ADITUM

Journal of Pediatrics and Child Health Issues

Open Access Research Article

Kawasaki-Like Multisystem Inflammatory Disease in Children During The Covid-19 Pandemic: Prospective Study

Mohamed Sellouti*, Abdelilah Radi, Hakim El Yajouri, Salahiddine Saghir, Anas Ayad, Abdelhakim Ourrai, Amale Hassani, Rachid Abilkassem, Aomar. Agadr

Departement of Pediatrics, Mohammed V Military Teaching Hospital, Rabat

Article Info

Received: July 08, 2021
Accepted: July 19, 2021
Published: July 22, 2021

***Corresponding author:** Mohamed Sellouti, Departement of Pediatrics, Mohammed V Military Teaching Hospital, Faculty of Medicine and Pharmacy, Rabat Morocco.

Citation: Mohamed Sellouti, Abdelilah Radi, Hakim El Yajouri, Salahiddine Saghir, Anas Ayad et al "Kawasaki-Like Multisystem Inflammatory Disease in Children During The Covid-19 Pandemic: Prospective Study", J Pediatrics and Child Health Issues, 2(5); DOI: http;//doi.org/03.2021/1.1031.

.

.

Abstract

A novel *disease* was *identified* in Wuhan in 2019 leads to a pandemic of severe acute respiratory distress syndrome. Initially, *children appear* to be relatively spared in terms of both frequency *and* severity of, but there were reports of cases similar to Kawasaki disease, and evidence emerges about a complication named paediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 or multisystem inflammatory syndrome in children Ten children (median age 8 (range 6-15) years) were admitted with features of Kawasaki disease over two months. 4(40%) presented with Kawasaki disease with myocarditis. 1 (10%) required intensive care support. Five patients had noticeable gastrointestinal symptoms during the early stage of illness and high levels of inflammatory markers. 10 (100%) had evidence of recent SARS-CoV-2 infection (positive RT-PCR result in 1/10, positive IgG antibody detection in 10/10). All patients received intravenous immunoglobulin. The clinical outcome was favourable in all patients. Moderate coronary artery dilations were detected in 2 (20%) of the patients during hospital stay.

Multisystem inflammatory syndrome in children associated with SARS-CoV-2 led to serious and life-threatening illness in previously healthy children and adolescents.

Introduction

The Coronavirus disease 2019 (COVID 2019) caused by severe acute respiratory syndrome coronavirus 2 has rapidly spread worldwide. In March 2020, Morocco began seeing increasing numbers of COVID-19 cases, although children have been relatively spared [1, 2].

A secondary Multisystem Inflammatory Syndrome in Children have described after a prior COVID-19 infection who have presented with manifestations of vasculitis especially in young asymptomatic patients in England (n=8) and France (n=21) [3,4].

Kawasaki disease is the most common primary vasculitis in childhood, with medium and small sized arteries predominantly affected [5]. Although the cause of Kawasaki's disease remains unknown, a preceding or active infection has been hypothesized, as several viral respiratory agents [6, 7]. One of the most severe complications of Kawasaki disease is coronary artery anevrysm [8]

The aim of this study was to describe the epidemiology, features and treatment of new cases of Kawasaki-like presentations during the SARS-CoV-2 epidemic.

Methods

A retrprospective, descriptive study was conducted in department of pediatrics at Mohammed V Military Teaching Hospital, Rabat including the notes of all children who were admitted with Kawasaki disease between 1 Nov 2020, and 31 Jan 2021.

Our department, located in the city of Rabat, capital of Morocco, is a tertiary pediatric referral centre with approximately 1000 pediatric admissions per year. This university service receives from all regions of the kingdom Cases were consists of all children

admitted with Kawasaki like to the service during the study period. Kawasaki-like presentations were defined according to the criteria of the American Heart Association to define the presence of complete and incomplete Kawasaki disease [8]. For each patient we obtained nasopharyngeal swabs to test for SARS-CoV-2 using polymerase chain reaction (PCR; SARS-CoV-2). To exclude hospital acquired SARS-CoV-2 infection. We also took blood samples to test for IgG antibodies against SARS-CoV-2.

Factors analyzed were the demographic data, presenting symptoms and history of previous treatments, contact with confirmed or suspected cases of COVID-19, vital signs, and laboratory data, including such as for inflammatory and cardiac markers. Standard cardiology investigations included regular electrocardiography and echocardiography. A coronary artery dilation was defined if the coronary artery diameter z score was between 2.0 and <2.5 and an aneurysm if the z score was 2.5 or greater [8].

All patients were administered intravenous immunoglobulin at 2 g/kg. Patients were also treated with aspirin at 80 mg/kg per day for 5 days. Aspirin was maintained until 48 h after defervescence, and then continued at an antiplatelet dose of 3–5 mg/kg per day for 8 weeks.. Response to treatment was defined as the normalisation of vital signs, CRP, and blood tests, and the resolution of symptoms and signs.

Statistical analyses were performed using SPSS version. The Mann-Whitney U test was used for the comparison of the proportions. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the sample

A total of 10 cases of Kawasaki like were included in the main analysis of this study. There was a higher proportion of males 7(70%), with a sex ratio of 2, 3. The median age at presentation was 8 (range 6-15). The 10 patients had no relevant personal or family medical history. All patients presented with a classic form of the disease. Among the principal criteria Two Patients had non-exudative conjunctivitis, hand and feet anomalies (33%), and polymorphous skin rash (90%). Five (50%) of ten patients had associated changes of the lips or oral cavity, or both; two patient also had laterocervical lymphadenopathy. Five patients had gastrointestinal symptoms, which occurred early in the course of Kawasaki disease and consisting of acute abdominal pain, often associated with vomiting and diarrhoe. One patient presented with headaches. In two (20%) patients, the echocardiography detected pericardial effusions. Myocarditis was diagnosed in 4 (40%) patients, with left ventricular ejection fraction ranging between 25% and 56%. Two patients had also a right coronary aneurysm (>6 mm)

Characteristics	Number	Percentage
Gender		
Girls	7	70%
Male	3	30%
Kawasaki disease (clinical criteria)	5	50%
Lips and oral cavity changes	9	90%
Skin rash	2	20%
Non-exudative conjunctivitis		
Cervical lymphadenopathy	5	50%
	1	10%
	2	20%
Other clinical features	4	40%
Gastrointestinal symptoms		
Headaches, irritability		
Pericardial effusions		
Myocarditis		

Table 1: Clinical characteristics of children presenting with Kawasaki disease during the coronavirus 2019 pandemic.

Laboratory evaluation and imaging

All patients had significant elevated inflammatory markers including C reactive protein, erythrocyte sedimentation rate, elevated ferritin level, and procalcitonin. One (10%) patient had lymphopaenia, and a mild elevation in transaminases was noted in five patients. Hypertriglyceridaemia was shown in five (50%); fibrinogen was high in seven (70%) of ten patients, as was D-dimer (>500 µg/L)in eight (80%) of ten patients. Elevation of both cardiac troponin I (>26 pg/mL) and B-type natriuretic peptide BNP (>100 ng/L) were found in 7/10 (70%) and 6/10 (60%) patients, respectively Echocardiography detected Coronary-artery aneurysms in four (40%) patients on the basis of a z score of 2.5 or higher and increased coronary visibility in two (20%) patients.

Evidence of SARS -CoV-2 infection

No recent history of viral like symptoms was reported in all patients. History of recent contact with family members displaying viral-like symptoms was reported in 3 patients. The median interval between the reported contact and Kawasaki disease was 32 (range 25-60) days. RT-PCR testing for SARS-CoV-2 was positive in 1 case. IgG antibodies against SARSCoV-2 were detected in all patients (100%) patients. Multiplex PCR searching human seasonal coronaviruses, respiratory syncytial viruses, parainfluenza and influenza viruses, and in nasopharyngeal swabs, was negative in all patients

Characteristics	Number	Percentage
Laboratory Markers		
Lymphocytopenia	1	10%
Neutrophilia	2	20%
Hemoglobin<9g/dl	3	30%
Platelets<150,000/mm3	1	10%
D-dimer>3000ng/ml	8	80%
Fibrinogen>500ug/dl	7	70%
C-Reactive Protein ≥3mg/dl	9	90%
Ferritin>500ng/ml	5	50%
ESR≥40mm/hr	6	60%

Increased Troponin	7	70%
BNP>400pg/ml	6	60%
ALT≥40U/liter	5	50%
Positive microbiological findings	1	10%
Nasopharyngeal SARS-CoV-2 RT-PCR	10	100%
Positive SARS-CoV-2 serum serology (IgG)	2	20%
	4	40%
Echocardiography performed		
Dilation (z score 2 to <2.5)		
Anevrysm (z score of ≥2.5)	10	100%
Treatment		
Intravenous immune globulin		

Table 2: Imaging and laboratory findings of children presenting with Kawasaki disease during the coronavirus disease 2019 pandemic

Treatment

All patients received intravenous immunoglobulin (2 g/kg) and low dose aspirin (3-5 mg/kg/day). Four (40%) patients received inotropic agents for myocarditis with cardiac dysfunction. Median duration of vasoactive or inotropic agents was 6 (range 4-12) days.

Discussion

During this global pandemic with SARS-CoV-2, few paediatric observations labeled a formerly unknown complication of COVID-19, matching criteria of typical or atypical Kawasaki disease [9, 10, 11]. We describe 10 patients younger who match the criteria developed by the Centre of Disease Control the USA that was designed to be sensitive for multisystem inflammatory syndrome in children with serologic evidence of a previous COVID-19 infection [12].

Kawasaki Disease is an acute vasculitis of childhood and the leading cause of acquired heart disease in children in developed countries, with 50% of cases occurring in those <2 years of age, and 80% in those <5 years of age.4 The diagnosis of "classic" Kawasaki Disease is considered in patients presenting with fever for 5 days together with at least 4 out of 5 clinical criteria in the absence of an alternate diagnosis. Various studies have described an association between viral respiratory infections and Kawasaki disease ranging from 9% to as high as 42% of patients with Kawasaki Disease testing positive for a respiratory viral infection in the 30-days leading up to diagnosis of Kawasaki Disease [13,14]. Interestingly, Turnier *et al.* in 2015 described that 28% of positive results were attributable to rhinovirus/enterovirus, 8.7% due to parainfluenza, and the remaining pathogens: respiratory syncytial virus, influenza, adenovirus and human coronavirus (strains 229E, HKU1, NL63, OC43) were each positive less than 5% of the time [13].

The physiopathology of Kawasaki disease remains unclear. A high level of circulating pro-inflammatory cytokines might contribute to the distributive component of shock. Indeed, Kawasaki disease shock syndrome has been found associated with high levels of IL-6, C reactive protein, and procalicitonin [14]. In our series, we observed high levels of C reactive protein. This major pro-inflammatory state, together with multiorgan dysfunction, recently named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection [15], might reflect a strong postviral immunological reaction to SARS-CoV-2 compared with other viral agents [16]. Of note, a cytokine storm syndrome with increased levels of inflammatory markers such as IL-6 was described in adults with covid-19[17,18]. Indeed, older age, higher D-dimer levels, lower haemoglobin and albumin levels, and more severe hyponatraemia were previously found to be associated with Kawasaki disease shock syndrome [19]. Gastrointestinal symptoms were also unusually common, affecting all of our 21 patients. A previous study reported intestinal pseudoobstruction in only 2% of 310 patients with Kawasaki disease[20]. As previously described, other symptoms of Kawasaki disease appeared after the intestinal ones in all patients, which could have led to diagnostic and therapeutic delays in some children [21]. In multisystem inflammatory syndrome, imminent treatment with intravenous immunoglobulins is associated with a beneficial outcome. In our cases, swift improvement with IVIG alone

Conclusion

This report may serve as a useful reference to other clinicians caring for pediatric patients affected by COVID-19 as understanding of the clinical presentation patterns continue to evolve. Further description of the clinical course of pediatric patients diagnosed with COVID-19 remains necessary, particularly regarding the potential association with KD.

Consent:

Written informed consent was obtained from the patient for publication of this case report.

Disclosure:

This clinical case was written based on clinical observation without any funding.

Conflicts of interest:

There are no conflicts of interest between the authors and between the authors and the patient.

References

1. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

in children and adolescents: a systematic review. JAMA Pediatr 2020 April 22 (Epub ahead of print).
2. Lu X, Zhang L, Du H, et al. SARSCoV-2 infection in children. N Engl J Med 2020; 382: 1663-5.
3. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020.
4. NYC Health. Health Alert #13: Pediatric multi-systeminflammatory syndrome potentially associated with COVID-19.; 2020.
5. Schnabel A, Hedrich CM. Childhood Vasculitis. *Front Pediatr* 2019;6:421.
6. Baker AL, Lu M, Minich LL, et al. Associated symptoms in the ten days before diagnosis of Kawasaki disease. J Pediatr 2009; 154(4): 592.e2-595.e2.
7. Benseler SM, McCrindle BW, Silverman ED, Tyrrell PN, Wong J, Yeung RS. Infections and Kawasaki disease: implications for coronary artery outcome. Pediatrics 2005; 116(6): e760-e766.
8. McCrindle BW, Rowley AH, Newburger JW, et al, American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017;135:e927- 99.
9. S. Riphagen, X. Gomez, C. Gonzalez-Martinez, N. Wilkinson, and P. ,eocharis, "Hyperinflammatory shock in children during COVID-19 pandemic," *0e Lancet*, vol. 395, no. 10237,pp. 1607-1608, 2020.
10. F. Licciardi, G. Pruccoli, M. Denina et al., "SARS-CoV-2-induced Kawasaki-like hyperinflammatory syndrome: a novelCOVID phenotype in children," *Pediatrics*, vol. 146, no. 2,Article ID e20201711, 2020.
11. P. Toniati, S. Piva, M. Cattalini et al., "Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in brescia, Italy," *Autoimmunity.Reviews*, vol. 19, no. 7, Article ID 102568, 2020.
12. Centers for Disease Control and Prevention.Emergency preparedness and response:multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19).
13. Turnier JL, Anderson MS, Heizer HR, Jone PN, Glode MP, Dominguez SR. Concurrent Respiratory Viruses and Kawasaki Disease. *Pediatrics.* 2015;136(3):e609-614.
14. Jordan-Villegas A, Chang ML, Ramilo O, Mejias A. Concomitant respiratory viral infections in children with Kawasaki disease. *Pediatr Infect Dis J.* 2010;29(8):770-772.
15. ECDC. Paediatric inflammatory multisystem syndrome and SARSCoV-2 infection in children, 2020.
16. Lee KY, Rhim JW, Kang JH. Kawasaki disease: laboratory findings and an immunopathogenesis on the premise of a "protein homeostasis system". *Yonsei Med J* 2012;53:262-75.
17. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497- 506.
18. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033- 4.
19. Li Y, Zheng Q, Zou L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-γ as biomarkers for early recognition. *Pediatr Rheumatol Online J* 2019;17:1.
20. Miyake T, Kawamori J, Yoshida T, Nakano H, Kohno S, Ohba S. Small bowel pseudo-obstruction in Kawasaki disease. *Pediatr Radiol* 1987;17:383-6.
21. Colomba C, La Placa S, Saporito L, et al. Intestinal Involvement in Kawasaki Disease. *J Pediatr* 2018;202:186-93.