ORIGINAL ARTICLE

Cardiovascular Spectrum and Cardiac Biomarkers in Pediatric Inflammatory Multisystem Syndrome with Kawasaki-Like Disease - Our Experience During the COVID-19 Pandemic in the West Part of Romania

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ABSTRACT

Aim. In COVID-19 Pandemic, a new hyperinflammatory syndrome was reported with clinical features of Kawasaki disease, named PIMS-TS. We want to present a single center experience where the patients were diagnosed with Kawasaki-like in PIMS-TS with cardiac affliction.

Material and method: The study was observational and retrospective, enrolled 14 patients fulfilling the criteria of PIMS-TS with the median age of 9 (IQR, 1.6-11), 9 male (64.2 %) and 5 female (35.8 %).

Results: ECG revealed tachycardia and ST-T changes in 60% of patients. In evolution, ECG modified in 20% and consisted of long QT in 7% of cases, bradycardia in 7%, 3% transitory sick sinus syndrome and 3% grade I/II degree atrio-ventricular block. Cardiac disfunction was evidenced in 4 patients (28%), with reduced ejection fraction under 50%, mitral insufficiency in 6 (42.8%), pericardial fluid in 8 (57.1%) and perivascular brightness in 8 (57.1%). The cardiac biomarkers: NT-proBNP (increased in 9), cTroponin T (increased in 7) and cTroponin I (increased in 5) confirmed heart dysfunction. During the hospitalization and under medical treatment, all the modifications recover. Evolution was good for 12 children.

Conclusions: Cardiac dysfunction and myocardial injury were confirmed by elevated cardiac biomarkers. Rapid recognition allows prompt treatment for a good outcome. NT-proBNP, cTroponin T and I are of capital significance in monitoring the myocardial injury, the treatment and evolution of these patients.

Keywords: PIMS-TS, Kawasaki-like disease, multisystemic hyperinflammatory syndrome, cardiac biomarkers, SARS-CoV-2.

Rezumat

Scop: În timpul pandemiei de COVID-19 s-a raportat un nou sindrom hiperinflamator multisistemic pediatric, similar cu boala Kawasaki, denumit PIMS-TS. Prezentăm experiența unui singur centru unde au fost diagnosticați pacienți cu boală Kawasaki-like din PIMS-TS cu afectare cardiacă.

Material și metodă: Studiul a fost observațional și retrospectiv, înrolând 14 pacienți cu criterii de PIMS-TS, cu vârsta medie de 9 ani (IQR, 1,6-11), 9 băieți (64,2%) și 5 fete (35,8%).

Rezultate: ECG a relevat tahicardie și modificări de segment ST-T în 60% din cazuri. În evoluție, ECG s-a modificat la 20% din pacienți, înregistrându-se QT lung în 7% din cazuri, bradicardie în 7%, 3% au prezentat disfuncție de nod sinusal tranzitorie și 3% bloc atrioventricular de grad I/II. A fost prezentă disfuncție cardiacă la 4 pacienți (28%), cu fracție de ejecție sub 50%, insuficiență mitrală la 6 (42,8%), pericardită lichidiană la 8 (57,1%) și hiperecogenitate perivasculară la 8 pacienți (57,1%). Biomarkerii cardiaci: NT-proBNP (crescuți la 9 pacienți), cTroponina T (crescuți la 7 pacienți) și cTroponina I (crescuți la 5 pacienți) au confirmat disfuncția cardiacă. Pe perioada spitalizării, sub tratament medicamentos, toate modificările s-au recuperat. Evoluția a fost favorabilă pentru 12 pacienți.

Concluzii: Disfuncția cardiacă și injuria miocardică au fost confirmate prin valori crescute ale biomarkerilor cardiaci. Recunoașterea timpurie permite inițierea promptă a tratamentului, cu rezultate favorabile. NT-proBNP, cTroponina T și I sunt de importanță capitală în monitorizarea injuriei miocardice, a eficacității medicatiei și evoluției acestor pacienți.

Cuvinte cheie: PIMS-TS, boală Kawasaki-like, sindrom hiperinflamator multisistemic, biomarkeri cardiaci, SARS-CoV-2.

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INTRODUCTION

A highly contagious Corona virus disease was described in Wuhan, China in 2019 and it was involved in producing a severe acute respiratory syndrome, named SARS-CoV2 or Corona virus disease, COVID-19. This viral infection was extremely contagious, affecting mainly the elderly, people with comorbidities such as diabetes, hypertension, obesity, with an increased risk for death in these categories, in contrast with children in which the infection was mild. Hardly any children developed pneumonia, acute respiratory failure or sepsis with indication for PICU admission and treatment.

In April 2020, journals in England informed about an increase number of children with fever, hyperinflammatory syndrome, clinical features similar to Kawasaki disease, toxic shock syndrome, macrophage activation, gastro-intestinal, neurologic and multiorgan involvement. It seemed to be a new inflammatory disease in children with diverse clinical features[1]. Soon after, France signaled the same problem[2,3]. Italy also confirmed an impressive number of Kawasaki-like patients admitted into hospitals with hyperinflammatory syndrome and multisystem involvement[4]. In April 2020, the National Health Service from England was the first institution in Europe to define the syndrome as Pediatric Inflammatory Multisystem Syndrome (PIMS) temporally associated with SARS-CoV-2 infection, or PIMS-TS. The Royal College of Pediatrics and Child Health (RCPCH), from England, define PIMS and elaborate a guideline[5]. They established the disease as persistent fever accompanied by inflammation, evidence of single or multiorgan dysfunction, with full or partial criteria for Kawasaki Disease, after exclusion of other microbial cause, toxic shock syndrome, where the confirmation of SARS-CoV-2 infection was a defining criterion. Across the ocean, the situation was similar. The Center for Disease Control and Prevention (CDC) and World Health Organization (WHO) simultaneously defined this disease as Multisystem Inflammatory Syndrome in children (MIS-C)[6,7]. A new definition came from Canada, similar to the one the RCPCH elaborated. In theory, the aspects defined by all were akin, with minor differences, except for the proof of COVID-19 infection, which was mandatory in the WHO definition and CDC and not necessary for RCPCH and Canadian Pediatric Surveillance Program (CPSP)[8]. The definitions from all these organizations are mentioned in Table 1.

The clinical features in PIMS are comparable to Kawasaki disease, but also to incomplete Kawasaki disease, which is why we made a comprehensive comparison in Table 2. following the criteria proposed by American Heart Association (AHA)[9].

There are some overt differences between KD and PIMS, after the definitions proposed by RCPCH, CDC and WHO, which are mentioned in Table 3.

AIM

We want to present a single center experience, from the west part of Romania, where patients were admitted between April 2020 until April 2021 with: fever for more than 5 days, features of Kawasaki Disease, complete or incomplete, various organ dysfunction and hyperinflammation, criteria related to PIMS-TS, after the RCPCH definition at that time. The study was observational and retrospective.

MATERIAL AND METHODS

A lot of 14 patients were admitted to the IIIrd Pediatric Clinic from the Emergency Hospital for Children „Louis Turcanu", Timisoara, Romania between April 2020 – April 2021, fulfilling the criteria for PIMS-TS. The patients were examined clinically, by ECG, Echocardiography, cardio-pulmonary Xray and abdominal ultrasound and had laboratory investigations done,

Table 1. Comparison between the definitions of PIMS-TS established by RCPCH and CPSP and MIS-C defined by CDC and WHO

Organization	RCPCH	CPSP	CDC	WHO
Name	PIMS-TS	PIMS-TS	MIS-C	MIS-C
Age of child	Child	< 18 years	< 21 years	0-19 years
Fever-duration	Not specified	> 3 days	> 24 h	> 3 days
Inflammation	+	+	+	+
Organs affected	1 or multiple	Not specified, but affected	≥ 2	≥ 2
Exclusion of other causes	Must	Must	Must	Must
Proof of the SARS-CoV-2 infection	**Not necessary**	**Not necessary**	Necessary	Necessary

Table 2. Diagnostic criteria for KD and incomplete KD, proposed by AHA

Kawasaki Disease (KD)	Incomplete Kawasaki Disease
Fever ≥5 days + 4 from 5 criteria:	Fever ≥5 days + <4 criteria of classic KD
• Bilateral aseptic conjunctivitis	And CRP ≥30 mg/dl, ESR ≥40 mm/h
• Erythema and cracking lips, strawberry tongue	With positive echocardiography
• Rash, erythroderma, erythema multiform like	Or 3 from the following:
• Unilateral lymphadenopathy	• Anemia
• Erythema and edema of the hands and feet	• WBC ≥ 15.000/mm^3
	• Thrombocytes ≥450.000/mm^3 after 7 days
	• Albumin ≤3 g/dl
	• ALT elevated
	• Urine ≥10 WBC/hpf

Table 3. Clinical features and laboratory findings in Kawasaki Disease children compared with PIMS patients

Clinical feature/Lab	Kawasaki Disease	PIMS
Age of child at presentation	<5 years old	7-8 years old
Gastro-intestinal symptoms	+/-	+++
Cardiac dysfunction	+	++
Coagulopathy	+/-	++
Macrophage activation syndrome (MAS)	+/-	++
Shock	+/-	++
CRP	++	++++
Ferritin	+/-	++
DDimers	+	++
Cardiac biomarkers: NT-proBNP, Troponin I	+	++
Thrombocytopenia	Rare	++

including cardiac biomarkers: NT-proBNP, cTroponin T and I, CPK-MB. Blood, urine and selective cerebrospinal fluid were collected, to exclude other viral infections such as: Ebstein Barr virus, Adenovirus, Coxsackie virus, Cytomegalovirus, Parvovirus, Enterovirus or bacterial infections. Interleukin 6 and Soluble receptor for interleukin 2 were collected from the beginning to confirm vasculitis and macrophage activation syndrome. The panel of laboratory investigations included: Complete blood count, CRP, ESR, Fibrinogen, Procalcitonin, blood gas with lactate, LDH, Coagulation, D-dimer, Ferritin, Triglycerides, TGO, TGP, amylase, glucose. All the patients were tested RT-PCR for SARS-CoV-2 infection at admittance and if the result came back negative, we collected IgG antibodies against SARS-CoV-2.

The ECGs were performed on a Schiller AT[10] machine with 12 leads, at admittance and in some cases were repeated daily. Echocardiography was performed with Vivid E9 GE and Toshiba Aplio XG machine, at admittance and when necessary, followed up daily. Left ventricle ejection fraction was performed using Teicholz and Simpson methods, with a normal range ≥50% and severe impairment <30%. The myocardial performance index was also performed for left ventricle function. Mitral annular plane systolic excursion (MAPSE) and tricuspid annular systolic plane excursion (TAPSE) were used to quantify the ventricular longitudinal function[10]. For the LV diastolic function, pulse wave mitral E/A and mitral E/E' with tissue Doppler, were measured. Mitral regurgitation was quantified in color Doppler, pulse and continuous wave Doppler. Coronary Artery Z score was calculated after measuring the left, right, circumflex and left anterior descending coronary arteries in 2D[11]. Pericardial fluid was measured, to reveal small, medium or large amounts of fluid.

Collected data were analyzed using Microsoft Excel and referred to as numbers and percentages. For continuous data, inter quartile range (IQR) was used, to

define median value, obtaining the highest and lowest result.

RESULTS

The 14 patients with PIMS-TS from this study had the median age of 9, (IQR, 1.6-11) a minimal age of 4 months and a maximal age of 16 years old. Under the age of 5 there were 5 patients (35.7%), the remaining patients were over the age of 6 (64.3%) (Figure 1).

From this lot of patients, 9 children were male, 64.2% and 5 were female, representing 35.8% (Figure 2).

All these patients presented with fever for more than 5 days. The clinical features corresponded with Kawasaki Disease in one case only and Incomplete Kawasaki, or Kawasaki-like, a new terminology used to cover this clinical spectrum, in the remaining 13 cases (Figure 3). The clinical aspect of complete Kawasaki disease consisted of: aseptic conjunctivitis due to vasculitis, red and cracked lips, strawberry tongue, unilateral latero-cervical lymph node, rash, edema of the hands and feet, picture which was not consistent in the remaining 13 patients with Kawasaki-like from PIMS.

At admission, fever was present in all patients and evidence of organ involvement was noted. In our cohort, organ involvement was represented by: the brain, in 9 patients (64.2%), with neurological signs: seizure 1 case (7,1%), aseptic meningitis 1 case (7.1%), marked restlessness due to cerebral vasculitis in 8 cases (57.1%), headache 2 cases (14.2%); the gastro-intestinal tract, involved in 9 cases (64.2%), with vomiting and diarrhea 1 case (7.1%), nausea and vomiting in 1 case (7.1%) and the remaining patients with diarrhea and abdominal pain; the skin tissue with rash due to vasculitis was found in 9 patients (64.2%); the respiratory tract involvement appeared in 2 patients (14.2%), expressed by respiratory distress due to pneumonia; the osteo-articular system, involved in 2 cases with symptomatic arthralgia (14.2%); 4 patients presented aseptic conjunctivitis at the beginning (28.5%). All data is disclosed in Figure 4.

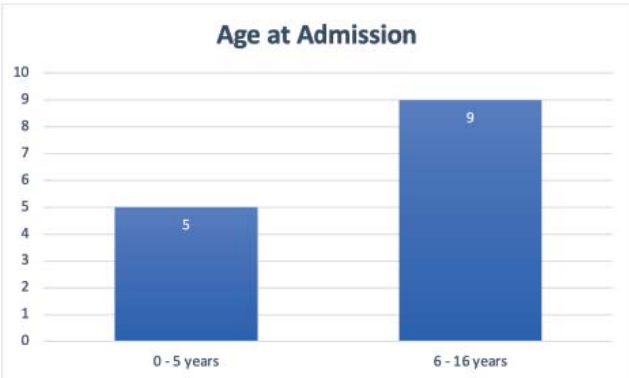

Figure 1. Age related cases.

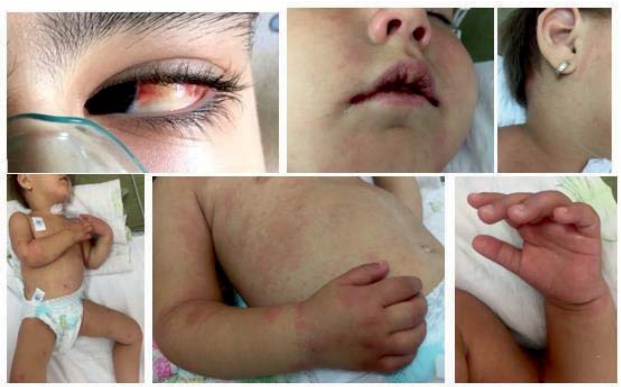

Figure 3. Patients with PIMS and Kawasaki-like clinical features (from left to right, upper and lower row: aseptic conjunctivitis, red and cracked lips, unilateral latero-cervical lymph node, rash, edema of the hands). From our personal collection.

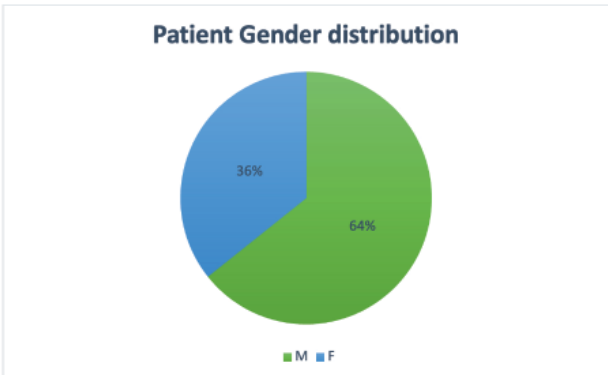

Figure 2. Gender distribution.

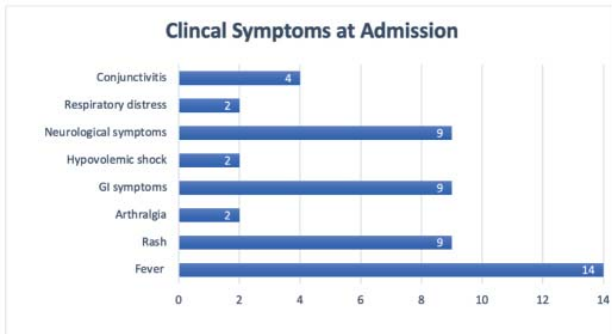

Figure 4. Clinical symptoms at admission.

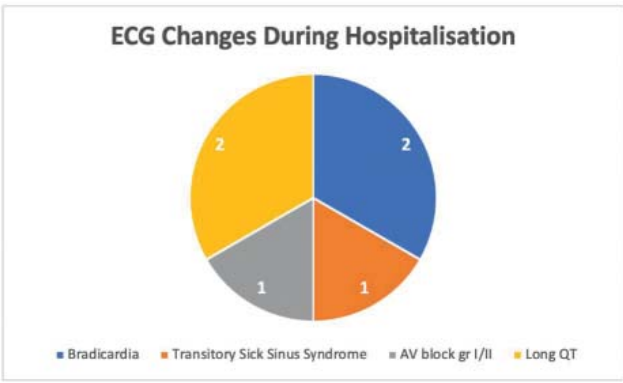

Figure 5. ECG changes during hospitalization in 6 patients.

Cardiac examination was clinical, ECG and Echocardiography. At the clinical examination, in the Emergency Department, almost all patients were tachycardic due to fever and anxiety. One patient had an uncorrected heart malformation, atrioventricular septal defect, complicated with heart failure and pulmonary hypertension. No significant modifications on blood pressure were registered at admittance. ECG was performed in all patients, where tachycardia and ST-T changes were detected in 60% of children. In evolution, abnormal ECG was detected in 20% of patients and consisted of long QT in 7% of cases, bradycardia in 7% of children, 3% transitory sick sinus syndrome and 3% grade I/II degree atrio-ventricular block (Figure 5). All these modifications normalized upon discharge. Echocardiography was performed in 100% of patients and revealed cardiac disfunction in 4 patients, 28% of children, with reduced ejection fraction under 50%, mitral insufficiency in 6 patients, 42.8% of cases, pericardial fluid in 8 patients, representing 57.1% of cases and perivascular brightness also in 8 patients, representing 57.1% of cases (Figure 6). No coronary artery dilatation or aneurysms were found, except for the perivascular brightness (Figure 7). During hospitalization and under medical treatment, all the alterations recovered in time, except for the perivascular brightness which persisted at discharge. The patients were monitored after discharge, weekly, to look for coronary artery dilatation and/or aneurisms, which were not found.

Regarding the SARS-CoV-2 infection, the RT-PCR (real time polymerase chain reaction) test was positive in one case only (7.1%). The remaining 13 patients were RT-PCR negative for Covid at admittance and were tested for SARS-CoV-2 IgG antibodies which were positive in 5 patients (35.7%) and negative in the remaining 8 patients (57.14%).

The laboratory investigations at admittance were collected for a general panel, but also focused on PIMS and on possible complications as macrophage activation syndrome. The most important laboratory investigations are described in Table 4.

Of the entire lot, 8 cases, which represent 57.1%, developed a severe complication, macrophage activation syndrome (MAS). The diagnosis was made based on high ferritin level >684 ng/ml, and two of the following: platelet count ≤181000/mm^3, aspartate aminotransferase (AST/TGO) >48 U/L, triglycerides >156 mg/dl, fibrinogen ≤360 mg/dl[12]. The confirmation came in 7 patients, 50%, where soluble receptor for Interleukin 2 was very high (median value 8749 kU/l; IQR, 1543-11383 kU/l), considering the normal range between 158-623 kU/l (Table 5). The 8th patient, due to the severity of his clinical status and evolution, the soluble receptor for Interleukin 2 was not collected. Thrombocytopenia was a sign of severe disease in Kawasaki-like patients. The inflammatory probes

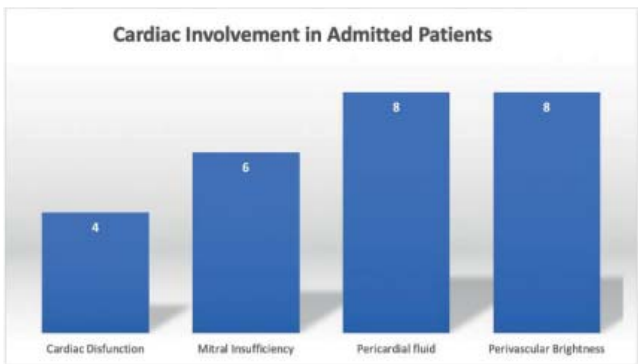

Figure 6. Cardiological involvement in Kawasaki-like from PIMS in COVID-19 Pandemic in our cohort, after admission.

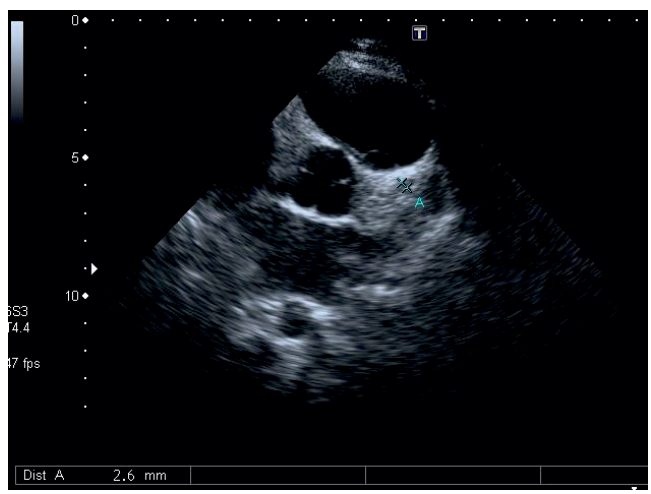

Figure 7. Echocardiography: parasternal short axis through aorta – perivascular brightness with normal coronary arteries.

Table 4. Laboratory investigations related with treatment

Patient	CRP < 5 mg/dl	Ferritin 20-200 ng/ml	D-dimer < 250 ng/ml	Fibrinogen 200-400 mg/dl	IgG Antibody against SARS-CoV-2 < 33 BAU	IVIG	Steroids	Anticoagulant	Inotrope medication
1.	128	895	6215	633	0.13	+		+	
2.	78	132	3578	310	0.54		+		
3.	260	792	8657	529	-	+	+	+	+
4.	17	67	209	240	0.61		+	+	
5.	3.43	98	278	238	60	+	+	+	
6.	107	651	3228	279	14.4		+		
7.	165.59	980	3080	148	8.4	+	+	+	
8.	232	1870	3347	509	4.84	+	+	+	+
9.	143	1612	409	362	76	+	+	+	
10.	258	1314	660	162	251	+	+	+	
11.	72.63	100000	3404	23	0,2	+	+		+
12.	0.6	17105	11987	107	716	+		+	+
13.	159	330859	69000	100	5		+	+	
14.	73.73	143	992	169	1420		+	+	

Table 5. Cardiac biomarkers, IL6 and Soluble receptor IL2 in our cohort

Patient nr.	NT-proBNP pg/ml NV depending on age	cTroponin T NV<14 pg/ml	cTroponin I NV<34.2 pg/ml	CK MB NV<5 ng/ml	IL6 NV<7 pg/ml	Soluble receptor IL2 NV 158-623 kU/l
1.	339.4	4.59	0.6	0.49	3.06	-
2.	468.8	8.39	-	-	38.41	-
3.	3101	34	36.2	2.15	162.3	11000
4.	131	30.31	19.9	1.41	-	-
5.	124	40.49	27.4	-	4.27	-
6.	27408	92.36	190.7	<0.18	44.44	6599
7.	7188	9.24	7.4	<0.18	251.56	11383
8.	14922	81	186	-	403	-
9.	6437	64.62	147.6	0.57	51.93	4842
10.	11972	18.7	25	0.58	74	9689
11.	-	-	-	-	468275	8749
12.	11043	-	848	-	13.96	-
13.	74	4.5	3	-	12.51	1543
14.	67	<3	<0.1	-	29.04	-

were positive. The CRP (C reactive protein) was increased in 12 patients (85.7%), with median 135.5 mg/dl (IQR, 17-260 mg/dl) as a marker of inflammation. It was confirmed by increased ESR. Fibrinogen, also an inflammatory marker, was increased in 3 patients (21.4%), normal in 5 patients (35.7%) and decreased in 6 patients (42.8%). Ferritin was increased in 10 patients (71.42%) due to the hyperinflammation and macrophage activation syndrome (median1460 ng/ml; IQR, 651-320859 ng/ml). The D-dimers were increased in almost all patients (92.8%), with one exception (median 3347 ng/ml; IQR, 278-69000 ng/ml). All data is mentioned in Table 4.

Cardiac biomarkers were collected in almost all, with some exceptions, marked in Table 5. NT-proBNP, biomarker for heart failure was increased in 9 patients

(64.2%), with median 7188 pg/ml (IQR, 339.4-27408 pg/ml), normal in 4 patients (28.5%) and missed in one very severe case who deceased shortly after admission (Figure 8). The second cardiac biomarker determined was cTroponin T, a protein released when the cardiac muscle is damaged. The values were increased in 7 patients (50%), with median 40.49 pg/ml (IQR, 18.7-92.36 pg/ml), normal in 5 patients (35.7%) and missed in the 2 most severe admitted cases (14.2%) (Figure 9). We decided to compare cTroponin T with cTroponin I at admittance, so blood samples were collected for cTroponin I also, which was increased in 5 patients (35.7%), with median 186 pg/ml (IQR, 36.2-848 pg/ml), normal in 7 patients (50%) and not collected in 2 patients (14.2%), data that is mentioned in Figure 10. CPK-MB (creatine phosphokinase MB), cardiac fraction of CPK (creatin phosphokinase), to detect myocarditis was collected in 7 patients (50%), and was negative in all.

Interleukin-6 determination, to demonstrate cytokine storm, was increased in 11 cases (78.5%), with median 118.15 pg/ml (IQR, 38.41-468275 pg/ml), normal in 2 cases (14.2%) and not collected in one

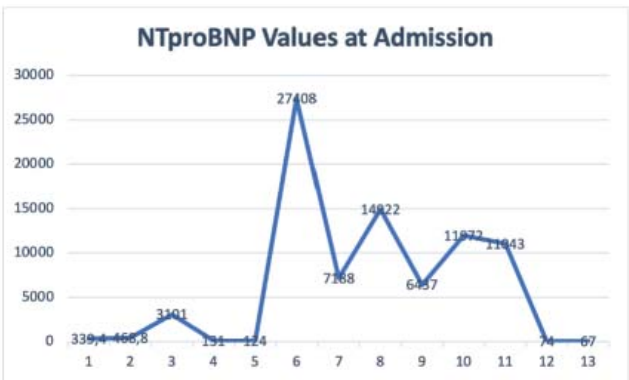

Figure 8. NT-proBNP values at admittance in our cohort.

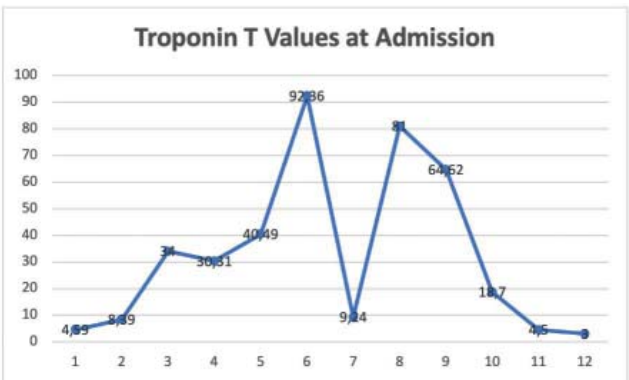

Figure 9. cTroponin T values at admission in our cohort.

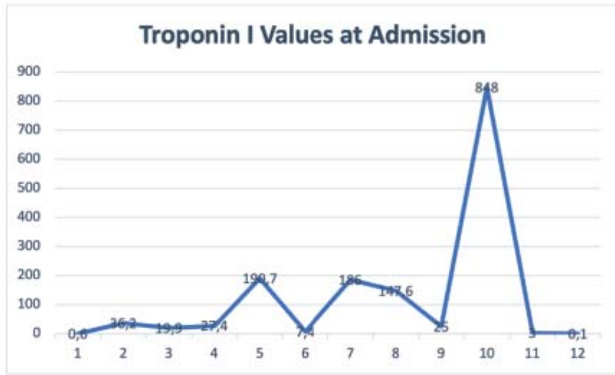

Figure 10. Troponin I values at admission.

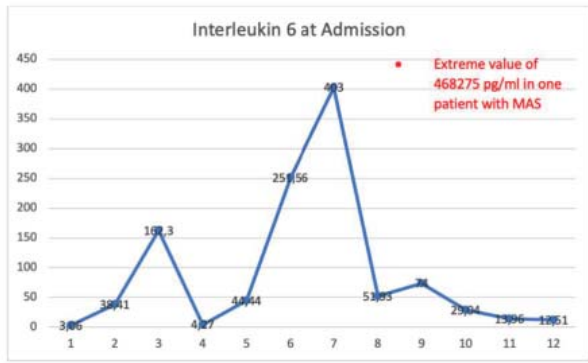

Figure 11. Interleukin IL6 at admittance.

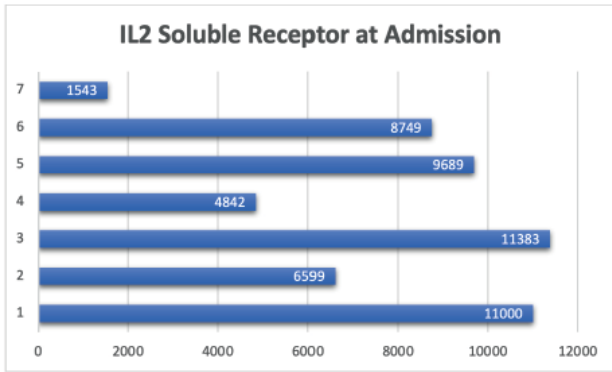

Figure 12. Soluble receptor for Interleukin IL2.

case (Figure 11). Soluble receptor for interleukin 2, a marker to confirm the macrophage activation syndrome, discussed above, was collected in only 7 patients (50%), and was positive for all of them, data mentioned in Figure 12.

Clinical features correlated with cardiological explorations, laboratory investigations and cardiac biomarkers aided us in the treatment decision for these patients, data corroborated in Table 4. Based on

the above, twelve children got steroid treatment at admittance, meaning 85.7% out of these patients, to slow down the inflammatory syndrome. First, we used Dexamethasone, but in some cases, it was replaced with pulse therapy with Methylprednisolone. During this time the lab tests were expected. From this group, only 5 children (35.7%) treated with steroids alone developed a favorable outcome. The rest of 7 children needed to associate intravenous immunoglobulin (IVIG). A total number of 9 patients were treated with IVIG representing 64.2%. Only 2 patients out of which one with clinical features of Kawasaki disease and the other with Kawasaki-like, were treated from the beginning with IVIG and aspirin, with a very good response. The dose of IVIG was 2 g/kg/day administered in one or two consecutive days. From our group, 7 patients (50%) received IVIG after steroid treatment.

Anticoagulation was necessary in 11 cases (78.57%), and was not administrated in 3 patients. The anticoagulant used was low molecular weight heparin (LMWH) in prophylactic dose and was administrated in patients with high value of D-dimers. Before discharge, low dose Aspirin, 3-5 mg/kg/day was introduced in parallel with LMWH. The latter was stopped at discharge. Patients were discharged with low dose Aspirin, which was maintained until normalization of the thrombocyte count.

Inotrope medication such as Dopamine or Dobutamine was necessary for 4 patients (28.5%). Out of these patients, 2 cases had a severe evolution towards exitus. Epinephrine was administrated in 2 cases with vasodilatory shock secondary to ventricular dysfunction in evolution. In patients with sepsis, empiric broad spectrum antibiotics were administered first, which were afterward replaced in accordance with the antibiogram.

The outcome of our patients was favorable with two exceptions. One patient with uncorrected heart malformation, complete atrio-ventricular septal defect, with heart failure, pulmonary hypertension, Kawasaki-like disease, hyperinflammatory syndrome, cytokine storm, multisystem involvement and macrophage activation, died despite all efforts. The second patient was admitted in a very poor condition, with hyperinflammatory syndrome, cytokine storm, macrophage activation syndrome, with severe low thrombocyte count and bleeding, periorbital ecchymosis, sepsis and shock, with no response to any treatment.

DISCUSSIONS

Since the pandemic occurred, COVID-19 infection affected many adults, but a small number of children, all of them with mild or lacking symptoms[13]. Despite that, a new affliction appeared, weeks from the COVID infection, very similar to Kawasaki disease, but accompanied by a hyperinflammatory syndrome affecting multiple systems of the body, mediated by a cytokine storm[14]. The RCPCH named this disease for the first time as PIMS-TS and soon after, WHO and CDC defined and named this affection as: MIS-C5-7. Cardiac involvement is a hallmark in all these patients, with the clinical aspect of Kawasaki disease, complete or incomplete, named Kawasaki-like, associated with other multiple organ involvement, hyperinflammation, toxic shock syndrome and/or macrophage activation syndrome, due to the cytokine storm[4,15].

Different articles mentioned the cardiac affliction in PIMS-TC/MIS-C in small or large cohorts of children[4,16-23]. The article of Verdoni mentioned that in the Italian epicenter of COVID in 2020, the incidence of Kawasaki disease increased 30-fold, it mainly affected older children than usual for Kawasaki disease, it induced myocardial injury and it could affect multiple organs due to a hyperinflammatory syndrome[4]. Belhadjer in another study of 35 patients with the same new illness, described cardiac disfunction with positive cardiac biomarkers, but with moderate increase in values and rapid resolution to normal, concluding that the heart failure was not determined by a real myocarditis[16]. Wittaker in his study on 58 children describes the differences between Kawasaki disease and MIS-C[17]. A very large study conducted by Valverde in 2020, based on a European survey, describes the myocardial involvement in PIMS, in a percentage of 93%, arrhythmia was present in 35% of children and shock in 40% of children[18]. Myocarditis could not be argued because the ventricular systolic function recovered very quickly, cardiac biomarkers, despite high values, stabilized rapidly, active COVID-19 infection could not be proven, no myocardial biopsy was necessary, and all of the clinical pictures were in the context of multisystem inflammatory involvement[18]. In their cohort, coronary artery involvement was present in 24% of children.

Our cohort of 14 cases comes to complete a clinical picture of Kawasaki-like disease in the context of PIMS in the west part of our country. Each pediatric hospital has its own patient particularities[22-24]. Regarding age, we separated the patients into groups, the

first one contained patients between the ages of 0 and 5 years, where 5 patients were included, the smallest of the group being 4 months old and the second group consisted of patients over the age of 6, where there were 9 patients, the oldest of which was 16 years old.

This separation in two groups could delineate the Kawasaki disease from Kawasaki-like from PIMS. Kawasaki Disease is characteristic for small children whereas, Kawasaki-like from PIMS includes older children with similar, but incomplete, clinical aspect as Kawasaki disease. In our cohort only one patient met the criteria for Kawasaki disease and was included in the 0-5 year age group, the remaining 13 patients were Kawasaki-like disease, with clinical signs consisting with the criteria elaborated by RCPCH, CDC, WHO, CPSP[5-8].

From this lot of patients, 9 children were male, 64.2 % and 5 were female, representing 35.8 % (Figure 2). In literature we found male dominance in varying percentage, between 51-73%[4,17,18,23,24], similar to our study.

At admission all patients presented fever, for more than 5 days, which did not respond to antipyretic drugs. There is a 100% similarity with all the other reports[18,23]. One patient fulfilled all clinical criteria for Kawasaki-disease, but the others, had only incomplete clinical features of Kawasaki. When referring to multiorgan involvement, the gastro-intestinal tract was affected in 64.2% with abdominal pain, nausea, diarrhea and vomiting, similar with the Valverde report in which gastro-intestinal involvement was 71.3%[18]. Neurological involvement was present in the same percentage, 64.2%, with: seizure, aseptic meningitis, marked anxiety, agitation and headaches. Compared with the European (EU) study on 286 children with MIS-C where neurological changes occurred in 15% of children, the percentage in our cohort was higher[18]. The skin involvement with rash due to vasculitis was found in 9 patients (64.2%), similar with the EU study, 62.6%[18]. The respiratory tract involvement appeared in 2 patients (14.2%), less than in EU, where it was 21.7%. The osteo-articular system, involved in 2 cases with symptomatic arthralgia (14.2%) and is less frequent compared with other studies. The same situation is with patients presenting aseptic conjunctivitis at onset (28.5%), lower than in EU study, where the percentage is 54.5%[18]. We found a similar percentage to the EU study in oral mucosa congestion and cervical lymphadenopathy[18]. Tachycardia was present in all patients at admission due to fever and anxiety. This was revealed on ECG at admission together with ST-T changes in 60% of patients, higher than in the European study where it was 20%, but the same with the report from the UK[18,24]. We stated changes in ECG during hospitalization with long QT in 7% of patients, also higher than in other studies (4.5%), bradycardia in 7% of patients, not mentioned in other studies, tachybrady arrhythmia in 3% of patients, also not mentioned, and grade I/II degree atrio-ventricular block in 3%, higher than in literature where it varies between 1.7-2.1%[18,24-26]. The ECG stabilized before discharge in all studies, like our findings.

Echocardiography revealed a reduction in ejection fraction in 28% of patients, lower than the data collected from EU centers, where it was 34%, and much lower than in England, where it was 80%, but the recovery was the same during hospitalization in almost all centers[18,24,27]. Mitral insufficiency was documented in all the studies with varying percentage values. Pericardial fluid was mentioned in 18% along Europe, but we found a higher value of 57.1%. The most interesting findings were the coronary arteries that were not affected in our study, compared with the report from England, where 93% of patients presented coronary artery abnormalities as: prominent, dilated or aneurysmal changes. Valverde reported the data collected from 55 centers along 17 European countries as: 24.1 % of coronary artery dilatation, affecting in order, the left main coronary artery in 16.4%, left anterior descending in 14%, right coronary artery in 11.9% and circumflex artery in 4.6%. Coronary artery echogenicity was described in a small number of patients by Henrina, however we found a study in which the perivascular brightness is present in 80% of the patients[22,25].

The SARS-CoV-2 infection was positive in 6 out of 14 patients in our cohort, despite the clinical picture and biological investigations that were similar in the remaining 8 children from the study.

This was also mentioned by the study of Valverde, where detection was positive in 65% of the 286 patients[18]. This is particular for Europe and Canada, where patients with criteria of Kawasaki-like and PIMS are accepted with or without proof of COVID infection. WHO and CDC do not recognize MIS-C without a positive RT-PCR or SARS-CoV-2 Antibodies[6,7,23]. We think that the RCPCH definition is more permissive and recommends treatment for patients with clinical features of PIMS with or without proof of COVID infection, which will promptly improve the clinical outcome of the patients.

All patients were tested for regular laboratory investigations, however special tests in order to detect

the cardiac involvement and macrophage activation syndrome, due to the hyperinflammation and cytokine storm were also collected. The cardiac biomarkers were NT-proBNP, cTroponin T and cTroponin I. The NT-proBNP was increased in 9 children, demonstrating heart disfunction. Unfortunately, it was not collected in one very severe case that deceased in the first 24 hours from admission due to the late presentation and severe multiorgan hyperinflammatory syndrome with severe cytokine storm, with an IL6 value of 468275 pg/ml (Normal value <7pg/ml), complicated with macrophage activation syndrome confirmed by Soluble receptor of IL2, with a value of 8949 kU/l (Normal value 158-623 kU/l). The NT-proBNP was very well correlated with cTroponinT and I, both increased in all the 9 cases. Between cTroponinT and I, much more sensitive was cTroponinI, with higher increased values, demonstrating cardiac injury. In two cases with borderline increased values of NT-proBNP, the cTroponin T and I were normal. CPK-MB was normal in all 7 children where it was collected, infirming myocarditis. Viral tests for infectious diseases that could affect the heart were all negative. The rapid normalization of the cardiac biomarkers came to confirm that heart affliction was not secondary to myocarditis, in which the evolution is not so swift towards normalization[28]. In Valverde and Henrina studies, the peak cardiac biomarker abnormality was at admission, with no increase during hospitalization, findings similar to our own[18,25]. Ten studies on the profile of NT-proBNP described a pooled mean of 13,590.78 pg/ml, higher than we obtained, 7188 pg/ml[25]. Regarding cTroponin T and cTroponin I, all data from 26 studies with 1228 subjects demonstrated increased values and confirmed cardiac injury, but with higher values of the pooled mean that we found[25]. When comparing sensitivity, we found that cTroponin I had a much higher sensitivity value than cTroponin T, these findings are in accordance with the data from the 26 studies[25].

The CRP and ESR were high from the beginning, with two exceptions. Eight cases developed Macrophage Activation Syndrome, a very severe complication, diagnosis based on the 2016 Classification criteria for Macrophage Activation Syndrome complicating Systemic Juvenile Arthritis (ferritin level >684 ng/ml, and two of the following: platelet count ≤181000/mm^3, aspartate aminotransferase (AST/TGO) >48 U/L, triglycerides >156 mg/dl, fibrinogen ≤360 mg/dl)[12,29,30]. The Ferritin levels varied in our cohort between 651 and 330859 ng/ml (Normal value 20-200 pg/ml). We found in literature a letter to the editor of Ravelly in which, the assumption was that a value of ≥ 10.000 ng/ml has the highest sensibility and specificity for MAS[12]. We had 3 values over 10 000 ng/ml (17105 – 100000 – 330859 ng/ml) considered to be with high sensibility and specificity for MAS, but the confirmation of MAS came from the Soluble Receptor for IL2, which was positive in all 7 cases, with a median of 8749 ng/ml (IQR, 4842-6158 ng/ml). The same data were mentioned by Hayden, Lin and Singh in their articles[31-33]. Interleukin 6 was positive in 11 children, with very high values, with a mean of 118,15 pg/ml (IQR, 38.41 – 468275 pg/ml) to confirm the cytokine storm, which was at the base of macrophage activation syndrome, confirmed in 7 cases from our study. One case who succumbed could not be evaluated for Soluble receptor for IL2, due to the severity of the disease at admittance. D-dimer were increased with one exception.

The treatment was started with corticotherapy: Dexamethasone or Metylprednisolone to reduce the inflammation in 12 patients. Two patients were treated from the beginning with IVIG and Aspirin, having clinical features of Kawasaki disease in one and Kawasaki-like in the other, both with good evolution. When the response to corticotherapy was not the one expected, with persistence of fever and clinical features of Kawasaki-like disease, IVIG was administered. This combination was given to 7 patients. Unexpectedly, 5 patients had a very good evolution on steroid treatment alone and did not need IVIG administration. MAS was confirmed in 7 patients, in which corticotherapy was maintained until inflammation was subdued. Thrombocytes were evaluated and Aspirin was maintained at a low dose, until thrombocytes stabilized. Broad spectrum antibiotics were associated when necessary. Anticoagulation was done with LMWH and maintained until DDimer normalization. Cardiac inotropes were introduced in 4 patients out of which two deceased due to heart failure and severe MAS. Epinefrine was necessary in the same four patients. The treatment was in accordance with the WHO, CDC, RCPCH indications, American College of Rheumatology and with Minnesota protocol[5-7,34-36]. Under treatment, the outcome was favorable with two exceptions. We did not find coronary artery aneurysms during the disease and after discharge, no thrombotic event, but we described perivascular brightness in almost all patients, fact found in literature, as we mentioned above.

We want to focus on 3 cases from our cohort, in which the diagnosis of PIMS was suspected from ad-

mittance, however, the first laboratory investigations collected could not sustain the inflammation. Further investigations, in evolution were necessary to confirm PIMS.

Patient number 4 was admitted for persistent fever, seizures, abdominal pain, vomiting, tachycardia, conjunctivitis. Despite the clear clinical picture, the inflammatory parameters were almost normal at admittance, with one exception, a slightly increased CRP. Cardiac biomarkers were negative. Soon after, the seizures became continuous, a rash appeared, and pulmonary rales were found. The blood pressure was normal. He was admitted in the ICU unit. A lumbar puncture revealed 5 elements, without any other pathological findings. Laboratory tests were repeated: Leucocyte count was 15600/mm^3, inflammatory probes increased: CRP became 42 mg/dl, Fibrinogen 402 mg/dl, Ferritin 242 ng/ml, D-dimers 399 ng/ml. This data is not mentioned in Table 4, because they were collected soon after admission. Cardiac examination revealed: mild mitral insufficiency, mild aortic insufficiency, pericarditis with small fluid accumulation and perivascular brightness of the coronary arteries. Cardiac biomarkers increased: NTpro BNP 2920 pg/ml, cTroponin T 100 pg/ml, cTroponin I 499 pg/ml. Complex treatment was initiated with favorable evolution.

Patient number 5 was admitted for persistent fever, seizures, restlessness, diarrhea, tachycardia and rash. At admittance, inflammatory probes were negative, normal Ferritin level, slightly increased D-dimers at 278 ng/ml, anemia 9.2 g/dl and thrombocytosis 580.000/mm^3, cTroponin T 40.49 pg/ml. The next day, echocardiography was performed and revealed mild mitral regurgitation and perivascular brightness of the coronary arteries. Repeated inflammatory probes increased over normal, Ferritin level became 390.5 ng/ml, platelets grew to 680.000/mm^3, NT proBNP became 126000 pg/ml. Under treatment, the evolution was favorable, cardiac biomarkers normalized, no aneurisms of the coronary arteries were detected in the follow up period, despite the thrombocyte level that increased at 1064000/mm^3. Aspirin treatment was maintained until thrombocyte level normalization.

Patient 12, with an unoperated heart malformation, complicated with heart failure and pulmonary hypertension, admitted for PIMS with Kawasaki-like disease, presented a significant discrepancy between the normal CRP and a huge Ferritin value of 17105 ng/ml due to Macrophage Activation Syndrome that rapidly developed, with thrombocytopenia 79.000/mm^3, high TGO 4209 UI/L and TGP 5601 UI/L, low Fibrinogen 107 mg/dl, high D-dimer 11987 ng/ml and unfavorable outcome. The CRP in evolution remained normal, without any explanation.

Regarding mortality in our cohort, it was higher than in the Valverde, where it was 1 case from 286 patients and Vhittaker, none from 58 patients[17,18]. The explanation has to come from the severity of the PIMS, rapidly complicated with MAS in two particular patients, one with heart malformation, heart failure and pulmonary hypertension and one supposed to be immunocompromised, in which genetic tests for primary HLH were collected. These situations were not mentioned in the above studies.

Limitation of the study consisted in the small number of children we had and, in the impossibility to collect special laboratory investigations, due to the severe clinical status in some patients at admittance.

CONCLUSIONS

PIMS-TS with Kawasaki-like disease from COVID-19 pandemic appears to be a rare but severe syndrome with hyperinflammation and multiorgan dysfunction, including the heart. Cardiac dysfunction, valvular regurgitation, pericardial fluid, perivascular brightness and myocardial injury were confirmed by elevated cardiac biomarkers. Rapid recognition allows prompt treatment for a favorable outcome. NT-proBNP, cTroponin T and I are of capital significance in monitoring the myocardial injury, the treatment and evolution of these patients. Complex teamwork: pediatrician, pediatric cardiologist, immunologist, rheumatologist, infectious disease and intensive care doctors need to collaborate in the diagnosis and treatment of these patients to reduce inflammation. Cardiac follow-up is necessary with vigilance after discharge, because the mechanisms of this syndrome are not fully understood.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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