

COVID-19 and Kawasaki like disease: the known-known, the unknown-known and the unknown-unknown

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Abstract

In the end of April nearly 100 cases of children aged between 6 month and 9 years with Kawasaki like disease were reported (mostly in Europe) probably linked to COVID-19. With the increasing awareness of this condition the number of cases reported is increasing worldwide. We aim to sum up the known data about this new entity based on published data (in a case report, a series of 8 cases and in newspapers and society statement) and using our knowledge of classical Kawasaki disease. It seems to be a post infectious disease with an onset between 2-4 weeks after the infection, probably in genetically predisposed children aged between 6 month to 17 years. A very rough estimation of incidence based on current data from Bergamo, Italy, and New York State and a lot assumption is between 0.016% (95% CI:0.013-0.02%) - 0.31% (95% CI: 0.2-0.47%) of infected children. Clinical signs overlaps with Kawasaki disease in some children, but another feature is prominent gastrointestinal manifestations. For the 9 detailed patients most had incomplete presentation for Kawasaki disease (with a mean 1.7 (+/- 1.2) criteria per patient for the 5 non fever criterion) and only one had a classical form. In some cases, presentation is closer to toxic shock syndrome or isolated myocarditis. Persistent fever seems to be constant and biological exploration are consistent with inflammation (elevated CRP, ferritin and D-Dimers). Management is described as supportive and children seem to improve rapidly, but can require cardiac or respiratory support. In date of 11 may 2020 there is 4 deaths confirmed linked to these new entities (1 in UK and 3 in New York). Paediatricians and general practitioners need to be aware of these possible evolution following COVID-19 infection. However it seems to be rare and children are probably still spared from most morbidities and mortality linked to COVID-19 infection .There are need of published detailed cohorts to better delineate these entities.

Keywords: Sars-Cov2; Covid-19; Children; Kawasaki disease; toxic shock syndrome

Introduction

In a famous conference held in 2002, United States Secretary of Defense Donald Rumsfeld popularize the concept of three level of knowledge about a threat, the last being the impossibility to predict or imagine some of them (wikipedia). The emergence of a Kawasaki-like disease in children is a perfect example of this unknown-unknown level. In one article (Jones et al. 2020), one statement from the NHS (PICS 2020) and on press declaration from the MC3C-Necker (Soun 2020) the existence of a Kawasaki-like disease probably related to COVID-19 became tangible and raised concern for the paediatric population, who has been to these date mostly spared from the most severe form of COVID-19. However very few elements are known and we try to sum and hint some hypotheses using our knowledge of classical Kawasaki disease, association between other coronavirus and Kawasaki disease, and known features of COVID-19 in children.

Kawasaki disease is a systemic vasculitis occurring mostly in children younger than 5 years, in which the most feared complications are coronary artery abnormalities. The diagnosis is clinical (association of prolonged fever >5 days, and in typical forms extremity change like oedema, erythema and desquamation, rash, conjunctivitis, oral change like cheilitis, glossitis, pharyngitis and cervical lymphadenopathy), and the management rely mostly on intravenous immune globulin and corticosteroids (McCrindle et al. 2017, De Graef 2019). The cause of Kawasaki disease is still unknown. Its incidence vary from about 5/100,000 in Europe to more than 300/100,000 in Japan, North America reached a prevalence of 19/1,000,000 (Kim 2019). It appears to have seasonality (Kim 2019). It has been suggested a temporal association with viral infection, notably Bocavirus and Enterovirus (Kim et al. 2014). A long list of pathogenic agents have been linked to Kawasaki disease, among them coronavirus, particularly HCoV-NL63 when it was first discovered in 2004 (Esper et al. 2005). However this association was not confirmed (Chang et al 2006, Lehmann et al. 2008). A study of viral infection in 222 patients

found that 93 had a positive respiratory viral PCR (54 Rhinovirus/enterovirus, 2 Hcov-OC43 and 3 Hcov-NL63), however there was no difference with the control population (Turnier et al. 2015). Finally, study of intracytoplasmic inclusion bodies in ciliated bronchial epithelium of Kawasaki disease patients have suggested the role of an unknown RNA virus (Rowley et al. 2011) and prompt the hypothesis (although not widely accepted) that Kawasaki disease is caused by an RNA virus causing an asymptomatic infection in most children but triggering inflammatory symptoms in a subset of genetically predisposed children (Rowley et Shulman 2018).

Method

We performed a research on NCBI (www.pubmed.com), preprint server (www.preprints.org, <https://www.biorxiv.org/>) and newspapers (news.google.com) using the term Kawasaki disease and COVID-19, maladie de Kawasaki et COVID-19 , Sindrome di Kawasaki e COVID-19. Scientifics articles were screened and included if relevant to COVID-19 pandemic and kawasaki like disease symptom, newspaper article and society statement were included if provide meaningful informations non included in scientifics articles. The search was performed till the 05/07/2020 and completed the 05/11/2020. Incidence was calculated using the tool epitool and confidence interval with Wilson method.

Results

Two Scientifics articles (Riphagen et al. and Jones et al.), 4 medical society or health department reports (NYC Health 2020, PICS 2020, RCPH 2020) and 8 newspaper articles (Barral 2020, INSERM 2020, Moran 2020, Marrone 2020, Reuters 2020, Russo 2020, Soun 2020, Sample and Campbell 2020) and a communication from Governor Cuomo (Cuomo 2020) were included.

Clinical presentation

The 7 April 2020 there was the publication of description of a 6 month infant with Kawasaki disease and confirmed COVID-19, effectively treated with intravenous immunoglobulin published in literature (Jones et al. 2020). And in the end of April various authors have described similar phenotypes to Kawasaki disease but with unusual presentation or outcome. The PICS Statement published the 04 27 2020 describe critically unwell children features of toxic shock syndrome and atypical Kawasaki disease, with prominent gastrointestinal symptoms and cardiac inflammation (PICS 2020). Publication of a 8 cases-series of Londonian children help to better delineate the syndrome (Riphagen et al. 2020). The 8 children present with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome, or toxic shock. The clinical signs were unrelenting fever (38–40°C) for more than 4 days (8/8), diarrhea (7/8), variable rash (4/8), conjunctivitis (5/8), abdominal pain (5/8), vomiting (4/8), myalgia, odynophagia (3/8) and headache (2/8). Thus gastrointestinal manifestation can be in the forefront and 2 children had surgery for acute abdomen symptoms (Barral 2020). In the Riphagen et al. series it was also noted the presence of small pleural (3/8), pericardial, and ascitic (5/8) effusion.

The mean age is 9 years old (2-17 years) in the Parisian cohort (Barral 2020) and 8.9 years old (4-14 years) in the Londonian series (Riphagen et al. 2020). The only detailed series is from Riphagen et al., it could be noted that 6/8 were Afro-Caribbean and 7/8 had a weight above the 75th centile, but no significant other comorbidities (autism for one, alopecia areata, Hay Fever for another).

An Inserm press release described 3 forms: Classical Kawasaki, atypical Kawasaki disease in older children presenting mainly with heart involvement, and a systemic inflammatory disease with myocarditis (Inserm 2020). NYC health reported 3 forms: Typical Kawasaki disease, incomplete Kawasaki disease, and/or shock (NYC Health 2020). For the 9 patients with some

clinical data, only one (the younger in Jones et al. 2020) had criteria for Kawasaki disease (table 1) . For the 5 non fever criteria, there was a mean 1.7 (+/-1.2) criteria per patients, with an inverse correlation with age for the number of criterion (pearson correlation p:-0.7534 CI 95% [-0.9448;-0.1786], p=0.019) figure 1.The RCPH guideline state that clinical presentation is persistent fever, often hypotension and oxygen requirement, and list 14 other clinical features (abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope or vomiting) associated with elevated inflammatory markers (CRP, ferritin, abnormal fibrinogen), hypoalbuminaemia and lymphopenia, in the absence of other potential pathogen than SARS-Cov-2 (RCPH 2020). In the Londonian series (Riphagen et al. 2020), mean CRP is 303.75 mg/l (+/-120.4), ferritin 1086.6 µg/l (+/- 1289.8), D-dimer 10.4 mg/l (+/-6.8), troponin 252.5 ng/l (+/-314) and albumin 22 g/l (+/-2.3), the Jones et al. case had a CRP of 133 mg/l and albuminemia of 28 g/l (Figure 2) . This description shows an overlap between Kawasaki disease and COVID-19 phenotypes, but without severe lung disease typically associated to COVID-19 (Sample and Campbell 2020). The Jones et al case had a normal echocardiogram whereas 6/8 in Riphagen et al. had ventricular dysfunction, 1/8 had dilated coronaries and a frequent echocardiographic finding was echo-bright coronary vessels .

Medical management and evolution

Most described cases improved rapidly in four days (Moran 2020, Marrone 2020, Riphagen et al. 2020), although some required mechanical ventilation (5/15 in NYC Health 2020 and 5/8 in Riphagen et al. 2020) or cardiac support (Milrinone 6/8, Noradrenaline 7/8, Adrenaline 3/8, Dopamine 3/8 in Riphagen et al. 2020) (Moran 2020, NYC Health 2020). Only Jones et al. and Riphagen and all describe the management. 9 children received intravenous immunoglobulin,

8 antibiotics, 4 methylprednisone, and 3 received aspirin. The RCPH recommendation suggests use of intravenous immunoglobulin for Kawasaki-like presentation and toxic shock syndrome.

Epidemiology

Initially, 100 children aged between 6 months and 9 years were reported at the end of April, mostly from Europe (Sample and Campbell 2020, Reuters 2020, Marrone 2020). Initially only 4 cases from the USA were reported (3 from New York and 1 from California) (Reuters 2020, Jones et al. 2020) but in less than 7 days the number of New York cases increased to 15 (age 2-15 years) (NYC Health 2020), and to 93 cases state wide (Russo 2020) most from the last half of April probably due to better awareness. 4 death (1 from IK and 3 from New York) were reported as confirmed in date of 11 may 2020 : one child aged 14 years from cerebral infarction (Riphagen et al. 2020), and 3 children aged 5, 7 years and a teenager in New York (Cuomo 2020).

The difference between Europe, USA and East Asia could be that they were more severely hit than Korea or China. The other hypothesis is that because prevalence of KD in Europe is usually lower than in East Asia (twenty fold less) or North America (one quarter less) (Kim 2019), increase of incidence could be more easily stressed.

Association of the Kawasaki like disease and toxic shock syndrome manifestation and with COVID-19

At first, reports were not conclusive for the link with COVID-19, as all the patient weren't positive for SARS-Cov-2 even if the temporal association was highly suggestive (PICS 2020, Marrone 2020, Soun 2020). However, later reports stated that most of the MC3C-Necker French cases were tested positive for SARS-CoV-2 by PCR or serological test (Moran 2020). It's unclear if the PCR were performed in nasopharyngeal swabs (usual clearance in 2 weeks) or in stool (clearance in 3 or 4 weeks) (Xing et al. 2020). Subsequent observation of MC3C-Necker

French reported a 70% of positivity for COVID-19 (Barral 2020). In Riphagen et al., initially 2 children were SARS-COV2 positive, 5 were SARS-COV2 negative among them 3 had a likely or confirmed familial exposure however it's stated that finally all had SARS-COV2 positive antibodies. As observed by MC3C-Necker team, an onset manifestation 3-4 weeks after the infection suggested a post infectious reaction. In Jones et al.'s case it's not clear if KD was concomitant of the COVID-19 infection. A 9-year-old sibling had upper respiratory symptoms 3 weeks prior, so assuming a 5 days incubation, KD symptoms may have appeared 2 weeks after the onset of COVID-19 (Jones et al. 2020). Bergamo, Italy's team suggest a correlation between the epidemic peak and the increase of Kawasaki disease cases (Marrone 2020). The most parsimonious is probably a delay between 2 to 4 weeks after the COVID-19 infection and could explain the delay between the peak of COVID-19 and the observed increase of cases (Soun 2020, NYC Health 2020).

Incidence

Incidence is hard to determinate as children are usually underrepresented in positive patients (0.8-15.8% according global world data, CDC 2020, Gudbjartsson et al. 2020, Italian National Health Institute 2020, Wu et al. 2020, Health Gouv Israel 2020). An estimation of incidence could be tried from the 20 cases diagnosed in Bergamo, Italy (Marrone 2020). Bergamo has been severely hurt by COVID-19 infection and recently it has been stated that between 20% and 60% of tested population had antibodies against COVID-19 (Di Landro 2020). In the area of Bergamo there are slightly fewer than 500,000 inhabitants (Wikipedia). Assuming (as for the whole of Italy) 13% of children aged less than 14 years, 65,000 children should live in this area. Using two hypothesis either that the rate is similar between children and adults (Bi et al. 2020) or half the adults (RIVM 2020), between 6,500 and 39,000 children should have been infected (10-60%), thus obtaining a ratio of 0.038% (95% CI:0.023-0.063%) to 0.31% (95% CI: 0.2-0.47%) of Kawasaki-like disease per infected children. The same method used for the New

York state data with a total of 93 cases reported (Russo 2020) a COVID-19 prevalence of 13.9% COVID-19 in population (Lucking 2020) and a population of 4068102 children found a ratio of 0.016% (95% CI:0.013-0.02%) to 0.033% (95% CI:0.027-0.040%) of Kawasaki-like disease per infected children.

Discussion

A lot of the discussion comes from the similarities between these symptoms and Kawasaki disease (acute unwell children, inflammation, heart implications). But there are also differences. In fact, patients seems to be older (median age of 9 years vs 3 years) than in classical Kawasaki Disease (Inserm 2020, Riphagen et al.). The importance of gastrointestinal signs is also striking, on one side SARS-Cov-2 can infect enterocytes through ACE2 (Lamers et al 2020) and diarrhea can be present in about a 1/3 of adults patient (Pan et al. 2020) on the other side if we assume a post infectious disease, the diarrhea is probably not directly related to the infection. In classical Kawasaki disease vomiting is present in 18.2%, diarrhea in 15.7% of cases, abdominal pain in 12.4%, thus gastrointestinal signs seems to be more present in COVID-19 linked Kawasaki like disease (Yun et al. 2011). It can't be ruled out that they are unrelated different diseases as there seems to exist several presentations (ranging from Kawasaki disease, atypical Kawasaki disease, toxic shock syndrome and myocarditis) and different mechanisms (post-infectious reaction or cytokine storm as observed in adults with COVID-19). For the 9 detailed patients only one as a classical Kawasaki disease and there seems to be an inverse correlation with age for the number of Kawasaki disease criteria suggesting different disease according the age. For two patients from New York, abnormalities in gene linked to immune response were reported (Reuters 2020). A possible continuum could exist between "classical Kawasaki disease" triggered by COVID-19, atypical Kawasaki disease and a systemic inflammatory presentation similar to cytokine storm observed in adults. We can't rule out the implication of other factors, either infectious or environmental. Indeed some children didn't

have proof of COVID-19 infection. For example, the most severely affected areas (Italy, France, United-Kingdom, New-York) are areas in lockdown, thus the determining factor could be linked to indoor environment.

Incidence seems to be fortunately low. However there are limitation, we don't know the true prevalence of COVID-19 in children, and with increase awareness and with the time lag between onset of COVID-19 and manifestation of Kawasaki like disease the number of cases will probably increase.

This disease seems different than adult COVID-19 even if there are some superficial similarities: in adults with severe pneumonia it has been suggested that regular intravenous immunoglobulins could reduce mortality and severity (Xie et al. 2020, Shao et al. 2020) and cardiac manifestations have been attributed to COVID-19 (Kang et al. 2020). The patient 1 of Riphagen et al. has the more similar presentation to adult. He didn't have Kawasaki criterion, he had a pulmonary disease and a significant overweight which is a risk factor of ventilation in adults disease onset COVID-19 (Simonnet et al. 2020).

The most important limit is that there are only one published case and a small series of 8 severe cases, all other data came from newspapers articles or paediatric societies' statements.

Conclusions

In conclusion in the last weeks has emerged a Kawasaki-like disease probably linked to COVID-19. It seems to be a post-infectious disease with an onset between 2-4 weeks after the infection, probably in genetically predisposed children aged between 6 month and 17 years. One article reports an over presentation of patients from Afro-Caribbean origin (6/8 in Riphagen et al. series for an estimated 4 % of London region's population Wikipedia) and weight above 75P. A very rough estimation of incidence based on a lot assumption is between 0.016% and 0.31% of infected children. Clinical signs overlap from Kawasaki disease in unwell

children with gastrointestinal manifestations to a severe inflammatory systemic disease with myocarditis. Management is supportive and most children improved rapidly, and one death has been reported so far. There is a definite need of published detailed cohorts to better delineate these entities. Appropriate follow-up and clinical evaluation in case of fever after COVID-19 affected children is important for early detection of this potentially severe disease. Open SARS-Cov-2 screening through a devoted platform may help to detect asymptomatic and moderately ill children or adolescents, especially in the context of a familial cluster, allowing for better follow-up and appropriate council. For all Kawasaki-like symptoms or toxic shock syndrome, even in the absence of certain diagnosis of COVID-19, this aetiology should be considered during the actual time of SARS-CoV-2 pandemic.

Web site used

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Table 1 : Sex, Age, number of days of fever and Kawasaki Criteria for Jones et al. and Riphagen et al. Patients (1 :yes, 0 : no)

	Sex	Age (years)	Fever (days)	fever >5 days	Conjunctivitis	Lymphadenopathy	Rash	Changes of lips or oral mucosa	Changes to extremitie	Total (/5) non fever criteria
Jones et al.	F	0,5	5	1	1	0	1	1	1	4
Riphagen et al. P1	M	14	4	0	0	0	0	0	0	0
Riphagen et al. P2	M	8	5	1	1	0	1	0	0	2
Riphagen et al. P3	M	4	4	0	1	0	1	0	0	2
Riphagen et al. P4	F	13	5	1	1	0	0	0	0	1
Riphagen et al. P5	M	6	4	0	1	0	1	1	0	3
Riphagen et al. P6	F	6	5	1	1	0	0	0	0	1
Riphagen et al. P7	M	12	4	0	0	0	1	1	0	2
Riphagen et al. P8	F	8	4	0	0	0	0	1	0	1

Figure 1 : Number of Kawasaki criteria according age (Jones et al. Riphagen et al. 2020)

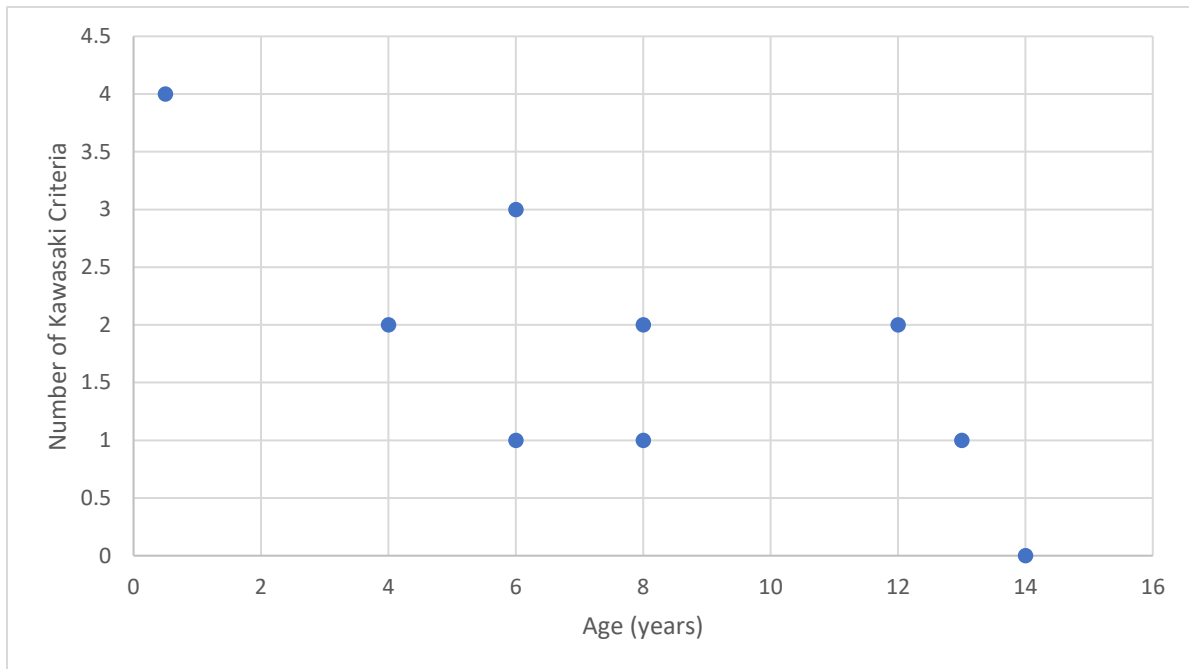


Figure 2 : A) CRP, Troponin and Platelet values, B) Albumin and D-dimer from Jones et al. and Riphagen et al.

