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Epidemiological Profile and Management of Kawasaki Syndrome at Rabat Children's Hospital: A retrospective study from Morocco

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Authors' contributions

This work was carried out in collaboration among all authors.. All authors read and approved the final manuscript.

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ABSTRACT

Kawasaki disease (KD) is a common pediatric vasculitis with a risk of coronary artery aneurysm. In this report, we review some particularities of KD disease, especially coronary involvement, and highlight its aspects during the COVID-19 epidemic which saw the emergence of a syndrome named multisystem inflammatory syndrome in children (MIS-C). Because of its many similarities with KD, MIS-C is often referred to as Kawasaki-like disease (KLD) or pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).We report on a retrospective study on the different epidemiological, clinical, and evolutionary aspects of KD and the coronary involvement resulting from this disease before and after the pandemic. The study is based on the echocardiography records of the P4 Department at Rabat Children's Hospital, from January 2002 to December 2021. A total of 379 patients were diagnosed with KD during that period. This

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includes 47 cases that were reported during the first year of the COVID-19 epidemic in Morocco (March 2020). Echocardiography results for our series show that cardiac complications wererelatively more frequent among KD patients during the COVID-19 period, perhaps because they were relatively older (67 months on average) than classic KD patients (37 months on average). However, all patients had a favorable outcome after treatment with a combination of intravenous immunoglobulin (IVIG) and aspirin. The few patients who did not respond to standard treatment received corticosteroids, and no mortality occurred. We conclude that as far as cardiac complications,KD, KLD, and MIS-C are the same core disease that is triggered under different conditions for different age groups.The emergence of the Sars-Cov-2 virus changed the epidemiologic profile of KD but not its treatment. Insights from this study would help in the decision to initiate targeted immunotherapy quickly and reduce the risk factors associated with KD.

Keywords: Kawasaki disease; KD; multisystem inflammatory syndrome in children; MIS-C; pediatric inflammatory multisystem syndrome; PIMS; SARS-CoV-2; Coronavirus disease 2019; COVID-19; Children; Pediatric.; Cardiac lesion; Coronary aneurysm.

1. INTRODUCTION

"Kawasaki disease (KD) is an acute multisystemic vasculitis, which primarily affects children, especially infants" [1,2]. "It was first described by a Japanese pediatrician named Tomisaku Kawasaki in 1967" [3]. "It is a form of vasculitiswhere inflamed blood vessels become incapable of carrying adequate blood, thus putting pressure on the heart, and producing cardiac complications" [1,2,4]. "Kawasaki disease is the most common cause of acquired heart disease in children. Multiple organs and tissues are affected, but the disease mainly targets small and medium-sized blood vessels, with a predilection for the coronary arteries. It can lead to aneurysms in nearly a quarter of untreated patients" [2,4]. Infants have much higher rates of coronary artery abnormalities even if treated within the first ten days.

KD patients typically present with a fever, skin and mucous membrane changes, and lymphadenopathy (swollen lymph nodes). None of these clinical signs, however, is specific to KD disease; the same signs are also observed in other pediatric diseases [1,2,4]. "No test can definitively diagnose the disease, and KD is generally diagnosed based on a constellation of characteristic clinical observations. Incomplete forms of this rare disease are very common, especially in infants, and atypical presentations are often encountered. These wide variations in presentations can create a diagnostic puzzle and delay the initiation of treatment" [1,2,4].

"Kawasaki disease is characterized by three distinct clinical phases: acute phase, subacute phase, and convalescent phase. The acute phase usually lasts 1 to 2 weeks and is marked by the onset of acute inflammation symptoms. The subacute phase occurs 2 to 4 weeks later and is characterized by periungual desquamation, thrombosis, and the development of coronary aneurysms. The convalescent phase occurs 6 to 8 weeks after the onset of the disease, and all symptoms disappear" [1,2,4].

Treatment is based on a combination of high-dose aspirin and intravenous immunoglobulin (IVIG). Several other treatment options have been proposed in recent years as a second and third-line treatment for patients who do not respond to standard treatment, including adjunctive treatment with corticosteroids, Infliximab, or other immunomodulatory agents. [1,2,4].

"Shortly after the World Health Organization (WHO) classified COVID-19 as a pandemic in March 2020, reports began to emerge of a post-infection syndrome with multisystem involvement with circulatory shock and systemic inflammation in children aged 0 to 19 years. A health alert from the United States described the condition, instituted mandatory reporting of cases, and the Center forDisease Control (CDC) created a case definition on May 13, 2020" [5]. "This syndrome has similarities with KD and was formally named Multisystem Inflammatory Syndrome in Children (MIS-C). By end of February 2023, 9,376 children in the United States have been diagnosed with MIS-C, and 76 children have died from it" [6]. "MIS-C is often referred to as Kawasaki-like disease (KLD) or Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS). Early on, it was suspected that MIS-C is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). One piece of

evidence is that 98% of MIS-C patients reported on the CDC website had a positive test result for SARS-CoV-2, and the remaining 2% of patients had contact with someone with COVID-19" [5]. "During the COVID-19 pandemic, reports continued to emerge of children with MIS-C among communities with high rates of COVID-19, with the peak of MIS-C usually lagging the peak of the COVID-19 wave by a few weeks" [5,7]. "The lag suggests that the development of the KD-like disease is likely the result of a post-viral immunological reaction. Per the WHO, a confirmed case of MIS-C is defined as follows: an individual aged 21 years or less, presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (more than 2) organ involvement (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, or neurological); no alternative plausible diagnoses; and positive test result for current or recent SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (RT-PCR), serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of symptoms" [5].

"Finally, KD can be associated with Macrophage Activation Syndrome (MAS)" [8,9]. "MAS is a condition in which there are uncontrolled activation and proliferation of macrophages and other cell lines" [8]. "MAS in children has also been associated with Juvenile Idiopathic Arthritis (JIA)" [8]. MAS can lead to multiorgan system dysfunction and is associated with high morbidity and mortality.

Despite the difference between MAS, KD, KLD, and MIS-C, the treatments for these diseases are the same.In terms of cardiac involvement, these are the same core disease that is triggered under different conditions for different age groups. The emergence of the Sars-Cov-2 virus changed the epidemiologic profile of KD but not its treatment.

2. METHODS

We describe a retrospective study of 379 cases who were diagnosed with KD from January1, 2002, to December 31, 2021. The study was performed in the pediatric cardiology department, P4, at the Children's Hospital in Rabat, which is one of the major referral public university hospital centers in the country [10,11]. The inclusion criteria used for the development of this study are essentially based on the recommendations of the Japanese committee for research on KD, and the American Heart Association (AHA [12]. All children who met the diagnostic criteria for KD were managed in the inpatient setting. Diagnostic criteria serve as a guideline to avoid overdiagnosis, however, they do not allow for identifying children with incomplete forms of the disease. For this reason, in the American Heart Association's (AHA) 2004 scientific statement, they proposed a diagnostic algorithm for these patients, based on high inflammatory parameters (sedimentation rate [SR] greater than 40 mm/h and C-reactive protein [CRP] greater than 3mg/dl), thrombocytosis, low albumin levels, anemia, elevated transaminases, leukocytosis, pyuria, and coronary artery abnormalities [13,14]. However, in the presence of a coronary aneurysm in a child with 2 or 3 main clinical manifestations, the diagnosis of Kawasaki disease can be considered if only the CRP and/or SR are elevated [15].

The exclusion criteria consist of all differential diagnoses of KD. To illustrate, there was a case that raised doubts about its diagnosis, as it presented with similar clinical features to those of KD, such as prolonged fever, rash, systemic inflammation, and even cardiac involvement. However, the chronicity of the symptoms led to the diagnosis of juvenile idiopathic arthritis. Data analysis was performed on anonymized clinical data.

Patients who do not have cardiac involvement on echocardiography are followed up in consultation and treated with intravenous immunoglobulin and acetylsalicylic acid until improvement of their general condition and disappearance of the inflammatory syndrome, followed by an annual check-up. However, for children with cardiac involvement, follow-up is done every 6 months with an electrocardiogram and transthoracic echocardiography.

3. RESULTS

3.1 Annual Number of Cases

Fig. 1 shows the trend of the number of cases for the period of our study. The number of cases increased steadily from 7, in 2022, and itsomewhat stabilized at around 28 cases per yearbetween 2015 and 2020. However, the number of cases recorded during the first year of COVID-19 is 47, meaning that the number of cases increased significantly during the COVID-19 period. About 42% of the KD patients during the COVID-19 period had a Sars-Cov-2 infection or were exposed to the virus.

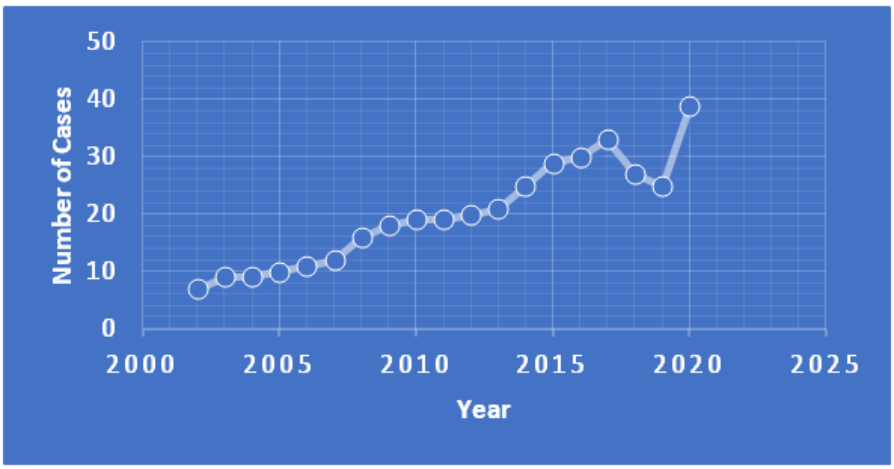

Fig. 1. Annual number of cases reported in our study

3.2 Patient Age Demographics

The patients in our study were predominantly male. The male-female sex ratio increased from 1.5, before COVID-19, to 1.9 after the pandemic.The average patient age also increased: more than half the cases in the pandemic period are at least 5 years old.For the period before COVID-19, the average agewasabout 36 months. About 18% of the patients were older than 5 years. However, after COVID-19, the average age increased to 67 months. As many of the patients recorded during the COVID-19 period met the MIS-C criteria, this result is consistent with the observation that one main distinction between MIS-C (PIMS) and classic KD is the age of the children affected.

3.3 Presenting Symptoms

Table 1 summarizes the presenting symptoms of our patients. All of our patients presented with high, persistent fever (between 39°C et 40°C for at least 5 days).Before COVID-19, buccopharyngeal involvement was observed in 80% of patients, while after COVID-19, it was observed in 94% of cases. Conjunctivitis, often bilateral, was observed in 72% and 82% of cases, respectively, before and after the pandemic. Cervical lymphadenopathy was observed in 37% of children (51% after COVID-19). Anoften generalized skin rash with a variable appearance was observed in less than 1% of cases before COVID, and in 70.2% of cases after. Extremity involvement was observed in 65% of patients, with inflammatory edema of the back of the hands and/or feet, and peeling of the fingers and/or toes. Various other symptoms, such as gastrointestinal symptoms, were observed in a small fraction of patients.

3.4 Complete vs. Incomplete KD

Kawasaki disease can be divided into two complete and incomplete forms, depending on the symptoms besides fever. In the complete form, fever is associated with at least 4 of the 5 main criteria of the disease (skin rash, extremity involvement, cervical lymphadenopathy, bilateral non-purulent conjunctivitis, and involvement of the oral mucosa). In incomplete KD form, fever is associated with less than 4 of the main criteria.

Our study shows that,before the COVID-19 period,79.4% presented with a complete form, and20.6% were classified as having an incomplete form. During the COVID-19 period, the incomplete form doubled to 40.5%.

3.5 Imaging Results

For the pre-COVID period, ECG and Chest X-ray imaging results were, respectively, abnormal for only 1% and 4.3% of the patients. During the COVID-19 period, ECG results were abnormal for 11% of the patients, and Chest X-rays were abnormal for 13% of the patients. However, while echocardiography results were abnormal for 43.5% ofthe cases before COVID-19, this number increased to 74.5% during COVID-19. Coronary artery aneurysm/dilation was observed for 26% of the patients (55.3% during COVID-19), and coronary vessel parietal thickening was observed for 11% of patients.

Table 1. Presenting symptoms (comparison between before and after COVID-19)

Symptom	Before 2020	COVID-Period
Persistent fevers	92%	100%
Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea)	13%	14.9%
Conjunctivitis	71.7%	85.1%
Bucco-pharyngeal involvement	80.4%	93.6%
Neurocognitive symptoms (headache, lethargy, confusion, seizures)	5.43%	2.22%
Respiratory symptoms (tachypnea, labored breathing)	4.35%	10.6%
Articulations/arthralgia	16.3%	23.4%
Adenopathy	37%	51%
Cutaneous eruptions	78.2%	70.2%
Extremities involvement	66.3%	63.83%

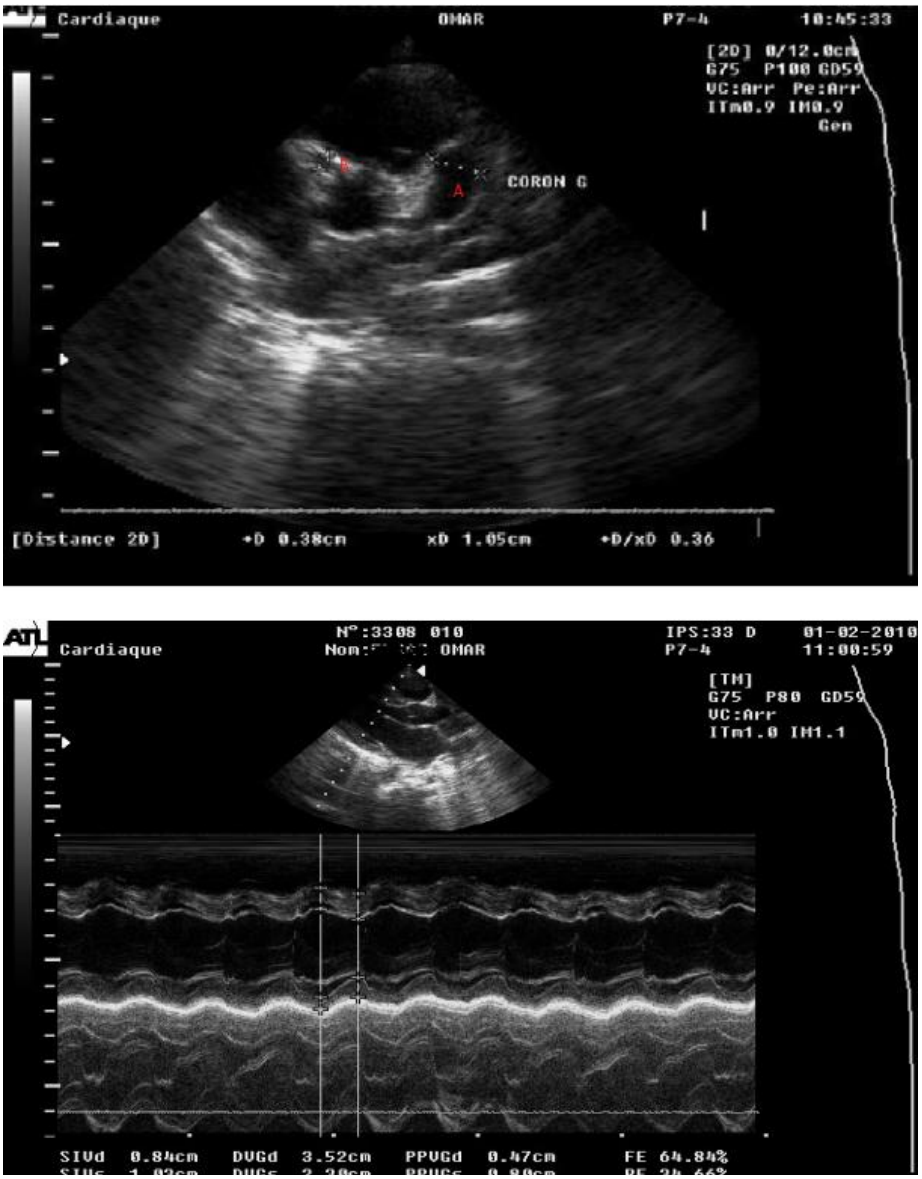

Fig. 2. 2D and TM Echocardiography of a 3-year-old child, showing (A): a 10 mm aneurysm of the left coronary artery, (B): right coronary artery: 4.9 mm, and (C):good VG function (Photo Pediatric Service 4 Rabat Children's Hospital)

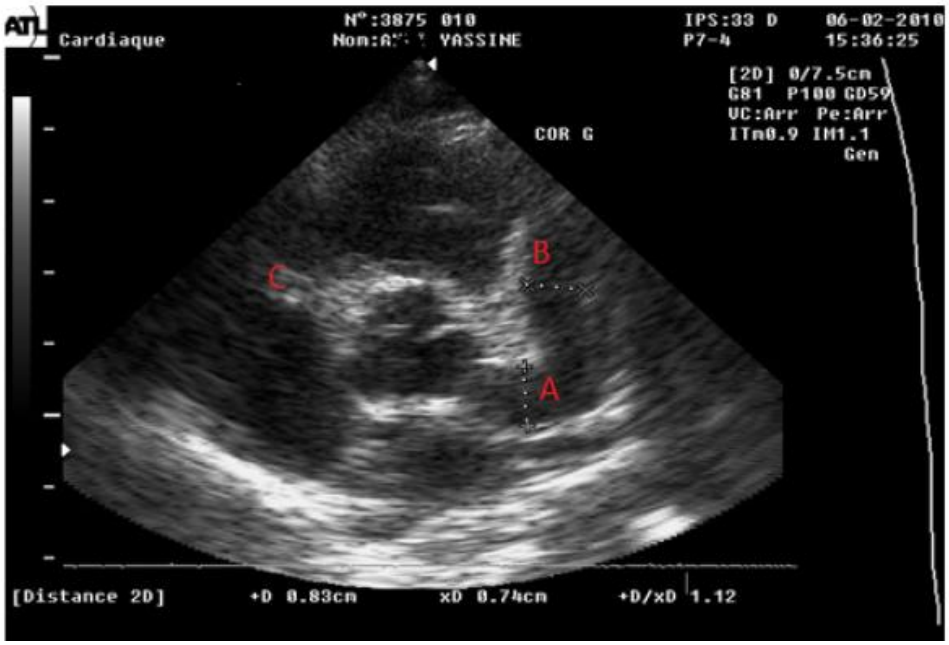

Fig. 3. Echocardiographyof 5 months-old child, showing a 9.3 mm aneurysm of the left coronary artery (A), Anteriorinterventricular, 8.2 mm (B) right coronary artery, de 6.2 mm (C). (Photo: Pediatrics Service 4, Rabat Children's Hospital)

3.6 Clinical Symptoms and Laboratory Results

Table 2. Laboratory results

Laboratory Finding	Units	Normal Range		Study Results (min-max)	
		Min	Max	Before 2020	COVID-19 period
Hemoglobin level	g/dl	13	16.5	6.8 – 14.4	8.0 – 13.8
Platelet count	10^9/L	150	400	64 - 913	120 - 985
Leukocyte count	10^9/L	4	10	4.93 – 41.61	6.078 – 49.30
Neutrophil count	10^9/L	1.5	7	0.82 – 14.00	0.9 - 17
C-reactive protein level	mg/L		5	5.2 - 412	0.2 - 433

For the post-COVID period, biology tests reveal a more significant inflammatory syndrome with:

- An increased sedimentation rate and CRP in 95.7% of the cases.
- Microcytic hypochromic anemia was reported in 80.8% of the cases.
- Neutrophil-predominant leukocytosis is present in 70.2% of the cases.
- Lymphopenia in 40.2% of the patients.
- Thrombocytosis was reported in 91.5% of the cases (*vs.* 93.5% before).
- Macrophage activation syndrome was present in 29.8% of the patients (*vs.* 1% before).
- Hepatic cytolysis was detected in 21.2% of the patients, with an increase in transaminase levels.
- Hyponatremia was observed in 42.5% of the cases.
- Hyperferritinemia in 57.4% of the cases.
- Increased triglycerides in 27.6% of the cases.

3.7 Treatment

All patients in our series received anti-inflammatory doses of acetylsalicylic acid (80 to 100 mg/Kg/day divided into four times).

Intravenous Immunoglobulins (IgIV)were administered to all but 7 patients, in the pre-COVID period, who were seen late (after more than 10 days of the disease's progression), had a good general condition, and showed no cardiac abnormalities on echocardiography. A small

fraction (6.4%) received a second infusion of IgIV due to persistent fever 48 hours after the first dose of IgIV.

Before COVID, only 16.3% of cases with severe forms of the disease and risk factors received Methylprednisolone (Solumedrol) boluses at a dose of 1g/1.73 m²/day. This rose to 29.8% after COVID-19. These boluses were administered for cases with severity factors such as early-onset aneurism, MAS, or persistent fever after two doses of Immunoglobulins.

4. DISCUSSION

“Kawasaki disease mainly affects children, especially infants. This disease can affect multiple organs and tissues, but it primarily affects small and medium-sized blood vessels with a preference for the coronary arteries, which can lead to aneurysms in nearly a quarter of untreated patients” [1,2,3,4]. “Infants have much higher rates of coronary artery abnormalities even if they are treated within the first 10 days. Kawasaki disease is considered the most common cause of acquired heart disease in children. Coronary artery aneurysm is a serious and potentially life-threatening condition, but the risk is reduced to almost 5% with prompt and appropriate treatment” [1,5].

“The diagnosis of Kawasaki disease is mainly clinical and based on the guidelines of the AHA and the Kawasaki Disease Research Committee (Japanese Ministry of Health), which are important reference points widely used by treating physicians around the world” [12-15]. However, one of the challenges of diagnosing this disease is that the main clinical features appear sequentially and may not all be present at any given time.

Although many researchers have attempted to unravel the etiology of KD and the pathogenesis of coronary aneurysms, the physiopathology of KD is not yet clearly elucidated [1]. However, many potential theories have been identified, such as infectious etiology or genetic susceptibility, due to having an epidemic pattern and marked seasonality. It is commonly assumed that one or more infectious agents induce an exaggerated inflammatory response ingenetically predisposed children. “For instance, since MIS-C was first reported, it was suspected that MIS-C is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). One piece of evidence is that 98% of MIS-C patients reported on the CDC website had a positive test result for SARS-CoV-2, and the remaining 2% of patients had contact with someone with COVID-19” [5]. “Reports continue to emerge of children with MIS-C among communities with high rates of COVID-19, with the peak of MIS-C usually lagging the peak of the COVID-19 wave by a few weeks” [5,7]. “ The lag suggests that the development of the KD-like disease is likely the result of a post-viral immunological reaction” [5].

There are many similarities and differences between MIS-C and COVID-19-triggered KD and subsequent MAS. MAS is typically characterized by high fevers, liver and kidney injury, and bone marrow suppression with evidence of intravascular coagulation [8]. MAS is also associated with an elevation of inflammatory markers particularly an elevation of ferritin [8]. The high serum ferritin levels encountered in MAS reflect the presence of histiocytic hyperactivity. As in classic KD, routine KD evaluation and management should be conducted. This includes a serial echocardiogram, the administration of IVIG, and the administration of antiplatelet therapy. The mainstay of treatment for MAS is anti-inflammatory and immunosuppressive agents. Prompt identification of MAS, the need for close monitoring of MAS patients, and fast initiation of appropriate therapies are highly important [8].

An exaggerated systemic inflammatory response (cytokine storm) leading to vascular endothelial damage and immune-mediated tissue damage is observed in both MIS-C and KD. Epidemiologically, however, there are important differences between MIS-C and KD. While classic KD has a higher incidence among children of Asian descent, data from the United States shows that MIS-C was diagnosed more in Black and Latino children than in other ethnic groups [5,7]. While the average age of patients suffering from KD is 2 years old, and 75% are under 5 years old, only 24% of children diagnosed with MIS-C were in that age group [5]. Most children diagnosed with MIS-C are children and adolescents who were previously healthy and had a median age of 10 years [7]. In our study, the average age of patients before the pandemic was 37 months; during the first year of the pandemic, older children were affected, and the average age rose to 67 months. The gender distribution before and during the pandemic did not change: 80% of the patients were male, and 20% were female. Yet, regardless of age, when a patient who is diagnosed with MIS-C has

cardiac complications, we observe that these complications are similar to KD's, and the KD treatments are prescribed for MIS-C.

As in classic KD, many children with MIS-C meet the criteria for complete or incomplete KD. Our study shows that, before the COVID-19 period, 79.4% presented with a complete form, and 20.6% were classified as having an incomplete form. During the COVID-19 period, the incomplete form doubled to 40.5%. It has been consistently observed that children with incomplete forms of the disease have a longer fever duration and that treatment is often delayed compared to children with complete forms of the disease. According to a study conducted in New York, this age difference can be explained by the expression of the gene for the angiotensin-converting enzyme 2 (ACE2) based on age in the nasal epithelium, the first point of contact between SARS-CoV-2 and the human body [16].

Echocardiography is the cornerstone of cardiovascular evaluation in Kawasaki disease, particularly during the acute phase but also during long-term follow-up, due to its non-invasive nature and good sensitivity and specificity for identifying and characterizing cardiac and coronary anomalies. Long-term management is guided by patient stratification based on the severity of their coronary artery disease and the resulting risk of myocardial ischemia. In our series, abnormal echocardiography results were observed during the COVID-19 period than before (74.5% vs. 43.5% of the patients). Coronary artery anomalies increased during the pandemic (26% of the cases before the pandemic vs. 74% after); coronary artery aneurysm/dilation,specifically, was 2.5 as frequent during the pandemic (55.3% compared to 20% before the pandemic). Artery dilatation was observed for 6.5% of the patients before COVID-19 and for 19% of the cases during the pandemic.

The standard 12-lead electrocardiogram is recommended in the acute phase for detecting signs of myocardial ischemia or necrosis, which complicates coronary occlusion, even in the absence of coronary involvement on echocardiography. The ECG should be systematically performed at least once a week during hospitalization or when symptoms such as chest pain or hemodynamic alterations are observed. In our series, before the pandemic, no ECG abnormalities were recorded in the children, except for one case with rhythm disorders and right ventricular hypertrophy. However, during the pandemic, ECG results were abnormal for about 11% of patients.

All patients who did not respond to IgIV presented with coronary involvement (11 cases, or 45.8%). It was also noted that the inflammatory syndrome was more pronounced in this group, with thrombocytosis in 23 patients, accounting for 95.8%, with a median of 650,000/mm^3, a significantly higher white blood cell and neutrophil count with a median of 14,500/mm^3 and 8,700/mm^3, respectively. A lower lymphocyte count was also observed with a median of 900/mm^3, and a higher CRP with a median of 140 mg/L.

Therefore, our results show that younger age, male sex, a more pronounced inflammatory syndrome, a high platelet count, a high white blood cells count, a high neutrophils count, high CRP, a low lymphocyte count, a late diagnosis, and resistance to IgIV are factors that favor coronary involvement.

In our series, clinical evolution was favorable in 315 cases, with regression of clinical signs from the second day of treatment. Nine cases had persistent fever, which only regressed after corticosteroid bolus administration. No deaths were reported. The inflammatory syndrome gradually decreased in all children, especially the C-reactive protein and the sedimentation rate, which normalized on average within 3 to 8 weeks. As for the platelet count, an increase was observed between the 2^{nd} and 3^{rd} week of evolution in the 3 patients admitted with thrombocytopenia, as well as in the 7 cases with a normal platelet count. This count normalizes within an average of 32 days. Patients admitted with thrombocytosis normalize on average within 36 days.

Coronary involvement, especially dilatation, and aneurysm of the coronary arteries regressed gradually until disappearance with a follow-up period of 1 to 48 months and an average of 13 months.

These results are admittedly based on a relatively limited number of cases, and further literature review is needed to confirm these observations. However, they highlight the importance of maintaining a high level of vigilance in patients who were exposed to infectious agents and consider the possibility of

Kawasaki disease, especially in patients with persistent or atypical symptoms.

5. CONCLUSION

Although most of our patients after March 2020 were diagnosed with KLD, the increase in the number of cases due toCOVID-19 supports the theory that KD might have an infection-related origin. Other studies made similar observations, e.g., a second significant peak of Kawasaki disease was observed in December 2009 in France during the H1N1 influenza pandemic [17]. In these two cases, the emergence of a new virus changed the epidemiologic profile of KD but not its treatment. The similarities of MIS-C with Kawasaki disease (KD) and macrophage activation syndrome (MAS) suggest that when MIS-C, MAS, and KD have cardiac complications, the coronary involvement is the same of the same nature. In all cases, using immunoglobulins as a first-line treatment, and corticosteroidsinthe presence of MAS features or early onset of an aneurysm is effective. The factors linked with severe manifestations of KD are mostly correlated with MAS or other scores such as Kobayashi.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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