



Clinical Manifestation of Children with Kawasaki Disease during the COVID-19 Pandemic in Iran: A Case Series

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ABSTRACT

Introduction: Kawasaki disease is a rare disease, but it is one of the most common childhood vasculitides. Given that the manifestations of Kawasaki disease overlap with acute infectious diseases such as COVID-19, timely identification of clinical symptoms and timely treatment in children with Kawasaki manifestations is essential to prevent acute and chronic complications in children. The aim of the present study was to investigate the various characteristics of Kawasaki disease in children during the COVID-19 pandemic.

Methods: In this study, the records of all children with Kawasaki or Kawasaki-like disease admitted to Imam Sajjad (AS) Hospital in Ramsar were reviewed from the beginning of the COVID-19 pandemic between February 2020 and May 2023. The data were analyzed using the specific Kawasaki code in the discharge files and using the National Health Information System (HIS).

Findings: In total, the various characteristics of 10 children with Kawasaki or Kawasaki-like disease were analyzed, and the data obtained were presented in the form of tables and percentages. The mean age ranged from 7 months to 8 years (mean: 3 years). Of the 10 patients, half were boys. Kawasaki disease criteria were observed in all (100%) of them (8 patients) and in the complete form in 6 patients (60%). Fever (100%), conjunctival and oral cavity changes (80%) in 8 patients, skin rash (80%) in 8 patients, and gastrointestinal symptoms (80%) in 8 patients were the most common symptoms. Pericarditis was observed in only 1 (10%) of the patients. The results of x-ray, CT-scan, and LP were positive for each in only 1 (10%) patient. The diagnosis of complete Kawasaki disease was observed in 6 (60%) patients and its incomplete form in 4 (40%) patients. 1 (10%) patient required intensive care unit admission, but there was no mortality.

Conclusion: Timely diagnosis of Kawasaki disease in children with COVID-19 plays an effective role in treating and preventing its possible complications.

Key words: COVID-19, SARS-CoV-2, Kawasaki disease, Multisystem inflammatory syndrome in children.



INTRODUCTION

Kawasaki disease is a rare disease, but it is one of the most common childhood vasculitis (34), with approximately 85% of affected children being under 5 years of age and the most common age of onset being 18 to 24 months (3). The diagnostic criteria for Kawasaki disease established by the American Heart Association include ≥ 5 days of fever, oral mucosal changes, bilateral no exudative conjunctivitis, eczematous rash, peeling of the hands and feet, and cervical lymphadenopathy. Apart from hyperthermia, at least four of the five main clinical features are required for a complete form of Kawasaki disease and fewer than four for an incomplete form of Kawasaki disease (4-5).

Coronavirus infection in children and rarely in infants is associated with acute respiratory syndrome (3-1). In contrast to severe forms of coronavirus infection in adults, children are more likely to have mild respiratory symptoms (3), a lower incidence (4), and fewer hospitalizations (5). Children with COVID-19 may present with fever, fatigue, cough, sore throat, rhinorrhea, congestion, and shortness of breath, and in severe cases, gastrointestinal problems, shock, respiratory failure, coagulation disorders, and renal failure (6). The COVID19 pandemic has brought Kawasaki disease into the spotlight in both overt and covert forms. The overt form is the most common primary vasculitis in children (6-7), primarily affecting medium-sized and small arteries. The covert form, on the other hand, is multisystem inflammatory syndrome in children (MIS-C), a rare but severe disease that affects children 2 to 6 weeks after infection with SARS-CoV-19, and was initially mistaken for Kawasaki disease (5). MIS-C has demonstrated a novel disease paradigm whereby exposure to SARS-Covid-19 has been associated with a systemic inflammatory disease known as a multisystem inflammatory syndrome, leading to hospitalization of children in intensive care units (4-5). However, there has been an increase in the incidence of Kawasaki-like disease among children with COVID, either concomitantly or after resolution of symptoms (8). However, recent reports from around the world have shown a significant decrease in the incidence of Kawasaki disease during 2008-2020 (9). Both diseases involve an acute innate immune response with high levels of inflammatory markers and common mucocutaneous symptoms (9-10). Although the etiology of Kawasaki is unclear, a role for a viral and infectious agent has been suggested (3-5). Since there is no diagnostic test for Kawasaki disease, these children are usually diagnosed based on international criteria after a thorough review of their clinical manifestations and exclusion of other possible causes (such as staphylococcal scalded skin syndrome [SSSS], Stevens-Johnson syndrome, streptococcal scarlet fever, viral infection, and drug allergy) (2-4). In a systematic review by Mardi et al. (2021) in Iran, the incidence of Kawasaki-like syndrome increased significantly during the COVID-19 pandemic (11). Other studies have also shown that the COVID-19 pandemic has increased the incidence of Kawasaki-like syndrome (5-8).



Given that the manifestations of Kawasaki disease overlap with acute infectious diseases such as COVID-19, timely recognition of clinical manifestations and timely treatment in children with Kawasaki manifestations are essential to prevent acute and chronic complications in children such as cardiac, pulmonary, and renal complications. The aim of this study was to investigate the demographic, laboratory, and clinical characteristics of 10 children diagnosed with Kawasaki symptoms during the COVID-19 epidemic admitted to a government hospital in Mazandaran province (northern Iran) between February 19, 2020, and May 5, 2023.

METHODS

In this study, the records of all children with Kawasaki or Kawasaki-like disease hospitalized in Imam Sajjad Hospital in Ramsar since the beginning of the COVID-19 pandemic between February 19, 2020 and May 5, 2023 were reviewed using the Kawasaki specific code in the discharge records in the Health Management System (HIS). This study is of the Existing Data type. The sampling method was available and the study type was descriptive and based on existing data. The number of patients studied was 10.

The inclusion criteria for the study included children aged 0-16 years and having typical and atypical symptoms of Kawasaki disease. Information was collected through a researcher-made data registration form by reviewing the patients' hospitalization records and calling the parents by phone while obtaining their consent to complete the information. The extracted information included general characteristics of patients (age, gender, place of residence, type of admission, family involvement in favor of COVID-19), specific characteristics of the disease, signs and symptoms of the disease, complications, laboratory tests, Para clinical tests, diagnostic features of Kawasaki and Kawasaki treatments. It should be noted that the differential diagnosis of Kawasaki patients from pseudo-Kawasaki was performed by a pediatrician and a cardiologist.

Results:

A total of 10 children aged 7 months to 8 years were included in the study. Half of the children were boys (Table 1). Fever was observed in all patients, 1 (10%) patients required intensive care, and gastrointestinal symptoms were observed in more than three-quarters of patients (Table 2). Pericarditis was observed in only 1 (10%) patients (Table 3). X-ray, CT-scan, and LP results were positive in only 1 (10%) patient (Table 4). Complete Kawasaki disease was diagnosed in 6 (60%) patients and its incomplete form in 4 (40%) patients (Table 5).

TABLE 1: Patient characteristics

| Characteristics | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 |
|-----------------------------------|-----------------|---------------|---------------|--------------|--------------|--------------|------------------|----------------|----------------|-----------------|
| Age and gender | 7month-old girl | 2yearold girl | 1yearold girl | 8yearold boy | 8yearold boy | 3yearold boy | 11month-old girl | 1-year old boy | 6-year-old boy | 1-year-old girl |
| Criteria met for Kawasaki disease | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| SARS-CoV-2 PCR positive | Yes | Yes | NO | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Sick contacts | No | No | Yes | Yes | Yes | No | Yes | Yes | Yes | No |
| Travel history | No | No | No | No | No | No | No | No | No | No |
| Any comorbidity | No | No | No | No | No | Asthma | No | No | No | No |
| Hospitalization period | 5 days | 5 days | 2 days | 2 days | 5 days | 3 days | 1 days | 6 days | 2days | 5days |

TABLE 2: Features of Kawasaki disease and Symptoms and signs

| Kawasaki Feature | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 |
|---|--------------|-------------------------------|-------------|-------------------------|-------------------------|--------------|-------------------------------|-------------|---------------|--------------|
| Complete presentation (fever >4 days and ≥4 principal criteria) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Fever with duration | Yes, >6 days | Yes, >5 days | Yes, 7 days | Yes, 10 days | Yes, >6 days | Yes, >3 days | Yes, 4 days | Yes, 5 days | Yes, >10 days | Yes, >3 days |
| Stop fever after hospitalization | 3 days | Stable during hospitalization | 1 day | 1 day | 3 days | 1 day | Stable during hospitalization | 2 days | 2 days | 5day |
| Redness of the eyes | No | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No |
| Rash | Yes | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes |
| Conjunctival injection | Yes | Yes | No | Yes | No | No | No | No | Yes | No |
| Lips and oral cavity changes | No | Yes (Straw berry tongue) | Yes | Yes (Strawberry tongue) | Yes (Strawberry tongue) | Yes | Yes | No | Yes | Yes |
| Cervical | No | No | No | No | No | No | No | No | No | No |



| | | | | | | | | | | |
|--|-----|-----|-----|-----|-----|-----|-----|--------------------------|-----|-----|
| Lymphadenopathy | | | | | | | | | | |
| Extremity changes (swelling, erythema) | No | Yes | No | Yes | No | No | No | No | Yes | No |
| Symptoms and signs | | | | | | | | | | |
| Sore throat | Yes | Yes | No | Yes | Yes | No | No | Yes | Yes | No |
| Respiratory symptoms | No | No | No | Yes | No | Yes | No | Yes | No | No |
| Cough | No | No | No | Yes | No | Yes | No | Yes | No | No |
| Dyspnea | No | Yes | No | No | No | Yes | No | No | No | No |
| Stuffy nose/sneezing/rhinorrhea | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Ear pain | No | No | No | No | No | Yes | No | No | No | No |
| GI symptoms | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Abdominal pain | No | No | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Diarrhea | No | No | No | No | No | Yes | Yes | No | No | Yes |
| Vomiting | No | Yes | No | Yes | Yes | Yes | No | Yes | Yes | Yes |
| Decreased appetite | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Dysuria | No | No | No | No | No | No | No | No | No | No |
| Neurological symptoms | No | No | No | Yes | Yes | No | Yes | Yes | Yes | Yes |
| Irritability | No | No | No | No | No | No | No | Yes (contin uous crying) | Yes | No |
| Anosmia | Yes | Yes | No | No | No | No | No | Yes | No | No |
| Headache | No | No | No | Yes | No | Yes | No | Yes | Yes | Yes |
| Confusion | No | No | No | No | No | Yes | No | Yes | No | No |
| Meningeal signs | No | Yes | No | No | No | Yes | Yes | No | No | No |
| Drowsiness | Yes | No | Yes | No | Yes | Yes | No | Yes | No | No |
| Perineal/periungal/facial desquamation | No | No | No | No | No | Yes | Yes | Yes | Yes | Yes |

TABLE 3: Complications

| Complication | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 | Patient 10 |
|-------------------------------------|-------------|------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Admission to the critical care unit | No | Yes (CCU) | No | No | No | No | No | No | No | No |
| Sending to other centers | No | Yes | No | No | No | Yes | Yes | Yes | No | Yes |
| Artificial ventilation | No | No | No | No | No | No | No | No | No | No |
| Hypotension/shock | No | No | No | No | No | No | No | No | No | No |
| Inotropic support | No | Yes (mil rinone) | No | No | No | No | No | No | No | No |
| Coronary artery dilatation | Uncheckable | Uncheckable | Uncheckable | Uncheckable | Uncheckable | Uncheckable | Uncheckable | Uncheckable | Uncheckable | Uncheckable |
| Coronary artery aneurysm | Normal | Normal | Uncheckable | Normal | Uncheckable | Uncheckable | Uncheckable | Normal | Uncheckable | Normal |
| Myocarditis | No | No | Uncheckable | No | Uncheckable | Uncheckable | Uncheckable | No | Uncheckable | No |

| | | | | | | | | | | |
|-----------------------------------|----------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Pericardial effusion/pericarditis | Yes (2-3 mm in echo) | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal | Normal |
| valvular disorder | Yes | Yes | No | No | No | No | No | No | No | No |
| Mortality | No | No | No | No | No | No | No | No | No | No |

TABLE 4: Hospital Investigations

| Inflammatory Markers | Patient1 | Patient2 | Patient3 | Patient4 | Patient5 | Patient6 | Patient7 | Patient8 | Patient9 | Patient10 |
|--|----------|----------|----------|----------|----------|----------|-----------|----------|----------|-----------|
| CRP1 (0-5 mg/L) | 79(H) | 3+ | 1+ | - | NEG | 3+ | No sample | 3+ | 2+ | +1 |
| CRP2 (0-5 mg/L) | 1+ | - | - | - | 1+ | 1+ | - | NEG | - | +2 |
| Ferritin (7-140 µg/L) | 34 | - | - | 337 | - | - | - | 385 | 124 | - |
| ESR (0-22 mm/hr) | 79 | 150 | 51 | 84 | 100 | 55 | 65 | 116 | 60 | 80 |
| IL-6 (<8.5 pg/mL) | - | - | - | - | - | - | - | - | - | - |
| D-dimers (100-560 ng/mL) | 462(H) | 588(H) | - | >200 | - | 200 > | - | >200 | 200 | - |
| LDH (125-243 U/L) | - | 467 | 675 | 579 | 640 | 514 | 575 | 554 | 430 | - |
| | | | | | | | | | | |
| Albumin (35-54 g/L) | 3.7 | 3.6 | - | - | - | 4.8 | - | 3.7 | - | 4.1 |
| Cardiac markers | | | | | | | | | | |
| Troponin (0-15 ng/L) | NEG | NEG | - | - | NEG | - | - | NEG | - | - |
| NT-proBNP (<300 pg/mL) | 578(H) | 170 | - | - | - | - | - | - | - | - |
| Blood profile | | | | | | | | | | |
| White cell count (4-15.5 x 10 ⁹) | 18900 | 20600 | 5100 | - | 9200 | 9300 | 17300 | 8300 | - | 15400 |
| Hemoglobin (111-147 g/L) | 11(L) | 7.8 | 11.7 | 9.6 | 12.6 | 9.5 | 9.2 | 11.2 | 12.2 | 11.1 |

| | | | | | | | | | | |
|------------------------------------|------------|------------|------------|------------|------------|------------|------------|--------|--------|--------|
| Platelets (200-450 x 109) | 4410 00 | 5800 00 | 3150 00 | 4210 00 | 4660 00 | 174 000 | 28400 0 | 135000 | 408000 | 780000 |
|------------------------------------|------------|------------|------------|------------|------------|------------|------------|--------|--------|--------|

| Diagnosis | Patient 1 | Patient2 | Patient 3 | Patient4 | Patient 5 | Patient6 | Patient 7 | Patient8 | Patient9 | Patient10 |
|----------------------|--------------------------------|----------|-----------|----------|-----------|-----------|-------------------|----------|----------|-----------|
| Initial diagnosis | FWLS(Fever of undetermined) | Kawasaki | Kawasaki | Kawasaki | Kawasaki | Influenza | Fever (Sepsis) | MISC | Kawasaki | Kawasaki |

TABLE 5: Diagnosis strategies

| | | | | | | | | | | |
|----------------------------|----------|----------|---------------|----------|---------------------|----------|---------------|---------------|----------|-------------|
| | origin) | | | | | | | | | |
| Diagnosis during treatment | Kawasaki | Kawasaki | Kawasaki | Kawasaki | Kawasaki | COVID-19 | COVID-19 | MISC | Kawasaki | Meningi |
| Final Diagnosis | Kawasaki | Kawasaki | Semi Kawasaki | Kawasaki | Kawasaki and Herpes | Kawasaki | Semi Kawasaki | Semi Kawasaki | Kawasaki | Se Kawasaki |

Discussion:

Kawasaki disease is an acute, self-limiting vasculitis characterized by vascular inflammation. It predominantly affects children [7]. In the acute phase, patients with Kawasaki disease may develop hemodynamic instability, a condition known as Kawasaki shock syndrome [8]. It is the leading cause of acquired heart disease among children in developed countries, leading to complications such as coronary artery ectasia, cardiac inflammation, and aneurysm in 15– 25% of patients if untreated. Kawasaki disease may also cause myocarditis, pericarditis, and abnormal heart rhythms [1]. There are numerous yet conflicting studies on the association between Kawasaki disease and acute respiratory infections as well as COVID-19 infection in children [10, 12, 13]. However, an association between the two diseases has been reported in several case reports [14]. The pathophysiology of Kawasaki disease and COVID-19 is similar, for example, a severe inflammatory response, leading to vascular endothelial damage and immune-mediated tissue damage. This may account for the overlap in their symptoms [9]. COVID-19 patients also show Kawasaki-like coronary changes; none of the patients developed coronary aneurysms, dilatations, or myocarditis. Pericardial effusion was seen in one patient (10%). Kawasaki disease has a wide range of clinical signs and symptoms [15]. The most common presenting symptoms are high fever, rash, conjunctivitis, lymphadenopathy, and strawberry tongue [15]. In addition, gastrointestinal manifestations of fever lasting more than 5 days have been suggested as a predictor of coronary artery involvement. In a study by Jafari et al. 2023 in Iran, the results of multivariate regression analysis showed that the duration of fever until diagnosis (fever more than 5 days) was a predictor of coronary artery involvement [16]. In the present study, more than threequarters of children had fever for more than 5 days, and coronary artery involvement was observed in one-quarter of children. Positive and high levels of inflammatory markers as a pro-inflammatory event may reflect the immunological reaction after COVID-19 infection in children [17,18]. In the present study, 7 children (70%) had positive CRP. Although cardiac manifestations were



less observed in the present study, gastrointestinal symptoms were reported in almost 100% of children. These findings were consistent with the study by Tobiana et al. in 2020 [10]. Early diagnosis and timely treatment when gastrointestinal symptoms are observed are recommended. The etiology of Kawasaki disease remains unknown, although it has been half a century since the first case of KD was reported [7]. The most widely accepted hypothesis supports an acute immune response to one or more pathogens in genetically susceptible patients [13]. Kawasaki disease lacks a definitive association with any single agent and several infectious triggers, such as rhinovirus, parainfluenza virus, respiratory syncytial virus, adenovirus [14], human coronavirus [15] and novel coronavirus, are known. However, some studies have ruled out the association of human coronavirus with Kawasaki disease [18]. At the same time, a study by Feldstein et al. 2020 in U.S reported Kawasaki-like disease during the COVID-19 epidemic. [2] Therefore, it is still unclear whether the diagnosis of COVID-19 in children with Kawasaki-related symptoms should be treated with a diagnosis of Kawasaki disease or whether a new separate diagnosis of COVID-19 infection is required. There is a need to differentiate coincidental COVID-19 infection with Kawasaki disease from Kawasaki disease caused by COVID-19.

Our study included only 10 cases, which limits its reliability due to the small sample size. However, the final diagnosis of Kawasaki disease in its incomplete form was observed in 4 (40%) patients and in its complete form in 6 (60%) patients. Fever was present in all patients. Conjunctival and oral cavity changes, including rash, were the most common features. 1 (10%) child required intensive care unit admission, but no mortality occurred. This article will help to understand and address the Kawasaki-like manifestations of pediatric COVID-19 infection, especially in intensive care units, and its possible complications. It will also help to make timely and appropriate decisions about its treatment and management. Further large-scale studies are needed to prove any association between pediatric COVID-19 infection and KD.

Conclusion:

Based on the results of the present study, the manifestations of Kawasaki disease overlap with acute infectious diseases such as COVID-19, so timely identification and treatment of children with Kawasaki manifestations is essential to prevent acute and chronic cardiac, pulmonary, and renal complications. The results indicate that; Given the diversity of COVID symptoms, in the epidemic of acute respiratory diseases whose clinical manifestations are similar to Kawasaki disease in children, clinical and laboratory manifestations of Kawasakilike disease should be considered by health care providers and home caregivers. Therefore, the preparation of standard guidelines for screening and early identification of children with symptoms of acute inflammatory diseases (MISC, COVID-19, and KD) seems necessary.



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