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Factors Associated with Severe Outcomes in Multisystem Inflammatory Syndrome in Children: A Retrospective Study from Morocco

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Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but serious complication that affects some children a few weeks after SARS-CoV-2 infection. The similarities of MIS-C with Kawasaki Disease (KD) and Macrophage Activation Syndrome (MAS) suggest that the syndrome represents a spectrum of diseases. MIS-C, which is initiated by an overactive immune response in children, puts pressure on the heart, as inflamed blood vessels become incapable of carrying adequate blood, hence producing cardiac complications. Here we describe the clinical and laboratory characteristics of 23 patients who were admitted to our unit and diagnosed with MIS-C. The outcome was favorable for all patients after receiving treatment with a combination of Intravenous Immunoglobulin (IVIG), aspirin, and, for some patients, a corticosteroid. Only one patient required intensive-unit care. The average hospital stay was 7 days, and no mortality occurred. For some patients, MIS-C's unopposed inflammatory state progresses rapidly to multiorgan failure. Cardiovascular complications consisting of shock, myocarditis, decreased cardiac function, and coronary artery dilatation was noted in 43% of the patients in our study. The goal of our study is to identify clinical features and laboratory results, if any, associated with severe clinical outcomes of MIS-C. Such information would help in the decision to initiate targeted immunotherapy quickly.

Keywords: Multisystem Inflammatory Syndrome in Children (MIS-C); Pediatric Inflammatory Multisystem Syndrome (PIMS); Hyperinflammatory shock; Severe Acute Respiratory Syndrome 2 (SARS-CoV-2); Coronavirus disease 2019 (COVID 19); Children; Pediatric

Introduction

Shortly after the World Health Organization (WHO) classified COVID-19 as a pandemic in March 2020 reports begun to emerge 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 of Disease Control (CDC) created a case definition on May 13th, 2020 [1]. This syndrome, which has similarities with Kawasaki Disease (KD), the most frequent vasculitis in children, and Macrophage Activation Syndrome (MAS), was formally named Multisystem Inflammatory Syndrome in Children (MIS-C). By mid-January 2022, 6,431 children in the United States have been diagnosed with MIS-C, and 55 children have died from it [2].

Early on, it was suspected that MIS-C is associated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). One evidence is that 98% of MIS-C patients reported in 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 [2]. 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 COVID-19 wave by a few weeks [3,4]. 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); and no alternative plausible diagnoses; and positive test result for current or recent SARS-CoV-2 infection by real-time Reverse Transcription Polymerase Chain

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Reaction (RT-PCR), serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of symptoms [1].

Many children with MIS-C meet the criteria for complete or incomplete KD. 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 other ethnic groups [2,3]. 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 [2]. Most children diagnosed with MIS-C are children and adolescents who were previously healthy and had a median age of 10 years [2,4].

Methods

We describe a retrospective study of 23 cases that were diagnosed with MIS-C from November 26th, 2020, to January 11th, 2022. The study was performed in the Pneumo-allergology and pediatric Infectiology Department at the Children's Hospital in Rabat. The inclusion criteria were set in accordance with the MIS-C criteria definition published by the WHO [5]. Data analysis was performed on anonymized clinical data.

All children who meet diagnostic criteria for MIS-C are managed in the inpatient setting. At admission, the patients were considered as suspected cases of COVID-19 and were managed according to the recommendations of the country's Ministry of Health. All patients undergo testing for SARS-CoV-2 at the time of presentation, and infection control precautions are used pending the results of initial testing. SARS-CoV-2 infection tests were based on RT PCR on nasopharyngeal swabs, as well as serological tests to detect the presence of antibodies specific to SARS-CoV-2 (IgM and IgG in the blood/serum of the patients). When the first RT-PCR test for a patient returns a negative result, we perform a second test for confirmation. A positive serological test (IgM or IgG, or both) associated with a negative RT-PCR test was considered consistent with a previous or current infection.

COVID-19 waves in Morocco

The first COVID-19 case in Morocco was reported on March 2nd, 2020. The epidemic curve of COVID-19 cases in the country recorded three waves at different time intervals: the first wave from April 2nd to 8th, 2020, was followed by a second, larger wave between April 18th and April 26th, 2020, coinciding with the large clusters registered in industrial, commercial, penitentiary and family settings. The third wave, which was less pronounced, occurred between April 28th and May 2nd, 2020. The positivity rate among children was initially high; at 20.8% in March 2020, it slightly exceeded the rate for the rest of the population, but it dropped to 6.5% in May of the same year. For comparison, when the total number of cases in Italy reached 58,000 in March 2020, only 597 cases (1%) were children aged 18 years or less. During the first wave, a single death was recorded in a 17-month-old infant admitted with a severe picture of respiratory distress, a history of delayed weight (7 kg at 17 months) and renal failure [6]. Among children aged 14 years or less, 57.3% of cases were asymptomatic, 39% had mild symptoms, and they were moderate for 3% of the patients. About 0.6% of cases had severe symptoms.

The patients described in this study presented to our hospital, which is one of the major referral public university hospital centers. Our findings support already published observations of the post-COVID-19 inflammatory syndrome in 5 children from a different region in Morocco [7].

Results

Patient age demographics

The 23 patients in our study were predominantly male (19 males and 4 females) and were 7.5 years old in average. While published report indicate that only 24% of children diagnosed with MIS-C are less than 5 years old [2], the proportion of patients in our study in that age group is 48%. In particular, 3 of the four female patients in our study are under 5 years old. None of the patients had a significant medical history, or prior pathological conditions.

SARS-CoV-2 test results

Results from RT-PCR tests to detect SARS-CoV-2 in nasal swabs were negative for all patients. For each patient in our study, we performed RT-PCR tests twice, and both results were negative. Only one patient had a confirmed COVID-19 infection 4-week before presentation. SARS CoV-2 IgM and IgG were both positive for 3 patients (13%). IgM serology was negative and IgG serology positive for 19 patients (83%), indicating previous infections. For one patient, IgM was positive and IgG serology negative. Contact with a confirmed COVID-19 case was reported in 11 cases (3 to 5 weeks prior to the consultation).

Table 1: Presenting symptoms (comparison with published reports [8]).

Symptom	Reported in [8]	% Cases in our study
Persistent fevers	100	100
Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea)	60 to 100	71
Rash	45 to 76	53
Conjunctivitis	30 to 81	76
Mucous membrane involvement	27 to 76	100
Neurocognitive symptoms (headache, lethargy, confusion, seizures)	29 to 58	18
Respiratory symptoms (tachypnea, labored breathing)	21 to 65	29
Sore throat	10 to 16	71
Myalgias	8 to 17	6
Swollen hands/feet	9 to 16	12
Lymphadenopathy	6 to 16	47

Table 2: Laboratory results (comparison with published reports [8]).

Laboratory Finding	Units	Normal Range		Study Results		
		Min	Max	Median	Min	Max
Hemoglobin level	g/dl	13	16.5	11	8.7	14
Platelet count	10^9/L	150	400	208	102	776
Leukocyte count	10^9/L	4	10	11.2	3.8	20.6
Neutrophil count	10^9/L	1.5	7	9.3	2.4	16.4
Lymphocyte count	10^9/L	1	4	1.5	0.61	5.8
Eosinophil's count	10^9/L	0.1	0.4	0.5	0	0.61
C-reactive protein level	mg/L		5	180	97	364
Erythrocyte sedimentation rate	mm/h		10	64	17	125
Serum ferritin	ng/ml	21	274	450	90	2500
Sodium level	mmol/L	136	145	129	119	138
Urea level	g/L	0.15	0.55	0.2	0.18	1.09
Creatinine level	mg/L	5.7	12.5	5	3	19.7
Alanine aminotransferase level	U/L		55	26	19	57
Aspartate aminotransferase level	U/L	5	34	30	13	148
Triglyceride's level	g/L	0.3	1.3	5	0.75	5.93
D-dimer	µg/mL		0.5	26	0.7	43.7
Fibrinogen	g/L	2	4	30	3.6	12

Table 3: Patients with severe manifestations.

Patient	Sex	Age (Months)	KD	MAS	Severity	Kobayashi score	Corticosteroids
1	M	56	Complete		5	1	
8	M	108	Incomplete		5	3	
19	M	50	Incomplete		5	2	
17	M	96	Incomplete	Yes	2,3,4	6	Yes
22	M	168	Incomplete		2,3,4	4	
12	M	56	Incomplete	Yes	2,3,4,5	4	Yes
21	M	192	Incomplete	Yes	2,3,4,5	7	Yes
7	M	180	Incomplete	Yes	2,4,5	6	Yes
14	M	188	Incomplete	Yes	2,4,5	6	Yes
16	M	28	Complete		2,5	4	

Severity codes: 1: Admitted to ICU; 2: Decreased cardiac function; 3: Shock; 4: Myocarditis; 5: Coronary artery abnormality; 6: Death

Presenting symptoms

The patients presented to our hospital 9 days in average after onset of symptoms. They all had prolonged fever (5 to 18 days, with an average of 9 days). All patients had been given antipyretics for fever control before their presentation to our unit, but none of them responded to the treatment. Nineteen (19) patients had been given antibiotics, but none of them responded to the treatment. Table 1 compares the incidence of various symptoms among our patient *vs.* the incidence rate reported in other studies [8-11].

Nineteen patients (83%) had digestive manifestations: 9 patients had diarrhea; 10 had vomiting; and 12 patients had abdominal pain. Extremities changes were noted in 6 patients (26%): 3 patients had palmar-plantar erythema, and 1 had palmar erythema; 3 had swelling of the dorsal hands, and 1 patient had swelling of the dorsal hands and feet.

Skin rash was noted for 17 patients (74%) in various forms: Macular rash (10 patients); maculopapular rash (3 patients), urticaria rash (3 patients), perineal rash (3 patients), and BCG reactivation scar area (1 patient). Lips and oral cavity changes were observed for 21 patients (91%): Cheilitis, 17 patients; pharyngitis, 14 patients, and glossitis, 4 patients. Fourteen patients (61%) presented with cervical lymphadenopathy (9 unilateral and 5 bilateral). Only one patient had Oliguria. Aseptic conjunctivitis was noted in seventeen patients (74%). Three patients (13%) had rhinorrhea.

Respiratory manifestations were observed for 13 patients (57%): Cough (11 patients), thoracic pain (2 patients), polypnea (4 patients), hypoxia (1 patient), and dyspnea (3 patients). One case presented with respiratory distress and desaturation, and 2 cases had dyspnea with chest pain. Mucocutaneous involvement has been reported in all patients. Cervicalgia was noted in 2 cases (8%).

Three patients (13%) reported muscle pain (myalgia). Six patients (26%) reported joint pain (all had arthralgia, and one had arthritis).

Nine patients (39%) had neurological manifestations: Headaches (8 patients), meningeal syndrome (5 patients), hallucinations

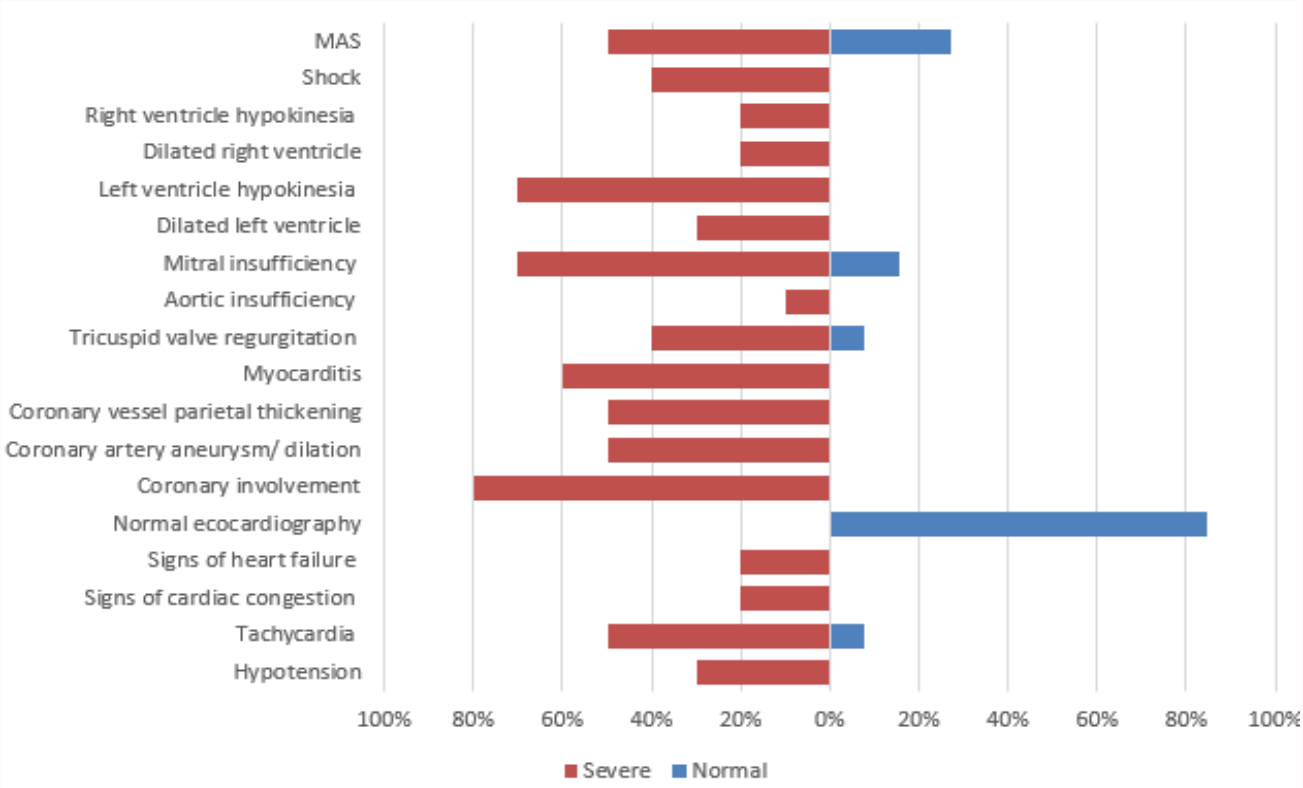

Figure 1: Features in patients with severe or non-severe manifestations.

Table 4: Percent severe cases for various demographic or clinical features.

Parameter	Normal	Severe
Male	47%	53%
Female	100%	0%
Complete KD	67%	33%
Incomplete KD	47%	53%
MAS	38%	63%
Average age	112	73
Average CRP	118.7	243.3

(2 patients), irritability (1 patient), convulsion (1 patient) and encephalitis (1 patient).

Tachycardia was observed for six patients (26%), cardiac congestion and signs of heart failure for 2 patients (9%). Hypotension was observed for 3 patients (13%). All other patients had normal hemodynamic variables. Most of the children had no significant respiratory involvement, although two patients who had less than 92% oxygen saturation.

Six (26%) children in our study met criteria for complete KD while 15 patients (62.5%) had incomplete KD.

Imaging results

Echocardiography results were normal for 12 patients (52%). Coronary artery aneurysm/dilation was observed for 5 patients (22%). Coronary vessel parietal thickening was observed for 5 patients (22%). Myocarditis associated was noted for 6 patients (26%). It was associated with left ventricle hypokinesia (6 patients), tricuspid valve regurgitation (5 patients), mitral insufficiency (5 patients), left ventricle dilatation (3 patients), right ventricle dilatation (2 patients), left ventricle hypokinesia (2 patients), aortic insufficiency (1 patient), mitral valve prolapsed (1 patient).

Chest X-ray showed abnormalities for 10 patients (43%): Bronchial syndrome (6 patients), cardiomegaly (7 patients), isolated blunting of the costophrenic angle (3 patients).

Brain scans were performed for two patients (9%) who presented a meningeal syndrome. For one patient, the scan showed enhancement of the meninges and falx cerebri and decreased of enhancement of the posterior longitudinal sinus, caused by cerebral thrombus.

Chest computed tomography was performed for 4 patients and it showed: ground glass opacity for 3 patients and pachypleuritis for 1 patient.

Abdominal echography was performed for 4 patients. The results were normal for 1 patient, mesenteric adenolymphitis for 1 patient and peritoneal and pelvic effusion for 1 patient.

As shown in Table 2, the Erythrocyte Sedimentation Rate (ESR) and elevated C-Reactive Protein (CRP) are elevated for all patients, indicating a marked inflammatory state. Microcytic hypochromic anemia was present in only 2 patients (9%). Leukocytosis with a predominance of neutrophils was noted in 4 patients (17%). Lymphopenia was found in 11 patients (48%). Thrombocytosis was observed in 3 patients (13%) and Thrombocytopenia in other 3 patients (13%). Hyper eosinopenia was identified for 5 patients (22%). Hyponatremia was found in 11 patients (48%). Hypertriglyceridemia was noted for 8 patients (35%). Hepatic cytolysis with Aspartate Aminotransferase (ASAT) was identified in 3 patients (13%). There were 3 cases (13%) of renal failure. Macrophage activation syndrome

was noted in 4 cases (17%). Cytobacteriological examination of the urine revealed aseptic leukocyturia in 6 patients (28%). D-dimer was elevated for all patients. Hyperferritinemia was observed for 11 patients (48%).

Blood culture test was performed in 14 patients (61%) and was negative for all of them. Lumbar puncture was performed in 4 patients and was also negative for all of them.

Severe manifestations

Ten patients (43%) presented with severe manifestations, which included state of shock, decreased cardiac function, myocarditis, and coronary artery abnormality (Figure 1). Table 3 shows the combination of features for each patient who showed a severe manifestation, and the type of severe manifestation. We note that patients who required corticosteroids have a high Kobayashi score (and thus are insensitive to IVIG) and had MAS manifestations.

As shown in Table 4, slightly more than half the male patients in our study had severe manifestations. None of the female patients had such manifestations. Only one third of patients with complete KD exhibited severe manifestations, but half the male patients with incomplete KD had severe manifestations. Two thirds of the patients with MAS also had severe manifestations.

Discussion

Patients in our study predominantly had fever with gastrointestinal (79%), cardiovascular (50%), and mucocutaneous (71%) manifestations, which is consistent with other reports about MIS-C [12-14]. Respiratory manifestations other than cough were observed in 30% of our patients. All but one patient had highly elevated levels of C-Reactive Protein (CRP), suggesting that a hyperinflammatory state.

In the addition to the epidemiological differences between KD and MIS-C discussed earlier, MIS-C patients meeting KD diagnostic criteria have lower white blood cell count and lower platelet levels, but greater levels of CRP and ferritin compared with classic cases of KD [12]. MIS-C cases exhibit greater prevalence of multisystem involvement, notably cardiac abnormalities such as myocarditis and shock [12]. These differences were confirmed for the patients in our study.

One of the most severe complications of KD is coronary artery aneurysm [9]. Possible mechanisms of myocardial involvement are speculative and include direct viral invasion of myocyte and systemic inflammatory response triggering myocyte injury, which can be compounded by myocardial ischemia secondary to hypotension [1]. Without adequate treatment, 20% of untreated children can develop a Coronary Artery (CA) aneurysm which poses a significant risk of thrombosis and myocardial infarction later in life. Large aneurysms can rupture and lead to death. The incidence of Coronary Artery (CA) abnormalities in our patients was 23%, slightly outside the range reported in the literature [8], highlighting the importance of routine echocardiography in all children with MIS C, regardless of apparent sub-phenotype.

Management of MIS-C has evolved over the course of the pandemic, and the American College of Rheumatology has published recently, the guidelines for the treatment of MIS-C, recommending using immunoglobulins and/or high dose corticosteroids as a first-line treatment. Since all patients meet criteria for incomplete or complete Kawasaki Disease (KD), standard therapies for KD were administered, including Intravenous Immune Globulin (IVIG), and aspirin, and glucocorticoids in the event of Macrophage Activation Syndrome (MAS) and in the event of cardiac involvement (myocarditis and significant aneurysm). Glucocorticoids are used in this event of MAS or cytokine release syndrome (CRS; also called cytokine storm) because it may not respond to IVIG therapy. The dosing for IVIG is 2 g/kg, administered in a single infusion over 8 h to 12 h. Acetylsalicylic acid was administered in anti-inflammatory doses (80 mg/kg/day to 100 mg/kg/day) upon admission of the patients and was maintained until thermal defervescence with regression of the biological inflammatory syndrome, then continued in anti-aggregating doses (3 mg/kg/day to 5 mg/kg/day) for 12 weeks. Glucocorticoid therapy is administered as intravenous methylprednisolone in bolus for 1 to 3 days at a dose of 30 mg/kg/day was administered. In case of persistence of fever 36 h after the end of the IVIG infusion, a second dose of immunoglobulins was given. The treatment response was defined as a resolution of clinical signs and inflammatory markers. This approach is consistent with published guidance from American medical bodies pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 [8].

All patients in our study were administered IVIG, aspirin, and, for some patients, methylprednisolone per recommendations based on Kobayashi score: IVIG at 2 g/kg, and aspirin at 50 mg/kg to 80 mg/kg per day (Kobayashi score <5) for 5 days or aspirin at 30 mg/kg per day plus methylprednisolone at 2 mg/kg per day for 5 days (Kobayashi score ≥ 5), followed by a tapering of methylprednisolone over 2 weeks [12]. Aspirin was maintained until 48 h after defervescence, and then continued at an anti platelet dose of 3 mg/kg to 5 mg/kg per day for 8 weeks. Response to treatment was defined as the normalization of vital signs, CRP, and blood tests, and the resolution of symptoms and signs.

Patients with persistent or recurrent fevers, persistently elevated or rising inflammatory markers, and/or worsening clinical status are considered to have an inadequate response. Assessment of the patient's response to initial therapy is typically made over 1 to 3 days; however, it may be reasonable to wait a longer duration in patients without severe manifestations. Adjunctive therapies include interleukin 1 inhibitors (e.g., anakinra, canakinumab), interleukin 6 inhibitors (e.g., tocilizumab), high-dose (pulse) glucocorticoids, and convalescent plasma from recovered COVID-19 patients.

Conclusion

Our study shows that the similarities of MIS-C with Kawasaki Disease (KD) and Macrophage Activation Syndrome (MAS) suggest that MIS-C represents a spectrum of diseases. Using immunoglobulins as a first-line treatment, and corticosteroids either at the presence of MAS features or when Kobayashi score is greater than 6 is effective. The factors linked with severe manifestations are mostly correlated with MAS or Kabayashi score.

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