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Multisystemic Inflammatory Syndrome in Children: A Retrospective Study

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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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Data Article

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ABSTRACT

Introduction: Pediatric Multisystem Inflammatory Syndrome linked to temporal with SARS-Cov2 is a new hyper inflammatory disorder that affects children with Covid-19 infection. It usually occurs 2 to 6 weeks following illness or exposure.
Materials and Methods: Descriptive retrospective study of a cohort of 11 patients with MIS-C treated in the pediatric department of the Mohamed V military hospital in Rabat between December 2020 and September 2021. We analyzed the epidemiological, clinical, biological, imaging, therapeutical and evolutionary data of our patients.
Results: The average age is 9 years; the sex ratio is 1,2. The average exposure gap is 3.7 weeks. All patients presented with fever with multivisceral involvement, 81% presented digestive signs, 100% mucocutaneous signs, 63% cardiac signs and 54% neurological signs. Inflammatory markers were consistently high. Anemia (91%), neutrophilic leukocytosis (91%), lymphopenia (73%) are constant. The Covid-19 RT-PCR was negative and the SARSCov2 IgG serology testing was positive in all our patients. 54% of our cases have echocardiographic signs. Treatment was based on polyvalent intravenous immunoglobulins (IVIG) in all cases associated with corticosteroid therapy in 45% of cases and antiplatelet therapy in 91% of cases. The outcome was favorable in all of our patients.

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Conclusion: MIS-C should be considered in children with fever, rash, headache, tachypnea, and gastrointestinal symptoms such as vomiting, diarrhea, and abdominal pain. Cardiogenic shock is the main complication. IVIG and systemic corticosteroid therapy are the fundament of treatment.

Keywords: Multisystemic inflammatory syndrome; children; SARS-CoV-2; clinical cases.

1. INTRODUCTION

The end of 2019 was marked by the discovery of the coronavirus in Wuhan, China, which quickly reached pandemic proportions. The World Health Organization has given the name COVID-19 to this disease, which means coronavirus disease 2019 (1). The virus that causes COVID-19 is responsible for severe acute respiratory syndrome (SARS-CoV2).

Shortly thereafter, in April 2020, multisystem inflammatory syndrome in children (MIS-C) associated with the SARS-CoV-2 virus was identified in the UK [1]. It's a serious disease characterized by immune dysfunction with multisystemic involvement and severe symptoms usually requiring hospitalization. This syndrome is also known as pediatric multisystemic inflammatory syndrome with a temporal link to SARS-CoV-2 (SIMP-TS or SIMP). Its main clinical signs are fever, the typical features of Kawasaki disease, cardiac dysfunction; and gastrointestinal, neurological and/or renal symptoms. In the laboratory, there is an inflammatory syndrome (a noticeable increase in the level of C-reactive protein, accelerated sedimentation rate), lymphopenia, neutrophil hyperleukocytosis, thrombocytopenia, hyponatremia, hypertriglyceridemia and hypo albuminemia. Immunomodulators used for Kawasaki disease, such as intravenous immunoglobulins and glucocorticoids, are treatment options [2].

The objective of this work is to specify the epidemiological, pathophysiological, clinical, biological, radiological, therapeutic and evolutionary characteristics of MIS-C in its patients and compare them with data from the literature.

2. PATIENTS AND METHODS

A retrospective study was carried out within the pediatric department of the Mohamed V military instruction hospital in Rabat, including children in whom the diagnosis of MIS-C was retained and who were hospitalized over a period of 10 months running from December 2020 to September 2021. The total number of patients included during this study period is 11, with 6 boys and 5 girls.

The collection of clinical, paraclinical, therapeutic and evolutionary elements was done retrospectively by analyzing clinical observations using a pre-established exploitation sheet based on the following elements: Identity of the patient, reason for hospitalization, his history (especially vaccination status, recent vaccination, etc.), History of the disease, clinical examination on admission, biological elements (assessment of crase, inflammation markers, covid 19 test), imaging data, treatment administered and evolution [3].

On May 15, 2020, the WHO released diagnostic criteria for MIS-C. There is no specific diagnostic test, although laboratory and echocardiographic findings may be useful in evaluating suspected cases and differentiating MIS-C from other conditions.

The inclusion criteria for the observations of our patients were selected in accordance with WHO recommendations:

Children and adolescents 0-19 years old with fever > 3 days;

AND two of the following:

a. Rash or bilateral non-purulent conjunctivitis or signs of mucocutaneous inflammation;
b. Hypotension or state of shock;
c. Signs of myocardial dysfunction, pericarditis, valve disease or coronary abnormalities;
d. Elements revealing a coagulopathy (by prothrombin rate, active thromboplastin time, high D-dimers);
e. Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain);

AND high markers of inflammation such as ESR, Creactive protein or Procalcitonin;

Table 1. Table of epidemiological data

Number	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Age (years)	12	6	9	15	11	9	4	8	6	5	14
Sex	girl	boy	boy	boy	girl	girl	boy	girl	boy	boy	Girl
Origin	Rommani	Rabat	Temara	Khouribga	Temara	Mohammedia	Tetouan	Laayoune	Nador	Khenifra	Ain Aouda
Environment	Rural	urban	urban	urban	urban	urban	urban	urban	urban	urban	Rural
Inbreeding	-	+	+	-	-	-	-	-	-	-	-
admission date	20.12.20	28.12.20	04.01.21	06.01.21	12.01.21	17.01.21	27.01.21	27.01.21	16.02.21	04.09.21	10.09.21
number of consultations before hospitalization	1	2	4	2	0	2	2	2	2	2	2
delay for hospital treatment (d)	5	7	6	7	7	6	6	6	6	7	5
length of hospitalization	9	8	13	11	11	10	8	7	7	11	7
reason for hospitalization	Fever	fever	fever	rash	fever	fever	fever	fever	fever	fever	Fever
Contact Covid-19	+	+	+	+	+	+	+	+	+	+	+
Covid-19 exposure interval	3	4	4	3.5	4	3	4.5	3.5	unspecified	unspecified	4

Table 2. Clinical data table

Number	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Age (years) / sex	12/♀	6/♂	9/♂	15/♂	11/♀	9/♀	4/♂	8/♀	6/♂	5/♂	14/♀
General exam											
temperature(°C)	38.9	38.8	39.5	38.8	40	39.4	39	39	38	39	40
BP (mm Hg)α	100/60	95/55	100/60	111/60	110/60	100/55	90/50	120/50	100/65	90/50	110/70
CF (bpm) β	112	117	70	72	102	110	74	108	102	98	132
RR (cpm) π	20	23	24	21	24	23	26	21	30	34	22
SaO2(%)	98	96	96	99	97	98	95	98	96	95	98
Weight (kg)	32	23	30	45	41	31	20	46	28	18	57
Cut (cm)	142	116	132	150	158	130	108	140	124	108	164
BMI (Kg/m2)	15,87	17,16	17,24	20	16,42	18,34	17,14	23,47	18,21	15,43	21,19
Interpretation of BMI	normal	normal	normal	normal	normal	normal	normal	overweight	overweight	normal	normal
digestive signs											
abdominal pain	+	-	++	+	++	++	++	+	-	++	-
diarrhea	-	-	+	-	+	+	-	+	-	-	+
vomiting	-	-	++	+	+	++	+	+	-	++	+
Cutaneomucosal signs											
Conjunctivitis	-	+	++	+	+	+	+	+	+	+	+
Skin rash	+	+	+	+	+	-	+	+	+	+	+
Types of rash	Scar;	Morb;	Morb;	Morb;	Morb;		Morb;	Morb;	Scar;	Morb;	Morb;
Achievement of oral mucosa	-	+	-	-	-	-	-	+	+	-	-
edema of the extremities	-	-	-	+	-	-	-	-	-	-	-
cheilitis	-	+	-	-	+	+	+	-	+	+	+
pharyngitis	+	+	-	-	+	-	-	-	-	-	+
Respiratory signs	-	-	-	-	-	-	-	-	-	-	-
Cardiovascular signs	-	-	-	-	-	-	-	-	-	-	-
neurological signs	+	-	-	-	+	+	-	+	-	+	+
Disorders Hemodynamics											
tachycardia	+	+	-	-	+	+	-	+	+	-	+
low blood pressure	-	-	-	-	-	-	-	-	-	-	-
CRT>2	-	-	-	-	-	-	-	-	-	-	-
Cutaneous pallor	-	-	-	-	-	-	-	-	-	-	-
Cyanosis of ends	-	-	-	-	-	-	-	-	-	-	-
others											
myalgia	-	-	-	-	-	+	-	+	+	+	+
arthralgia	-		-		-		+			-	+
Lymphadenopathy	-	-	-	-	-	-	-	+	-	-	-

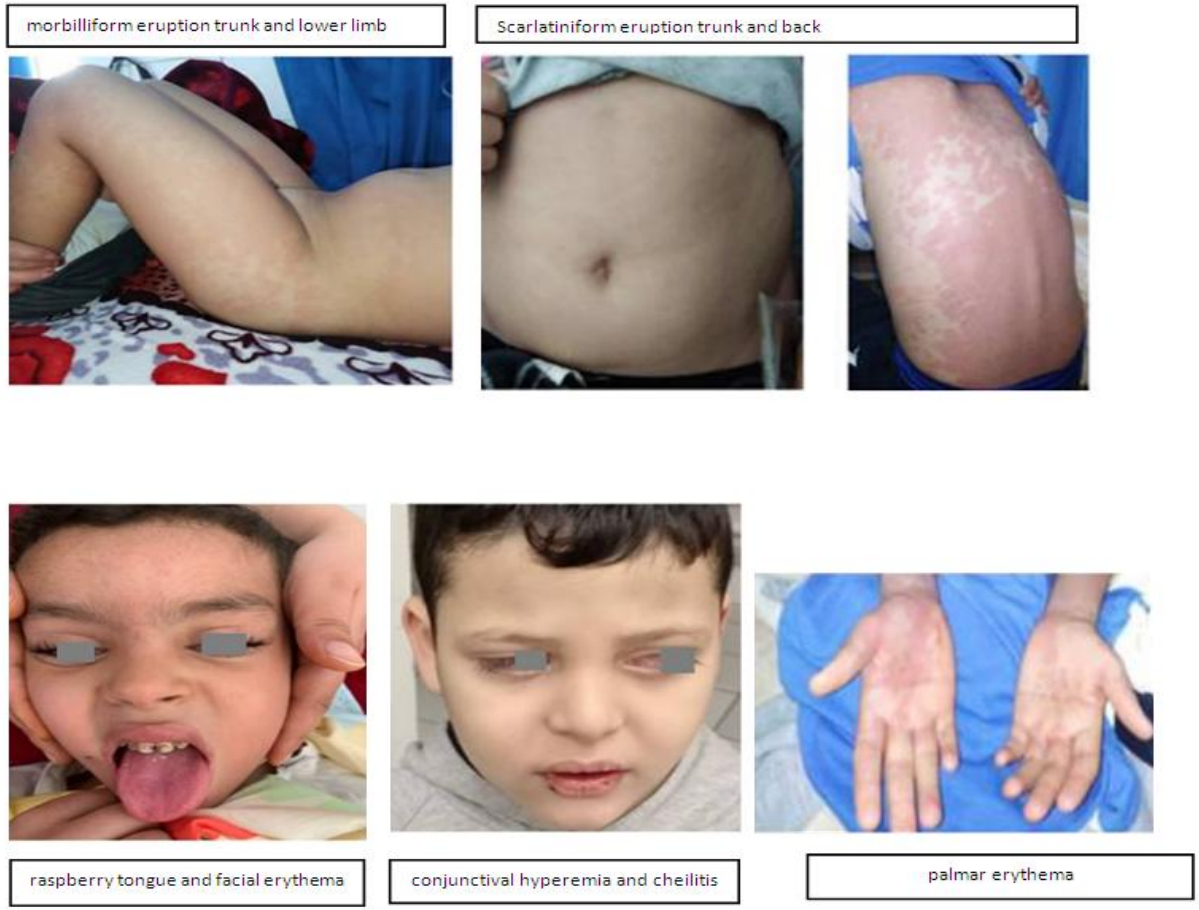

Fig. 1. Cutaneous and acrofacial involvement in our patients

Table 3. Table of biological data

Number	P1	P2	P	P4	P5	P6	P7	P8	P9	P10	P11
Age (years) / sex	12/♀	6/♂	9/♂	15/♂	11/♀	9/♀	4/♂	8/♀	6/♂	5/♂	14/♀
complete blood count											
Hemoglobin(g/dl)	10,4↘	10.1↘	8.2↘	10.5↘	10.9↘	10.2↘	9.1↘	11.1↘	9.8↘	11.6↘	10↘
Leukocytes(e/mm3)	11500	20900	16600	13500	19300	22500	7000	11100	21500	13400	9100
Neutrophils(e/mm3)	9400↗	19000↗	13500↗	11800↗	16400↗	20500↗	3600	8300↗	16600↗	10800↗	8100↗
Lymphocytes(e/mm3)	200↘	1200↘	200↘	300↘	1100↘	800↘	2400	1400↘	9680↗	2280	400↘
Blood plt(e/mm3)	1146000↗	308000	625000↗	125000↘	161000	181000	217000	176000	523000↗	70000↘	102000↘
blood rash/inflammation markers											
PT (%)	87	59↘	88	82	77	81	96	92	81	82	89
ATT ratio	1.2	1.6↗	1		1.2	1.2	1.2	1.1	1	1.4↗	1.2
D-dimers	1200↗		1700↗	1100↗	2480↗	3490↗	2300↗	2100↗	1500↗	1600↗	2100↗
Fibrinogen(g/l)	5.3↗	6.8↗	7.6↗	3.6	8↗	9↗	4.6↗	8↗		4	5.9↗
CRP (mg/l)	263↗	129↗	234↗	126↗	179↗	301↗	123↗	212↗	415↗	166↗	223↗
SR (mm/h)	65↗	90↗	95↗	60↗	70↗	100↗	40↗	85↗	137↗	50↗	
Ferritin (µg/L)	2000↗	252↗	1271↗	2000↗	307↗	433↗	65	491↗		1837↗	304↗
Hydro-electrolyte / kidney balance											
NA+(mmol/L)	131↘	127↘	129↘	125↘	131↘	128↘	135	137	136	125↘	134↘
K+(mmol/L)	3↘	3.5	4.1	2.9↘	5↗	2.9↘	3.7	3.1↘	3.9	4	4
total calcium (mg/L)	80↘		88	77↘	81↘		85↘	83↘	80↘		
Urea (g/L)	0.2↗	0.24↗	0.42↗	0.47↗	0.85↗	0.41↗	0.15	0.17	0.44↗	0.34↗	0.19↗
Creatinine (mg/L)	5	5	6	8	8.3	6	4	5	5	6	7
blood sugar (g/L)	0.67		1.18↗	1.54↗	0.7	1.04↗		0.9		0.7	0.96
Hepatic check											
Albumin (g/L)		27↘	28↘	25↘		33↘	34↘		36	26↘	
ASAT (UI/L)	42↗	20	46↗	97↗(x2)	44↗	24	30	50↗(x1,5)	20	133↗(x3)	58↗(x1,5)
ALAT (UI/L)	32↗	11	29	90↗(x2)	56↗(x1,5)	17	49↗	71↗(x2)	10	123↗(x5)	38↗
LDH (UI/L)			467↗	257↗		296		369↗		338↗	244↗
TB (mg/L)	5		23↗	5	4	6	1	2			7
CB (mg/L)			9↗		2	3					
lipid profile											
TC (g/L)	1.22		1.19	0.77	1.55	0.75	1.15	1.21	1.45		0.63
HDL(g/L)	0.13↘		0.2↘	0.13↘	0.33↘	0.13↘	0.13↘	0.08↘			0.11↘
LDL(g/L)	0.355		0.76	0.43	0.56	0.35	0.74	0.63			0.38
Tg (g/L)	2.7↗	1.45↗	1.62↗	1.45	3.32↗	1.37↗	1.42↗	2.51↗	1.66↗	1.63↗	0.68
cardiac assessment											
Troponin HS-Ic (ng/L)	6↗	166↗	2035↗	147↗	1232↗	1515↗	11↗	159↗	1	78↗	1
NT-ProBNP (pg/mL)						25000↗		2649↗	138	2466↗	2140↗
infectious balance											
ECBU	-	-	-	-	-	-	-	-	-	-	-

Number	P1	P2	P	P4	P5	P6	P7	P8	P9	P10	P11
Cerebrospinal fluid	normal				normal	normal				Normal	
blood culture	-	-	-	-	-	-	-	-	-	-	-
covid-19 report											
Quantitative Covid-19 RT-PCR	-	-	-	-	-	-	-	-	-	-	-
Covid-19 IgG serology	+	+	+	+	+	+	+	+	+	+	+

Table 4. Table of therapeutic data

Number	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Immunoglobulins intravenous	+	+	+	+	+	+	+	+	+	+	+
corticosteroids	-	+	-	-	+	+	-	-	-	+	+
Paracetamol	+	+	+	+	+	+	+	+	+	+	+
Antibiotic therapy	+	+	+	+	+	+	+	+	+	+	+
Acetylsalicylic acid at antiplatelet dose	+	+	+	+	+	+	+	-	+	+	+
Oxygen therapy	-	-	-	-	-	+	-	-	-	-	-
Vasopressors/Inotropes	-	-	-	-	-	-	-	-	-	-	-
others	-	-	Captopril; Furosemide	-	-	Filling Vascular; Captopril; Furosemide	-	-	-	-	Captopril; Furosemide

AND no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND elements indicative of COVID-19 (RT-PCR, antigen assay or positive serology) or probable contact with patients with COVID19.

Patients aged 0 to 19; who have an isolated fever and who have no biological confirmation elements; are excluded from the study.

3. RESULTS

3.1 Epidemiology

Our serie concerns 11 observations collected in the pediatric department of HMIMV Rabat between December 2020 and September 2021. The study included 5 girls and 6 boys, i.e. a sex ratio of 1.2. The age was 4 to 15 years old with an average of 9 years old. The distribution of patients according to geographical origin showed a clear urban predominance (9/11). 10 cases had confirmed contact with subjects with Covid-19. Only one case was symptomatic when infected with Covid-19. The interval between contact with patients with Covid-19 and the appearance of MIS-C in our patients is found in 9 cases, it varies between 3 and 4.5 weeks with an average of 3.7 weeks. Among all patients, three of them have comorbidities (see Table 1).

3.2 Clinic

All patients presented with fever with multisystem involvement; 81% showed digestive signs; 100% of mucocutaneous signs such as bilateral conjunctivitis, cheilitis, morbilliform or scarlatiniform rash or impairment of the oral mucosa; 63% cardiac signs and 54% neurological signs.

3.3 Biology Report

Biologically, all our patients have a major inflammatory syndrome (100%) with a very significant elevation of markers such as CRP, PCT, ESR and/or serum ferritin. Frequently, there is lymphopenia (72%), neutrophilic polynucleosis (91%), thrombocytopenia (27.2%) and high D-dimer levels (100%). Some patients have hyponatremia (72.2%), renal failure (81.8%) or hypoalbuminemia (85%). The PCR test was performed for all patients and was negative in 100% of cases. On the contrary, viral IgG serology was positive in all patients, i.e. 100% of cases.

3.4 Radiology

Echocardiographic signs are present in 54% of cases, such as mitral and pulmonary valve involvement, dyskinesia of the interventricular septum and impaired systolic function. Chest X-ray was normal in 100% of cases.

3.5 Treatment

The treatment was based on intravenous polyvalent immunoglobulins (IGIV) in all cases associated with corticosteroid therapy in 45% of cases and antiplatelet therapy in 91% of cases. All patients were put on empirical antibiotic therapy based on 3rd generation cephalosporin which was stopped after the results of the blood cultures were recovered.

3.6 Evolution

In the short term, there was an improvement in systemic damage as well as markers of inflammation. The medium and long-term evolution was favorable in all patients with follow-up in consultation.

4. DISCUSSION

4.1 Epidemiological Profile

Internationally, the lack of consensus on the case definition of MIS-C and the overlapping of the clinical presentation with that of Kawasaki disease initially contributed to the misdiagnosis of the syndrome and the difficulty of appreciation of its development [4].

SARS-CoV-2 infection has spread rapidly around the world since it was first identified in China in late 2019. Early studies of this new infection indicated that young children were disproportionately spared compared to adults [5,6]. In April 2020, the first articles about MIS-C series emerged in Europe [2,7] followed by other American and English series [8,9].

The first publication of MIS-C was a series of eight children living in the South East of England [10]. In larger series subsequently reported from the UK and US, more than 70% of affected children were previously healthy [11,12].

In France, 254 potential cases of MIS-C were identified by Santé Publique France between

March 16, 2020 and November 17, 2020, out of a population of 16.4 million people under the age of 20 [13]. In Morocco, over the period extending from March 2 to May 3, 2020, 495 children under the age of 15 were infected with Covid-19, i.e. 9.4% of the total number of Covid-19 cases over the same period and a cumulative incidence of 4.8 cases/100,000 inhabitants. The sex ratio was 1.3 and the mean age 7.3 years. 54.3% of positive cases were asymptomatic.

The incidence of MIS-C appears to vary by race and ethnicity, Black and Hispanic children are more affected than Asian children [14]. In three large series, the distribution according to ethnicity showed that 25 to 45% of cases were black children, 30 to 40% Hispanic children, 15 to 25% of white children and 3–28% of Asian children [11,12].

4.2 Definitions

The characteristics of this syndrome resemble certain known entities such as KS, toxic shock syndrome or macrophage activation syndrome [15,16]; but there are specific criteria that should raise suspicion of the diagnosis, as initially proposed by the World Health Organization (WHO) and already mentioned before [17].

Recently, the Center for Disease Control and Prevention (CDC) adapted and supplemented certain criteria proposed by the WHO [18]:

- An age of up to 21;
- clinical criteria:
    a. a fever > 38.0℃, lasting at least 24 hours and,
    b. a severe picture requiring hospitalization and,
    c. two or more organ damage (gastrointestinal, dermatological, cardiological, neurological, renal or hematological);
- biological inflammation, with one or more abnormalities:
    a. high C-reactive protein (CRP), procalcitonin (PCT), sedimentation rate (ESR), fibrinogen, D-dimer, ferritinemia, lactate dehydrogenase (LDH) or interleukin (IL-6); neutrophilic polynucleosis or lymphopenia; low albumin;
- SARS-CoV-2 infection
    a. biologically proven (PCR, serology or antigen) or,
    b. contact with a person infected with SARS-CoV-2 within the previous 4 weeks;
- No differential diagnosis.

The clinical and biological picture similarities between these different entities mean that the diagnosis of MIS-C must be justified so as not to omit a differential diagnosis for which the appropriate therapeutic management would be different.

4.3 Pathophysiological Profile

It is believed that the inflammation and endothelial damage caused by SARS-CoV-2 mainly affects blood vessels [19], which corresponds to the immunobiological characteristics of Kawasaki disease. Although the exact pathophysiological mechanisms of childhood multisystem inflammatory syndrome remain to be determined, the presence of antibodies to SARS-CoV-2, the specific T cell-mediated immune response, and the onset of symptoms after peak of acute infection suggest that acquired immunity plays a role in its development, for example by promoting the penetration of the virus into cells or by triggering a pro-inflammatory response mediated by antibodies or immune complexes [19,20]. This possibility has important implications for vaccine development and is being actively studied by researchers.

4.4 Typical Table

Analysis of different studies shows that the average age is around 8 years old, but MIS-C can affect all pediatric age groups [2], [21], [8], [9], [22]. Most patients have few comorbidities in European series. However, overweight or obesity seem to be more represented [21,22].

The majority of patients have fever for more than 3 days. In our series, the clinical picture is dominated by digestive signs (83% of cases) such as abdominal pain; vomiting and diarrhea; mucocutaneous signs in almost the majority of patients with at least one sign in each of them; and hemodynamic disorders such as myocarditis and cardiogenic shock which seem to be frequent acute complications of this infectious

syndrome. In European studies, the clinical picture includes gastrointestinal symptoms which are often very common (85% of cases) such as diarrhea, vomiting or abdominal pain, mucocutaneous symptoms (75%) reminiscent of KS (rash, non-purulent conjunctivitis, cheilitis, edema of the hands or feet) and poor general condition with lethargy rather than irritability. Some children have a surgical abdomen and have had a laparotomy with finding of mesenteric lymphadenitis, peritonitis or white laparotomy. In the American study of 186 cases [8], cardiac involvement was present in 80% of cases, with hypotension or a state of shock requiring vasoactive drugs in 48% of cases. Half of the children therefore have acute circulatory failure at the time of diagnosis or within 36 hours of their hospitalization. In this situation, they must be hospitalized in intensive care units, as soon as possible, for inotropic support ± non-invasive or invasive ventilation, in combination with immuno-modulator treatment [23]. Unlike KD, there is no significant coronary involvement, or it is rare and transient. It is possible that these children have a higher thrombotic risk due to significant abnormalities of hemostasis, but the various pediatric studies do not describe clinical thromboembolic events.

Biologically, all patients have a major inflammatory syndrome with a very significant elevation of markers such as CRP, PCT, ESR and/or serum ferritin. Frequently, lymphopenia, neutrophilic polynucleosis, thrombocytopenia and elevated D-dimer levels are noted. Some patients have hyponatremia, renal failure or hypoalbuminemia. In the American series, 73% of patients had very high BNP and 50% high troponin. Although the troponin level can be abnormal in MIS-C, it is usually moderate [8]. Indeed, it is essentially the level of NT-proBNP or BNP which is very high in the severe forms, going up to 20,000 pg/mL for a norm lower than 400. This shows that heart failure, secondary to myocardial stupefaction, is at the forefront in this disease, much more than myocarditis. The NT-proBNP or BNP assay must therefore be part of the initial biological assessment, when MIS-C is suspected. At the peak of the epidemic in April 2020, some pediatric emergency services acquired a relocated biology device to help guide patients. Thus, the significant elevation of BNP, which is a sign of heart failure, required transfer to intensive care rather than to a traditional hospital ward. This mode of screening has enabled emergency physicians to have a biological evaluation, at the patient's bedside, of the degree of heart failure. In addition to being of great help in hospitals that do not have rapid access to echocardiography, this screening makes it possible to limit referral errors (secondary emergency transfer to intensive care) and to optimize management. beds during the endemic period. Finally, as KS is very well known to pediatric emergency physicians, the BNP assay can help differentiate MIS-C with cardiac involvement requiring vasopressor/ inotropic support from severe KS but without heart failure. In the English study of 58 cases [9], the presence of a state of shock was correlated with an elevation of inflammation markers (CRP, neutrophils, etc.) and cardiac markers (NT-proBNP and troponin).

It should be kept in mind that when SARS-CoV-2 infection is not proven by positive serology, PCR or antigen detection, tracing contact with patients with COVID -19 in the 4 weeks preceding the diagnosis is sufficient to consider it. The initial interview, if well conducted, can therefore be of great help in the diagnostic process.

4.5 Assessment and Support

In July 2020, the American College of Rheumatology (ACR)13 and the Canadian Pediatric Society (CPS) [24] published clinical guidelines on the diagnostic evaluation and management of suspected cases of multisystem inflammatory syndrome of the child. When suspecting this syndrome, the clinician should consider the possibility of other infectious and non-infectious etiologies. It must also take into consideration the local prevalence of COVID-19, since the syndrome has a temporal link with infection and exposure to SARS-CoV-2. Given the lack of data on which to base decisions, most guidelines err on the side of caution and cast a wide net in identifying patients at risk.

The clinical picture can deteriorate rapidly, after the admission of a child with MIS-C, with the onset of hypotension or a state of shock, within 36 hours of hospitalization. Therefore, patients with biological markers of heart failure (BNP over 1000 pg/mL) or significant inflammation (CRP over 200 mg/L) should be transferred immediately to a pediatric hospital with medical facilities. an intensive care unit. The additional examinations, to be prescribed on admission, are summarized below:

- Clinical evaluation with transfer to a pediatric intensive care unit for cardio-respiratory monitoring, if necessary.
- Opinion in a pediatric hospital in the slightest doubt.
- Biological evaluation:

    a. complete blood count with formula,
    b. blood ionogram, urea, creatinine,
    c. liver function: ALT, AST, albumin, bilirubin,
    d. cardiac markers: troponin and NTpro-BNP or BNP,
    e. ECBU,
    f. blood gases, lactates,
    g. inflammation markers: CRP, procalcitonin, ESR, ferritin, triglycerides ± IL-6,
    h. coagulation: TP, TCA, fibrinogen, D-dimers,
    i. creatinine kinase, lactate dehydrogenase,
    j. blood culture,
    k. SARS-CoV-2 serology,
    l. SARS-CoV-2 PCR,
    m. copro/virology in the event of gastrointestinal symptoms.

- Imaging:

    a. chest X-ray,
    b. abdominal ultrasound or computed tomography in case of symptoms.

- Electrocardiogram
- Echocardiography/cardio pediatrician opinion
- Early advice from specialists to help with treatment.

In our series, all patients received intravenous immunoglobulins at a dose of 2g/kg and empirical antibiotic therapy based on Ceftriaxone at 100mg/kg/d. 45.45% of patients received systemic corticosteroid therapy 10mg/kg/day of Methylprednisolone followed by oral relay in whom the fever persisted 36 hours after the IVIG injection. 27.27% took advantage of diuretics and ACE inhibitors for heart failure. A patient benefited from oxygen therapy and vascular replacement for manifestation of signs during her hospitalization. In multiple series, treatment with IVIG, systemic corticosteroid therapy and oxygen therapy constitutes the basis of the therapeutic management of MIS-C. Due to the pathophysiological similarities with Kawasaki disease, the interest of IVIG can be assumed through the various already known effects of IVIG and their projection on the pathophysiology of MISC such as inactivation and triggering of apoptosis of T lymphocytes. self-reactive [25]; blocking the proliferation and differentiation of B lymphocytes as well as the production of antibodies by plasma cells [26,27]; and the reduction and control of the destructive activity of Macrophages [28,29].

The interest of corticosteroids, in particular Methylprednisolone, in controlling hyper inflammatory states and reducing the incidence of coronary lesions has already been proven [30]. However, their use in combination with IGIV for the management of myocarditis is of greatest importance and specifically in patients with extremely impaired LVEF [31,32].

4.6 Evolution

The prognosis of MIS-C requires further characterization, but overall appears positive as most children have full clinical recovery. The course in MIS-C can be quite severe, with many cases requiring intensive care unit management; The vast majority of children survive, but deaths have been reported [33-35].

In a meta-analysis of 16 case series including a total of 655 patients with MIS-C, there were 11 deaths (1.7%) [35]. In another case series of 2818 patients hospitalized with MIS -C from February 2020 to March 2021, of whom 35 died, the risks of death were higher among 16 to 20 year olds than among 6 to 11 year olds and among those with at least one comorbidity [36]. People with stroke, kidney failure or liver failure were 38, 12 and 11 times more likely to die, respectively, than those without the complications. Of more than 5,000 cases reported to the US CDC in October 2021, less than 1% of patients had died [37].

4.7 Outlook

Elucidating the pathogenesis of MIS-C will be critical for information strategies and possible preventive measures. More robust data are needed to determine risk factors for MIS-C, the most effective treatment, and prognosis. The presence of genetic factors predisposing to severe forms of SARS-CoV-2 in adults, discovered in 15% of cases, could also be identified in some children, thus predisposing them to severe MIS-C [38,39]. Long-term follow-up of patients with MIS-C is imperative to identify

possible sequelae. Immunological studies on the cell- and cytokine-mediated immune response should provide insight into the pathogenesis of this novel entity. The creation of MIS-C patient registries in different countries (and therefore in different ethnicities) should lead to a better understanding of the pathogenesis of MIS-C. Therapeutic management was largely inspired by that of severe KD. We can hope that the numerous studies in progress on MIS-C will also serve to better understand KS, the etiopathogenesis of which has still not been fully deciphered more than 50 years after its discovery [40], and also to optimize treatment in therapeutic management [41].

5. CONCLUSION

The multisystem inflammatory syndrome in children is a new pathology recently described following exposure to SARS-Cov2. Although it has similarities with MK, it has its own epidemiological, clinical, biological, radiological, therapeutic and evolutionary specificities making this syndrome a separate entity. The pathophysiology of MIS-C is not well understood. It is thought to result from an abnormal immune response to the virus occurring after the acute infection has passed. Most affected children have positive serology for SARS-CoV-2.

MIS-C can occur at any age, most commonly in previously healthy children between the ages of 6 and 12. They usually occur after 3 to 6 weeks following exposure to Covid-19 [8]. This syndrome should be suspected in any young child with persistent fever for more than 3 days, gastrointestinal symptoms, mucocutaneous involvement and/or signs of shock. The rarity of this syndrome does not detract from its seriousness: Cardiogenic shock following myocarditis is the most frequent and serious complication. IVIG and systemic corticosteroid therapy form the basis of therapeutic management.

To better understand this new syndrome and guide the decision clinical decisions, we must apply a rigorous scientific approach in the collection and analysis of data, including agreeing on universal definitions.

DISCLAIMER

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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