Comparison laboratory data between children with Kawasaki Disease and COVID-19

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Research article

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Abstract

Background: The 2019 coronavirus disease (COVID-19) has been an emerging, rapidly evolving situation in China since late 2019 and has even become a worldwide pandemic. The first case of severe childhood novel coronavirus pneumonia in China was reported in March 2020 in Wuhan. The severity differs between adults and children, with lower death rates and decreased severity for individuals under the age of 20 years old. Increased cases of Kawasaki disease (KD) have been reported from New York City and some areas of Italy and the U.K., with almost a 6-10 times increase when compared with previous years. We conducted this article to compare characters and laboratory data between KD and COVID-19 in children.

Methods: We obtained a total of 24 COVID-19 children from the literature review and 234 KD cases from our hospital via retrospective chart review.

Results: We found that patients with KD had higher levels of white blood cell (WBC), platelet, neutrophil percentage, C-reactive protein (CRP), procalcitonin, Aspartate Aminotransferase (AST), and body temperature, while patients with COVID-19 had higher age, hemoglobin levels, and lymphocyte percentage. After performing multiple logistic regression analysis, we found that age, WBC, platelet, procalcitonin, and AST provide identical markers for distinguishing COVID-19 from KD in children.

Conclusion: In this COVID-19 pandemic period, clinicians should pay attention to children with COVID-19 infection when high WBC, platelet, procalcitonin, and AST values are present in order to provide precision treatment with intravenous immunoglobulin (IVIG) for KD or multisystem inflammatory syndrome in children (MIS-C).

Background

The novel coronavirus has been reported as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been designated as COVID-19 (coronavirus disease 2019). (1) So far, according to a systemic review (2), children have comprised only 1-5% of total diagnosed cases of COVID-19. Common presenting symptoms of COVID-19 include cough, pharyngeal erythema, headache, and fever. (3) Because the symptoms or clinical characteristics in patients with COVID-19 and patients with Kawasaki disease (KD) have considerable overlap, identification of laboratory markers that may be indicative of COVID-19 disease would be highly helpful in an acute care setting.

KD is a systemic vasculitis syndrome with five major clinical criteria of symptoms (the 1-2-3-4-5 rapid memory method) including one mouth (fissure lips and/or strawberry tongue), two eyes (bilateral non-purulent conjunctivitis), three fingers check neck lymph node enlargement (>1.5cm in diameter, usually unilateral), four limbs changes (induration, redness and/or desquamation), and five days of fever as with as polymorphism skin rash. (4) Some KD patients also have respiratory tract or gastrointestinal tract symptoms like cough, rhinorrhea, sore throat, headache, vomiting, diarrhea, abdominal pain, and joint pain. (5, 6) The clinical symptoms of COVID-19 somewhat overlap with those patients of KD. The Bacillus Calmette-Guérin (BCG) vaccine scar reaction was reported with regard to KD mostly in routine vaccination countries like Taiwan, China and Japan. (7) In addition to its specific effect against tuberculosis, the BCG vaccine has beneficial non-specific (off-target) effects on the immune system that protect against a wide range of other infections and is also routinely used to treat bladder cancer (8) or as a functional survey for T cell of delayed-type hypersensitivity. Some reports have suggested that vaccination with BCG may also have a role in protecting individuals against COVID-19. (9, 10)

Skin rash over the toe area has been reported by dermatologists, indicating some similar symptoms between COVID-19 and KD in vasculitis. (11) Other symptoms like the loss of smell or taste in COVID-19 may overlap with hearing

loss in KD patients. The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) proposed "that anosmia could be added to the list of screening tools for possible COVID-19 infection". (12) Skin rash, headache, sore throat, rhinorrhea, diarrhea, abdominal pain, and cough are the shared symptoms between KD and COVID-19. The aim of this article is to compare differences between childhood patients with KD and COVID-19 to provide clinical information for precise treatment.

Materials And Method

A retrospective analysis was conducted on the medical records of patients admitted to the Shenzhen Baoan Women's and Children's hospital in China from 2017 to 2020. All the children were under the age of 18 years old. KD diagnosis was given according to the American Heart Association (AHA) criteria with at least four of the following five clinical manifestations: bilateral bulbous conjunctival congestion, fissure lips or oral cavity changes, hand and foot symptoms, dysmorphism skin manifestations, and cervical lymph node enlargement. (13, 14) We excluded incomplete or atypical KD. (15) We collected a total of 24 children patients (8+10+6) with age less than 18 years old, with COVID-19 diagnosis, and with laboratory data available online from PubMed. (16-18) Laboratory data of white blood cell count/differential count (WBC/DC), C-reactive protein (CRP), procalcitonin (PCT), Aspartate Aminotransferase (AST), age, and gender were all enrolled for analysis. The aim of this report was to identify laboratory markers to help clinicians distinguish KD from COVID-19 during this pandemic period and review the disease characteristics.

Statistics

The data in this study were analyzed with median values, with quartile, Q1, and Q3) being used for measurement data, and n and percentage used for enumeration data. We adopted the non-parametric Mann-Whitney *U* rank sum test for comparison between the two groups. The Chi-square test was used for counter measurement. The receiver operating characteristics (ROC) curve method was used to differentiate between groups. The best cut-off points for accurate diagnosis were based on the highest sensitivity value plus the specificity identified by the ROC curve and the cutoff values are as followed (age: 59months, WBC: 9.71*10^9/L, platelet: 273*10^9/L, PCT: 0.13ng/L, AST: 21.71U/L). Multivariate logistic regression was applied to analyze the influencing factors that showed significance in univariate analysis. Statistical significance was defined as a p-value of less than 0.05. SPSS 13.0 statistical software was used for all analyses.

Results

We enrolled 234 KD patients and 24 COVID-19 patients for analysis. As shown in Table1, lymphocyte percentage ($p=0.012$) and Hb levels ($p<0.001$) were significantly higher in patients with COVID-19 than KD children. Meanwhile, the WBC ($p<0.001$), neutrophil percentage ($p<0.001$), platelet counts ($p<0.001$), CRP ($p<0.001$), procalcitonin ($p<0.001$), and AST levels ($p=0.019$) were significantly lower in patients with COVID-19 when compared with that of KD. Meanwhile, the cut-off value of WBC and CRP were 9.71(10^9/L) and 38.57 ((mg/L), respectively. There was no significant difference in regarding the levels of ALT between patients with KD and COVID-19 ($p=0.513$).

After performing multiple logistic regression, we found that age, WBC, platelet counts, procalcitonin, and AST levels showed significant difference between patients with KD and COVID-19 ($p<0.05$). The comparison of disease characteristics is shown in Table 2. The etiology of KD remains unknown, but COVID-19 is caused by the human

coronavirus. Diagnostic criteria for KD include five major symptoms and fever for more than five days, but the clinical symptoms or signs in COVID-19 are non-specific or even asymptomatic or without fever. Furthermore, KD has a male predominate characteristic, and the global prevalence of KD is higher in those of Asian descent than in European or in Americans descent. (19) While the prevalence of COVID-19 is higher in Americas than Europe and Asia.

Discussion

The COVID-19 pandemic has already reached over 80.8 million infections and caused over 1,760,000 deaths till December 2020. While the exactly prevalence of COVID-19 in children is still unknown, mounting evidence has highlighted that the clinical severity of COVID-19 in children and young adults appears significantly milder compared to older individuals with comorbidities. (20, 21) COVID-19 was also reported to induced the Kawasaki-like disease, the multisystem inflammatory syndrome in children (MIS-C), a novel syndrome linked to SARS-CoV-2. In this study, we compared the difference between children patients with COVID-19 (not MIS-C) and KD (not including KD shock syndrome, KDSS) and demonstrated that higher WBC, platelet, procalcitonin, and AST provide laboratory markers for distinguishing COVID-19 from KD. We further revealed that KD patients have lower age and higher characteristics of fever than COVID-19 children. Other laboratory data including lactate dehydrogenase (LDH), D-dimer, creatine kinase (CK) and serum creatinine were also increased in children with COVID-19. According to the statement of American Heart Association (AHA) (13, 22), LDH, D-dimer, CK and serum creatinine didn't in the list of supplementary criteria of suspected incomplete KD. However, LDH, CK, serum creatinine and D-dimer levels were reported to be higher in KD patients and associated with IVIG resistance or coronary artery lesions formation. (23-26)

The golden period for IVIG treatment in KD patients is around five to nine days after disease onset; therefore, early awareness of KD is very important both for clinicians and parents. However, the challenge for clinicians in pediatric emergency departments is early identification of KD because KD shares many clinical signs with other febrile illnesses in childhood. (27) Furthermore, with “stay at home” orders and trepidation related to COVID-19 infection, many parents now hesitate or fear seeking in-person consultation for their children. Harahsheh *et al.*, raised the concern of a future surge in the prevalence of CAAs caused by the potential for missed or late diagnosis and treatment of KD in children. (28)

In 1974, Tomisaku Kawasaki first described 50 cases of KD in English language. (29) The etiopathogenesis of KD remains unknown even today, and many studies have failed to identify a pathogen responsible for KD or any identified pathogens could not be repeated between studies. (30) Furthermore, growing evidence has demonstrated that KD may be the result of a combination of infection, genetics, environment and immunity. (31) In addition to standard diagnostic criteria, KD patients may experience a variety of nonspecific clinical features, including uveitis, aseptic meningitis, gastrointestinal symptoms, maculopapular rash, impaired liver function, and anemia. (7, 32, 33) Hepcidin-induced iron deficiency was reported to be related with transient anemia and disease outcomes in KD patients but anemia was not found in children with COVID-19. Neutrophil percentage was higher in KD patients than COVID-19 while lymphocyte percentage showed higher in COVID-19 children than KD indicating viral immune response in COVID-19.

In the most severe cases of KD, patients may develop hemodynamic instability, known as KD shock syndrome (KDSS), and secondary hemophagocytic lymphohistiocytosis fulfilled the criteria of macrophage activation syndrome (MAS). (34) Surprisingly, several lines of study have suggested that COVID-19 children have presented significantly unwell across Europe and the US with a novel syndrome linked to SARS-CoV-2 (MIS-C). (35, 36) This rare syndrome of COVID-19, children shares common features with other pediatric inflammatory conditions, including KD, staphylococcal/streptococcal toxic shock, macrophage activation syndrome, and sepsis. (36)

In 2005, Esper *et al.* identified a novel human coronavirus tested by RT-PCR, designated New Haven coronavirus (HCoV-NH), in the respiratory secretions of eight of 11 children with KD versus one of 22 controls. (37) Notably, Jones *et al.*, reported a six-month-old infant diagnosed with KD and treated with IVIG and aspirin and positive screening of COVID-19 in Italy. (38) Thereafter, Verdoni *et al.*, reported a case series of a 30-fold increased incidence of Kawasaki-like disease at the Italian epicenter of the COVID-19 epidemic. (39) The patients who showed evidence of an immune response to the COVID-19 virus were older, had a higher rate of cardiac involvement, and macrophage activation syndrome features. (39) Consistently, in Whittaker et al.'s study, pediatric MIS-C patients were generally older than those with KD or KDSS and had higher WBC, and CRP, as well as more profound lymphopenia and anemia. (40) The COVID-19 epidemic has also been associated with a high incidence of a severe form of KD (41). They also identified that the Kawasaki-like disease described here remains a rare condition, probably affecting no more than one in 1000 children exposed to COVID-19. (39) The very limited COVID-19 children (N=24) included in this study is the limitation and weakness of this study. However, the association between KD and COVID-19 still warrants further investigation. In the era of the COVID-19 pandemic, multisystem inflammatory presentations of COVID-19 children and typical KD patients will be more challenging for clinicians and pediatricians in the future.

Conclusion

In conclusion, a younger age, male predominate, with higher levels of WBC, platelet, procalcitonin, and AST provide identical markers for distinguishing KD patients from COVID-19 in children. In this pandemic period of COVID-19, clinicians should pay more attention to children with COVID-19 infection while laboratory data showing high WBC, platelet, procalcitonin, and AST levels to provide treatment with IVIG for KD. Likewise, children with KD should also be screened for COVID-19 infection.

Declarations

Ethics Approval and Consent to Participate: This study was conducted in accordance with the Declaration of Helsinki. It was approved by the Institutional Review Board of Shenzhen Baoan Women's and Children's Hospital, Shenzhen, China (IRB No. LLSCKS 2020-4-01-KS) and Chang Gung Medical Foundation (IRB: 202000966B1).

Consent for publication

Not applicable

Availability of supporting data

The dataset containing results from this article are available from the corresponding author (HC Kuo) upon request.

Conflicts of interests

The authors declare that they have no conflicts of interest to declare in relation to this article.

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Authors' contributions

XPL, YHH and HCK designed the study. XPL, YHH, SFL and HCK conceived the study. XPL, YHH, SFL and HCK extracted the data for the study. YCT and SFL revised the article. All authors read and approved the final version of the manuscript.

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Tables

Table 1: Comparison laboratory between children with COVID-19 and Kawasaki Disease

	COVID-19 (N=24)	Kawasaki disease (N=234)	Univariate P value	Multivariate P value	Multivariate (B)	odds ratio	95% Confidence interval	
							Lower	Upper
Age (month)	54 (16, 105)	20 (12, 35.5)	0.290	0.012	-1.965	0.140	0.030	0.651
Male gender (%)	12 (50%)	143 (61.1%)	0.290	-				
white blood cell count (*10^9/L)	6.59 (3.87, 9.57)	14.25 (10.11, 17.52)	<0.001	0.025	1.858	6.409	1.267	32.415
Neutrophil %	47.51 (28.59, 58.8)	60.71 (49.62, 74.29)	<0.001	-				
Lymphocyte %	35.31 (20.5, 50.88)	26.88 (16.99, 38.93)	0.012	-				
Platelet (*10^9/L)	207 (156.75, 301.25)	353.5 (278.75, 449.5)	<0.001	0.03	1.728	5.627	1.178	26.886
Hemoglobin (g/L)	122 (113, 134.75)	108.5 (100, 115)	<0.001	-				
C-reactive Protein (mg/L)	10.85 (5.82, 30)	65.59 (33.34, 115.55)	<0.001	-				
Procalcitonin (ng/L)	0.07 (0.048, 0.095)	0.44 (0.16, 1.33)	<0.001	0.001	2.890	17.985	3.219	100.493
AST (U/L)	31.5 (20.35, 40)	35.99 (29.0, 51.75)	0.019	0.009	3.150	23.333	2.166	251.365
ALT (U/L)	18.5 (13.7, 42.25)	20.2 (13.45, 44.63)	0.513	-				

Data were present as medium with (quartile, Q1, Q3)

AST: Aspartate Aminotransferase

ALT: Alanine Aminotransferase

Multivariate (B): Coefficients of variables in Multivariate analysis. OR odds ratio, CI confidence interval

Male gender was analyzed by Pearson Chi-square test and others were analyzed by Mann-Whitney *U* test.

Table 2: Different characteristics between Kawasaki disease (KD) and COVID-19

	Kawasaki disease (KD)	COVID-19
Etiology	Unknown (corona virus may be one of the triggers of KD)	Human corona virus
Symptoms	5 major symptoms (fissure lips and/or strawberry tongue, bilateral non-purulent conjunctivitis, neck lymphadenopathy, limbs induration and polymorphic skin rash)	Upper respiratory tract symptoms (non-specific or even asymptomatic)
Fever (> 38°C)	100%	60-70%
Treatment	IVIG + aspirin	anti-IL6, hydroxychloroquine, remdesivir…etc. (effect not with conclusion yet)
Age	85% < 5 years-old	2% < 19 years-old
Gender	Male > female, 1.5 folds	Male≒Female
BCG vaccine	Scar indurations	May have protective role
Prevalence	Asia > America > Europe	Europe, America > Asia

℃: centigrade of body temperature

IVIG: intravenous immunoglobulin

IL6: interleukin 6

BCG: Bacillus Calmette–Guérin

5 major symptoms (1-2-3-4-5) of Kawasaki disease: 1 mouth (fissure lips and/or strawberry tongue), 2 eyes (bilateral non-purulent conjunctivitis), 3 fingers to check neck lymph node enlargement (neck lymphadenopathy), 4 limbs changes (induration or desquamation) and 5 days fever with skin rash (polymorphic skin rash).

List Of Abbreviations

COVID-19	The 2019 coronavirus disease
KD	Kawasaki disease
WBC	White blood cell
CRP	C-ractive protein
AST	Aspartate Aminotransferase
IVIG	Intravenous immunoglobulin
MIS-C	Multisystem inflammatory syndrom
SARS-COV-2	Severe acute respiratory syndrome coronavirus-2
PCT	prcalcitonin
KDSS	KD shock syndrome

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