pre-pandemic group compared with 0% in KD patients diagnosed during the pandemic.

CONCLUSION. Changes in KD incidence and phenotype were seen during the COVID-19 pandemic. Patients diagnosed with KD during the pandemic had complete KD, higher liver transaminases and significant IVIG resistance but no coronary artery involvement.

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TRIAL REGISTRATION. The study was approved by the Danish Data Protection Agency (DK-634228).

In Scandinavia, Kawasaki disease (KD) is a relatively uncommon medium vessel vasculitis most commonly affecting coronary arteries in young children [1]. The diagnosis of KD is clinical, but heterogeneity in symptoms, especially in infants, and limited awareness in the low-prevalence Scandinavian population [2] pose a risk of diagnostic delay. Ensuing delayed treatment increases the risk of coronary aneurysms, placing KD as the most common acquired cardiac condition in children in developed countries [1]. Although the aetiology of KD remains unknown, several studies have suggested a combination of genetic factors and immune response, suspected to be triggered by an infectious agent as part of the pathogenesis [3].

In Denmark, the first detection of SARS-CoV-2 was registered on 27 February 2020. After the outbreak of the COVID-19 pandemic, an inflammatory multisystem syndrome in children (MIS-C) has been reported from

Europe and USA with clinical features overlapping those of KD and presenting weeks after SARS-CoV-2 infection [4, 5]. It was documented in East Asia and USA that COVID-19 preventive initiatives produced a reduction in KD incidence [6-8]. However, whether this had an impact in the Nordic population remains unknown. In this study, we examined the incidence, presentation and outcome of KD patients from a Danish tertiary paediatric department before and during the COVID-19 pandemic.

METHODS

We included children admitted to the Department of Paediatrics at Aarhus University Hospital, Denmark, from 1 January 2008 to 1 September 2021, given the International Classification of Diseases, 10th version (ICD-10) code DM303 for KD. Patients diagnosed until 27 February 2020 were defined as the "pre-pandemic" group, whereas those diagnosed after 27 February 2020 were defined as the "pandemic" group. Electronic medical records were reviewed to collect clinical data. According to the American Heart Association diagnostic criteria, patients with ≥ 5 days of fever (> 38.5 ^{o}C) and presence of ≥ 4 of five principal clinical features like peripheral extremity changes, rash, bilateral non-purulent conjunctivitis, oral mucosal changes such as red, cracked lips and strawberry tongue and cervical unilateral lymphadenopathy of > 1.5 cm were classified as complete KD; and patients who presented with two or three of these criteria were classified as incomplete KD [9].

Echocardiography

Two-dimensional echocardiography was performed routinely by experienced paediatric cardiologists at KD diagnosis, two and eight weeks after disease onset, and were repeated if clinically relevant. The internal diameters of the left main coronary artery (LMCA), right coronary artery (RCA) and the left anterior descending artery (LAD) were measured from inner edge to inner edge on digital images. Z scores for all of the coronary artery (CA) measurements were calculated as previously described [10]. Z scores > 2 were considered abnormal. Aneurysms were defined with Z scores > 2.5.

Treatment

All KD patients diagnosed with ongoing fever received intravenous immunoglobulin (IVIG) 2 g/kg body weight, max 70 g, combined with acetylsalicylic acid (ASA) (80 mg/kg/day) until normalisation of fever followed by low-dose ASA 3-5 mg/kg/day for two months after onset and discontinued unless CA abnormalities were detected. IVIG resistance was defined according to the American Heart Association as persistent or recrudescent fever 1.5-7 days after completion of the first IVIG infusion [9]. These patients received an additional IVIG dose often combined with high-dose intravenous methylprednisolone (IVMP, 30 mg/kg/day for three days) and less frequently biological treatment.

Statistics

The collected data were stratified into complete or incomplete KD, with or without CA involvement, before and during the COVID-19 pandemic. For the description of demographics and clinical characteristics, medians and interquartile ranges were used. Differences between groups were analysed using Pearson's χ^2 test, and the Mann-Whitney U test was used for continuous variables. p values < 0.05 expressed significance.

Trial registration: The study was approved by the Danish Data Protection Agency (DK-634228).

RESULTS

Eighty patients were identified with ICD code DM303. Six patients were excluded from the study: one with systemic juvenile idiopathic arthritis, one with acute pharyngitis and four with long-term fever but no additional

KD criteria. A total of 74 patients, aged from three months to 13.5 years (**Table 1**), met the KD criteria of whom 64 were diagnosed in the pre-pandemic period and ten after the COVID-19 outbreak in Denmark. More than 60% were younger than four years of age. The male/female ratio was 1.96:1. According to the childhood population in our uptake area, the incidence of KD was 4.3:100,000/y during the pre-pandemic period. The ten patients in the pandemic group were exclusively diagnosed within the first six months of the pandemic, corresponding to an incidence of 16:100,000/y, but hereafter none were diagnosed with KD the following year. All ten were negative by nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) and SARS-CoV-2 serology and without known exposure to SARS-CoV-2-positive individuals.

TABLE 1 Demographic data of patients with Kawasaki disease before and during the COVID-19 pandemic.

	All patients (N_{all} = 74)	Pre-pandemic group[a] (N_{pre} = 64)	Pandemic group[b] (N_{pan} = 10)	p value
Demographic features				
Male sex, n (%)	49 (66.2)	42 (65.6)	7 (70)	0.546
Age, median (IQR), mos.	37 (19-63)	35.5 (15-60)	41.5 (31.5-88)	0.206
Clinical features				
Fever duration before diagnosis, median (IQR), days	5 (5-7)	5 (5-7)	5.5 (5-9.5)	0.417
Complete KD, n (%)	58 (78.4)	48 (75)	10 (100)	0.074
Extremities, n (%)	64 (86.5)	56 (87.5)	8 (80)	0.519
Exanthema, n (%)	68 (91.9)	59 (92.2)	9 (90)	0.814
Conjunctivitis, n (%)	68 (91.9)	58 (90.6)	10 (100)	0.312
Lips, oral mucosa, n (%)	69 (93.2)	59 (92.2)	10 (100)	0.360
Cervical adenitis, n (%)	52 (70.3)	46 (71.9)	6 (60)	0.445
Lab results at diagnosis, median level (IQR)				
ALT, U/l	24 (13-74)	22.5 (11.75-54.75)	85 (41.5-128.5)	0.017
Albumin, g/l	31 (27-33)	31 (26.5-33)	32.5 (27-35.25	0.302
CRP, mg/l	108 (62-180)	107.5 (61.75-176)	106 (55.25-232)	0.760
ESR, mm	70 (50-89)	70 (46-91.5)	68 (47-85)	0.679
Hb, mmol/l	6.7 (6.2-7.4)	6.7 (6.2-7.3)	6.85 (6.2-7.9)	0.307
WBC, × 10^9/l	13.1 (10.5-17.4)	13.1 (11-17.5)	13.2 (9.0-15.9)	0.546
Platelets, × 10^9/l	380 (302-521)	387 (305-531)	374 (275-419)	0.356

ALT = alanine transaminase; ESR = erythrocyte sedimentation rate; Hb = haemoglobin; IQR = interquartile range; KD = Kawasaki disease; WBC = white blood cells.
a) Include KD patients diagnosed 1 Jan 2008 – 27 Feb 2020.
b) Include KD patients diagnosed 27 Feb 2020 – 1 Sep 2021.

Children diagnosed during the pandemic were slightly older (median 41.5 versus 35.5 months, not significant, Table 1). The clinical KD criteria were met equally in the pre-pandemic and pandemic group. Incomplete KD was observed in 16 patients (21.6%, Table 1), all of whom were from the pre-pandemic era. Incomplete KD patients were significantly younger than patients with complete KD (15 versus 44 months, p = 0.002), and eight out of ten with incomplete KD were younger than three years of age.

In general, laboratory data revealed elevated c-reactive protein (CRP) and erythrocyte sedimentation reaction, anaemia, leukocytosis, thrombocytosis and hypoalbuminemia. High levels of alanine transaminases were observed in the pandemic group (Table 1).

Intravenous immunoglobulin was given to 70 patients. The fraction of IVIG responders, responding to the first IVIG dose and not experiencing relapse, was higher in the pre-pandemic group (71.7%) than in the pandemic group (40%, p = 0.048) (**Table 2**). IVIG was refrained in four patients, where fever and clinical features had abated at the time of diagnosis. IVIG was given within ten days of fever in 57 patients (81.4%) with no difference between the pre-pandemic and the pandemic group. Patients with IVIG treatment > 10 days after onset had higher thrombocyte count (p < 0.001, not shown). Patients not responding to the first IVIG dose were retreated

with a second dose, often in combination with high-dose IVMP and/or biological medicine. High-dose IVMP was given to 18 patients, who more frequently belonged to the pandemic group (50%) than to the pre-pandemic group (20.3%). Seven (9.5%) patients received anti-tumour necrosis factor treatment (infliximab) and three (4.1%) received anti-interleukin-1 receptor antagonist treatment (anakinra).

TABLE 2 Treatment and coronary artery abnormalities in patients with Kawasaki disease.

	All patients (N_{all} = 74)	Pre-pandemic group[a] (N_{pre} = 64)	Pandemic group[b] (N_{pan} = 10)	p value
Fever duration before IVIG, days	6.0 (5.0-8.0)	6.0 (5.0-7.8)	5.5 (5.0-9.5)	0.671
IVIG treatment, n (%)				0.048
0	4 (5.4)	4 (6.3)	-	
1	47 (63.5)	43 (67.2)	4 (40)	
≥ 2	23 (31.1)	17 (26.6)	6 (60)	
IVIG duration, n (%)				
≥ 8 days	18 (25.7)	15 (25)	3 (30)	0.503
≥ 10 days	13 (18.6)	11 (18.3)	2 (20)	0.596
IVMP treatment				
Yes, n (%)	18 (24.3)	13 (20.3)	5 (50)	0.042
Anti-TNF				
Yes, n (%)	7 (9.5)	5 (7.8)	2 (20)	0.221
Anti-IL-1-RA treatment				
Yes, n (%)	3 (4.1)	3 (4.7)	0	0.485
Coronary artery, n (%)				
Dilatations	14 (18.9)	14 (21.9)	0	0.105
Aneurysms	7 (9.5)	7 (10.9)	0	0.345

IL = interleukin; IVIG = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; KD = Kawasaki disease; RA = receptor antagonist; TNF = tumour necrosis factor.
a) Include KD patients diagnosed 1 Jan 2008 – 27 Feb 2020.
b) Include KD patients diagnosed 27 Feb 2020 – 1 Sep 2021.

Coronary artery abnormalities with dilatation (CAD) were found in 14 patients (18.9%) among whom coronary artery aneurysms (CAA) were observed in 7/74 (9.5%); all these patients were diagnosed before the COVID-19 pandemic. None of the patients within the pandemic group showed CA abnormalities (Table 2). Patients with CA abnormalities were significantly younger than patients without CA involvement (median 18 versus 43 months, $p \leq 0.001$) and 35.7% were younger than one year (**Table 3**). Four patients with CAA were younger than one year (57%). We found no gender differences regarding CA sequelae. Patients with incomplete KD had a higher risk of CAA but not of CAD than patients with complete KD (Table 3). CAA were observed significantly more often in patients who received initial IVIG 10 days of fever ($p = 0.006$, Table 3). Patients with CAA had significantly lower haemoglobin, albumin and higher platelet count at diagnosis than patients without CAD (**Table 4**).

TABLE 3 Kawasaki disease patients with or without coronary artery involvement.

			CAD		CAA	
	All patients (N_{all} = 74)	No CAD (N_{no} = 60 (81.1%))	CAD, yes (N_{CAD} = 14 (18.9%))	p value, CAD vs no CAD	CAA, yes (N_{CAA} = 7 (9.5%))	p value, CAA vs no CAD
Demographic features						
Male sex, n (%)	49 (66.2)	40 (66.7)	9 (64.3)	0.865	6 (85.7)	0.252
Age, median (IQR), mos.	37 (19-63)	43 (22-80)	18 (6-38)	0.005	8 (5-15)	< 0.001
Fever duration, median (IQR), days						
Before diagnosis	5.0 (5.0-7.0)	5.0 (5.0-7.0)	5.0 (5.0-8.3)	0.893	12.0 (4.0-18.0)	0.498
Before initial IVIG treatment	6.0 (5.0-8.0)	6.0 (5.0-7.8)	5.0 (5.0-12.8)	0.796	12.0 (4.0-18.0)	0.326
Kawasaki disease, n (%)						
Complete	58 (78.4)	48 (82.7)	10 (17.2)	0.483	3 (5.2)	0.016
Incomplete	16 (21.6)	12 (75)	4 (25)	-	4 (25)	-
IVIG treatment, n (%)						
No treatment[a]	4	4	0	-	0	-
Response, 1st dose	47 (63.5)	39 (65.0)	8 (57.1)	0.373	4 (57.1)	0.553
Duration ≥ 8 days with fever	18 (25.7)	14 (25.0)	4 (28.6)	0.784	4 (57.1)	0.045
Duration ≥ 10 days with fever	13 (18.6)	9 (16.1)	4 (28.6)	0.282	4 (57.1)	0.006
Duration < 10 days with fever	57 (81.4)	47 (83.9)	10 (71.4)	-	3 (42.9)	-
IVMP treatment, n (%)	18 (24.3)	10 (16.7)	8 (57.1)	0.001	6 (85.7)	< 0.001

CAA = coronary artery aneurysm; CAD = coronary artery dilatation; IQR = interquartile range; IVIG = intravenous immunoglobin; IVMP = intravenous methylprednisolone.
a) IVIG was omitted in 4 patients, where fever and clinical features faded away at the time of diagnosis.

TABLE 4 Laboratory results from Kawasaki disease patients with or without coronary artery involvement.

			CAD		CAA	
	All patients (N_{all} = 74)	No CAD (N_{no} = 60 (81.1%))	CAD, yes (N_{CAD} = 14 (18.9%))	p value, CAD vs no CAD	CAA, yes (N_{CAA} = 7 (9.5%))	p value, CAA vs no CAD
Lab results at diagnosis, median level (IQR)						
ALT, U/l	24 (13-74)	23 (12-69)	26 (16-179)	0.273	50 (19-161)	0.242
Albumin, g/l	31 (27-33)	31 (27-33)	29 (24-32)	0.142	25.5 (23-28.8)	0.018
CRP, mg/l	108 (62-180)	101 (59-176)	117 (62-200)	0.665	115.4 (53.6-198)	0.923
ESR, mm	70 (50-89)	64 (40-85)	89 (69-104)	0.018	87 (54-120)	0.198
Hb, mmol/l	6.7 (6.2-7.4)	6.8 (6.4-7.4)	6.2 (5.7-6.8)	0.017	5.7 (5.2-6.2)	< 0.001
WBC, × 10^9/l	13.1 (10.5-17.4)	13.4 (11.0-16.9)	12.6 (9.3-19.6)	0.963	9.8 (7.4-19.2)	0.531
Platelets, × 10^9/l	380 (302-521)	378 (300-463)	670 (287-757)	0.127	723 (314-775)	0.049
Lab results, max or min., median level (IQR)						
$Albumin_{min.}$, g/l	25 (22-29)	26 (21-29)	24 (22-28)	0.477	23 (22-25)	0.144
CRP_{max}, mg/l	123 (87-230)	119 (82-230)	126 (106-264)	0.398	146 (99.7-257.4)	0.550
ESR_{max}, mm	85 (67-111)	83 (61-108)	106 (74-119)	0.175	87 (67-120)	0.936
$Hb_{min.}$, mmol/l	6.2 (5.5-6.9)	6.2 (5.7-7.3)	5.6 (4.3-6.0)	0.002	4.5 (3.4-5.6)	0.002
WBC_{max}, × 10^9/l	15.4 (12.2-20.0)	14.3 (12.2-18.4)	22.2 (16.1-28.7)	0.002	25.3 (20-40.2)	0.005
$Platelets_{max}$, × 10^9/l	577 (488-744)	559 (470-650)	742 (678-921)	< 0.001	775 (738-1255)	0.002

ALT = alanine transaminase; CAA = coronary artery aneurysm; CAD = coronary artery dilatation; ESR = erythrocyte sedimentation rate; Hb = haemoglobin; IQR = interquartile range; WBC = white blood cells.

The first echocardiography was performed a median 7.0 days (interquartile range (IQR): 6.0-16.3) after onset of fever. CADs and CAAs were detected at a median of 13 days (IQR: 6.25-18.5). The majority of CADs were detected at the first echocardiography (71.4%) after a median of 6.5 days. Maximal z-scores for patients with CAA were in RCA (median = 7.3 (IQR: 3.7-11)), LAD (median = 8.2 (IQR: 5.7-10.5)) and LMCA (median = 4.2 (IQR: 3-6.5)). At follow-up, normalisation of CA dimensions was achieved in ten patients (71.4%) after a median of nine months (IQR: 5.5-35 months). Four patients still had CA abnormalities after a median of 19 months (range: 10-96 months).

DISCUSSION

During the 12-year period leading up to the COVID-19 pandemic, we observed a KD incidence of 4.3:100,000/y, which is comparable to previous reports from Denmark and other European countries [2]. During the first six months of the COVID-19 pandemic, we observed a transient increase in KD; but during the ensuing 12 months, we did not have any patients with KD. None of the KD patients during the pandemic were related to previous confirmed or suspected cases of COVID-19 infection. From countries with a high prevalence of SARS-CoV-2 during the initial phase of the pandemic, an increased number of children with KD or MIS-C was published,

notably with confirmed COVID-19 history [4, 5, 11, 12]. This was unlike our patients among whom no known COVID-19 history could be confirmed. However, COVID-19-preventive initiatives like restriction of person-to-person contacts and face masks lead to a substantial reduction of the transmission of respiratory infections like respiratory syncytial virus and influenza, also in Denmark [13, 14]. Accordingly, a significant reduction of KD incidence was reported following the COVID-19-preventive initiatives in East Asia with an otherwise high KD prevalence rate [6, 7] and in the USA [8], but so far not from the Nordic countries. This may support the role of a postinfectious aetiology in KD [4]. The reason for the incidence changes in 2020/2021 in this study remains unclear, but the drop in KD cases from September 2020 to September 2021 may be a result of fewer infection triggers. Conceivably, it was not due to underdiagnosing since we observed an increase in KD cases during the first six months of the pandemic.

Similar to other studies, the present study reports a predominance among males and young children (< 5 years) [1]. Patients diagnosed from the COVID-19 era were slightly (but insignificantly) older than patients of the pre-pandemic group. We found that the gender distribution and the frequency of clinical KD criteria were similar in both groups. Likewise, two Japanese studies did not observe clinical differences between KD patients diagnosed before and during the pandemic [6, 15]. However, in our study, patients diagnosed during the COVID-19 pandemic had elevated liver transaminases.

Timely treatment with IVIG 2 g/kg along with ASA within the first ten days of fever has been the mainstay of KD treatment [16]. Different treatment options have been suggested for IVIG non-responders [1], including additional IVIG, high-dose IVMP and anti-cytokine therapy [17]. We observed a failing response to first IVIG dose in 36.5% who then responded to additional IVIG, typically in combination with IVMP. The rate of IVIG non-responders was higher in the pandemic group and they often received additional IVMP. This was not explained by an increased inflammatory response or treatment delay since 80% or more received their first IVIG within ten days in both groups, which is comparable to the findings by Bal et al. [18]. It has been shown that patients with abnormal liver parameters are at risk of IVIG resistance [19], which was also observed in this study during the pandemic.

We observed CA involvement in 18.9% of KD patients of whom half developed aneurysms. This was a relatively high rate considering that the majority had been treated with IVIG within the first week after disease onset. Considering patients before the COVID-19 pandemic, we observed CA involvement in almost 22%, which contrasted with no CA involvement being observed during the COVID-19 pandemic. However, the numbers were small. In two Japanese studies, the authors observed a much lower CAD prevalence before the COVID-19 pandemic (5.0%), which essentially remained unchanged during the pandemic [6, 15].

Wilder et al. described that in their study, 25% of KD patients had received IVIG later than the tenth day of illness due to diagnostic delay, which posed a risk for development of CA pathology [20].

The rate of CAD involvement in our study remained high (16.4%) despite timely IVIG treatment within ten days of fever. The rate of late treated patients was the same for both the pre-pandemic and the pandemic group. Furthermore, no significant difference was observed in the occurrence of CAD between early and late treated patients, but 57% of the patients with CAA received IVIG after ten days of fever compared with 16% of the patients without CAA ($p = 0.006$).

A number of factors have been associated with an increased risk of developing CAA, of which early age, male gender and delayed IVIG administration are those described in most studies [1, 9]. Thus, we found that more than one third of the patients with CAD were younger than one year, and only two children were older than four years, but these children did not develop aneurysm. The increased risk of developing CAA in infants is particularly concerning because, at this young age, the clinical characteristics of KD are more subtle with a high

frequency of incomplete KD, increasing the risk of diagnostic delay [20].

Low haemoglobin, thrombocytosis and low albumin have previously been reported as predictors for CAA development [1, 9], which was confirmed in our study. KD is a relatively uncommon vasculitis in Denmark, limiting the sample size, which may well hamper the generalisability of our conclusions.

CONCLUSION

A transient increase in KD incidence was seen during the first six months of the COVID-19 pandemic, followed by 12 months without any KD cases presenting. All patients in the COVID-19 pandemic group had complete KD, higher liver transaminases and a significant IVIG resistance, but no coronary artery involvement. This study supports that extra clinician vigilance is warranted for any child presenting with unexplained fever, especially children under the age of three years.

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