

Cardiovascular involvement in Pediatric multisystemic inflammatory syndrome temporally associated with COVID-19 infection

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ABSTRACT

In 2020, World Health Organization declared the infection with COVID-19 a pandemic. Even though the risk of infestation and mortality is lower in children than in adults, children are more prone to develop a hyperimmune state after COVID-19 infection called pediatric multi-system inflammatory syndrome or PIMS. In PIMS, cardiovascular involvement with myocardial injury is present in most patients. Due to the novelty of this pathology, little is known about the implication on the cardiovascular system.

This review focuses on the most recent data published on the pediatric multi-system inflammatory syndrome associated with COVID-19 infection, pathophysiological mechanisms, and especially cardiovascular involvement. Furthermore, it emphasizes the role of pediatric cardiologists in its management.

Keywords: multisystemic inflammatory syndrome associated with COVID-19 infection, cardiovascular involvement, myocardial injury

INTRODUCTION

The novel Corona Virus (SARS COV 2- Severe Acute Respiratory Syndrome Coronavirus-2) was first reported in December 2019, with a rapidly spreading worldwide. The latest data from World Health Organization (WHO) reports a total number of over 7 million COVID-19 cases in children that are less likely to present with severe disease compared to adults [1,2]. In 2020, were first described cases of children that presented with a multi-inflammatory syndrome similar to Kawasaki disease (KD) [3]. Also, in May 2020, WHO presented for the first time a preliminary case definition for this Kawasaki-like disease [4]. Due to multi-systemic involvement and the hyperinflammatory state, in Europe was named pediatric inflammatory multi-systemic syndrome temporally associated with COVID-19 (from now on we will refer to it in this paper as **PIMS**), and in the

United States of America (USA) multi-systemic inflammatory syndrome in children (MIS-C) [5]. Since then, multiple cases were reported in children. Most patients present with severe cardiovascular involvement that may persist even in early follow-up. Therefore, this review aims to understand the cardiovascular involvement in children with PIMS and identify the role of a pediatric cardiologist in managing these patients.

DEFINITION

Multi-systemic inflammatory syndrome in children was first reported in April 2020 in the USA and Europe, after numerous previously healthy patients presented with Kawasaki-like symptoms, with a 30 times higher incidence of Kawasaki-like disease compared with previous years [3,6]. At the same time, the New York State Department of Health re-

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leased a health alert regarding PIMS [7]. However, despite the similarities with these pathologies, PIMS is now characterized as a standalone disease. World Health Organization, Royal College of London (RCPCH), and the Center for Disease Control and Prevention (CDC) have produced similar definitions of PIMS based on the case reports from different countries [4,8,9]. According to all definitions, PIMS is characterized by persistent fever, evidence of inflammation, multi-organ involvement, and evidence of SARS-COV 2 infection with Covid-19 (positive PCR or positive serology). However, there are some differences between the diagnostic criteria proposed. According to CDC, diagnosis of PIMS should be suspected in all patients below 21 years that present with fever ≥ 24 h and evidence of 2 or more systems involved [8]. The World Health Organization criteria of PIMS include patients from 0 to 19 years old with persistent fever ≥ 3 days, with evidence of 2 or more systems involved [4]. In contrast, RCPCH criteria do not specify the patients' age interval and the fever duration and state that the diagnosis of PIMS should be suspected if one or more organs are involved, without the necessary positive SARS COV-2 PCR or serology [9]. The majority of studies reported the presence of IgG antibodies (75-90% cases) with a negative polymerase chain reaction to COVID 19, suggesting a post-infectious inflammation caused by an immune response [10].

PATHOPHYSIOLOGY OF SARS COV-2 INFECTION AND PIMS IN CHILDREN

SARS COV-2 is a ribonucleic acid virus that belongs to the Coronavirus family. Like other Coronaviruses, SARS-COV-2 contains a spike protein that binds to the angiotensin-converting enzyme receptor (ACE-2 receptor) in targeted cells from the respiratory tract [2]. It is known that ACE-2 receptor expression in respiratory tract cells increases with age, with a lower expression in children [11]. Furthermore, it has been hypothesized that young children can present in the respiratory tract other types of viruses that can limit viral replication due to viral competition. Therefore, early infection with COVID-19 (viral phase) is usually mild or even asymptomatic in children. Once the infection is established and the virus enters in the target cell, an inflammatory response releases cytokines (pulmonary phase) [2]. In adults, the pulmonary phase is characterized by increased pro-inflammatory cytokines, with pulmonary barrier disruption and alveolar edema that leads to cytokine storm and acute respiratory disease syndrome (ARDS) or shock [11]. However, the immune system of children is different from adults: T cells from infants and children release a lower amount of pro-inflammatory cytokines after stimu-

lation, and B cell response to antigens is weaker [12]. Therefore, the pulmonary phase in children is characterized by increased immunomodulatory cytokines, without a hyperinflammatory response [2]. Due to an increased expression of focal adhesion kinase-1, the pulmonary endothelial cell barrier is better protected, with a lower risk of developing ARDS [13]. However, continuous stimulation of the immune system, with activated T-helper and B cells leads to an immune dysregulation with a hyperimmune response that is seen in PIMS. But the exact pathogenesis of PIMS is still unknown. At first, it was believed that the hyperinflammatory state from PIMS is similar to the hyperinflammatory response seen in adults with severe COVID-19 diseases. Despite the similarities, there are some significant differences in their immunological profile: the antibody response in PIMS produces mostly IgG anti-spike protein, while adults with COVID-19 presented also with IgA or IgM [14,15]. Some hypotheses claim that PIMS is caused due to early inflammation phase associated with a delayed immune response [2]. Also, autoantibodies against endothelial cells were found in PIMS, which leads to endothelial dysfunction and multi-organ failure [14]. For example, Consiglio et al. have found autoantibodies in patients with PIMS that bind to structural proteins from the myocardium and the blood vessels [15].

In children, PIMS symptoms present after one to six weeks of COVID-19 infection. In the majority of studies, the age of the patients ranged from 3 to 16 years old [3,5,6]. Most patients haven't associated any comorbidities or preexisting cardiac diseases. However, there were reports that obesity or baseline chronic conditions are associated with an increased risk of developing PIMS [7]. In all reported cases, persistent fever, asthenia, and gastrointestinal symptoms were present [3,6,16]. Mucocutaneous symptoms such as conjunctivitis or rash and cervical adenopathies were present in almost 85% of patients below 5 years [17]. In all cases reported, inflammatory markers (C-reactive protein, ferritin, or erythrocyte sedimentation rate) were elevated. Also, lymphopenia and thrombocytopenia are more pronounced in PIMS [8,15]. Particular attention should be paid to cardiac markers. It is important to mention that B-type natriuretic peptide values were higher in patients with PIMS compared with children with severe acute infection with SARS COV-2. Additionally, almost 95% of patients displayed evidence of coagulopathy demonstrated by elevated D-dimers [18]. Therefore, a complete laboratory evaluation should be performed in all patients that should include markers of inflammation, systemic assessment, and exclusion for other causes of fever.

DIFFERENCES AND SIMILARITIES WITH OTHER SYNDROMES

One major problem in clinical practice was the fact that some of the characteristics of PIMS overlapped with other diseases that also are associated with an infectious trigger of hyperimmune states such as KD or toxic shock syndrome. Despite the similarities with Kawasaki disease, there are some major differences between KD and PIMS. First, the age of patients affected by PIMS ranges from 2 to 20 years with a higher incidence in African or Hispanic patients, whereas KD patients are usually below 5 years with a higher incidence in Japan or Eastern Asian countries [5,19]. Second, even though almost half of the patients with PIMS present with clinical features that overlap with diagnostic criteria for KD, in PIMS, gastrointestinal and cardiovascular symptoms are much more common [3,20]. Regarding the haematological abnormalities, PIMS patients present with lymphopenia and thrombocytopenia, compared with the KD patients that tend to present with leukocytosis with neutrophilia and thrombocytosis [3,5]. Also, it is important to emphasize that in PIMS, patients have a worse clinical course [19]. This hyperinflammatory state in PIMS is also somehow similar to toxic shock syndrome caused by the hyper-activation of the immune system by „superantigens”. In 2004, Li et al. showed that the proteins from the SARS-COV virus expressed many motifs associated with superantigens and cytokines that could generate a strong immune response [21]. Similar motifs were recently discovered by Cheng et al. in the novel SARS COV-2 spike protein that could explain the hyperinflammation that is seen in children with PIMS [22].

CARDIOVASCULAR IMPLICATIONS

In adults infected with COVID-19, myocardial injury is seen in almost 20% of cases, however, the mechanisms of cardiovascular involvement in PIMS are still unknown [10]. There are some hypotheses regarding the direct effect of the virus on the myocardial tissue or microvascular dysfunction resulting in direct cellular damage and ischemic manifestations [17]. Furthermore, PIMS is also associated with endothelial damage, vasculitis, and a hypercoagulability state suggested by elevated D-dimer values that can lead to arterial thrombosis and hence myocardial ischemia [10].

The most common cardiac implication in patients with PIMS is acute myocardial injury, suggested by elevated cardiac markers (BNP, NT-proBNP, and Troponin) [3,6,18]. Echocardiographic, the most common finding is left ventricular systolic dysfunction (Table 1) [3,10,16]. One of the largest studies published in 2021 by Valverde et al. (n=286 patients),

reported that half of the patients presented impaired ejection fraction at admission, with mild mitral regurgitation and abnormalities in wall motions [23]. Matsubara et al. reported that PIMS patients presented also with diastolic left ventricle dysfunction, despite preserved systolic function (ejection fraction $\geq 55\%$). Speckle tracking echocardiography deformation parameters such as global longitudinal strain, longitudinal diastolic strain, and peak left atrial strain was lower compared with KD patients and healthy patients. Interestingly, echocardiographic parameters revealed impaired right ventricle systolic function with low right ventricle strain. These echocardiographic findings suggest that the left and right myocardium are injured during PIMS. It is important to emphasize that patients with higher values of cardiac markers presented with worse biventricular dysfunction [24]. Usually, during early follow-up, conventional echocardiographic parameters reveal normal left ventricular function. However, diastolic dysfunction persisted and deformation parameters remained low.

Subclinical myocardial injury demonstrated by low deformation parameters and myocardial edema that was found on cardiac magnetic resonance imaging resembles viral myocarditis [23,24]. However, there are a few characteristics that are against the fact that virus-induced myocarditis is the main cause of PIMS: first of all, the hyperinflammatory state with multisystemic involvement; second of all, after immunotherapy, in most cases, a rapid resolution of the echocardiographic changes is reported; third, in most cases, the majority of patients were negative for active infection.

Coronary artery aneurysms with a Z score > 2 were reported in patients with PIMS, suggesting a similar pathogenic mechanism with KD. The incidence of coronary artery dilatation is higher in PIMS (almost 20-45% of cases) compared to KD ($\leq 10\%$) with a predilection for the left coronary artery [6,19]. Furthermore, coronary artery aneurysm is now seen in more cases of PIMS than Kawasaki disease (14-36% vs. 4%) [25]. Recent studies haven't found any correlations between coronary aneurysms and the level of inflammation markers [6]. These findings suggest that coronary abnormalities are not only a consequence of inflammation but also other immunological mechanisms are involved such as autoantibodies. Although there are reports that state that coronary abnormalities are reversible, Valverde et al. and Sperotto et al. reported that coronary abnormalities usually persisted during hospitalization and even after discharge [23,26]. It is important to emphasize that some patients present with hypotension and cardiogenic shock [10,17,23]. Belhadjjer et al. reported 35 patients that presented with acute ventricular dysfunction, from which 68%

of them developed cardiogenic shock [16]. Matsubara et al. also reported a higher incidence of cardiogenic shock in PIMS (85%) versus KD (5%) [24]. Despite the low rate of mortality (almost 2%), a significant number of patients require admission to the Intensive care Unit (ICU) [17]. Invasive ventilation and extracorporeal membrane oxygenation support are required in a limited number of patients [18,23]. However, it is reported one case of a 17-year-old boy that developed severe dilated cardiomyopathy and currently is listed for a heart transplant [23]. Electrocardiogram abnormalities that were most commonly seen include abnormal ST segment or T wave. However, due to persistent myocardial injury, rhythm disturbances such as premature beats or sustained arrhythmias were reported [23,26].

MANAGEMENT AND FOLLOW-UP

As COVID-19 is a novel disease, there is no standardized treatment available at this moment. Due to multi-systemic involvement, proper management of PIMS should involve a multidisciplinary team that includes an infectious disease specialist, pediatric

cardiologist, and intensive care specialist. Also, due to the similarities with other syndromes, most patients are treated based on the treatment extrapolated from KD or toxic shock guidelines and on the opinions of the experts. As many studies demonstrated the inflammatory mechanism involved in PIMS, the main target of the treatment is to decrease inflammation. Therefore, intravenous Immunglobulin (usual dose of 2 g/kg/day) is used as a first-line of therapy [15]. At first, there were concerns regarding the stimulation of viral replication regarding corticosteroid therapy. However, recent studies reported that Immunglobulin therapy associated with corticosteroids led to a shorter period of hospitalization and normalization of cardiac function [16]. Because some patients were refractory to immunomodulation or corticosteroids, cytokine blockers such as recombinant Il-1 receptor antagonist (Anakinra) or Il-6 inhibitors (Tocilizumab) were added to the management of PIMS. Due to the elevated high risk of thrombosis, anticoagulants and/or antiplatelet therapy are used in the management of PIMS, especially in cases with coronary dilatation and elevated D-dimer levels [18,26].

TABLE 1. Reported cardiovascular involvement in pediatric multisystemic syndrome temporally associated with COVID-19 infection

Study /year	No.	Age group (median)	Cardiovascular involvement					Ref. No.
			Decreased LVEF% (<55%)	Coronary dilatation	Shock	Increased NT-proBNP/Troponin I	Pericardial/Pleural effusion	
Valverde et al. 2020	286	8.4 yr (3.8-12.4)	34% (71)	24.1% (69)	40.2% (115)	NT-proBNP: 94% (144/153) Troponin I: 93% (173/187)	27.9% (80)	23
Feldstein et al. 2020	186	8.3 yr. (3.3-12.5)	20% (36)	9% (16)	50% (93)	NT-proBNP: 73% (94/128) Troponin I: 50% (77/153)	26% (47)	20
Dufort et al. 2020	99	31%: 0-5 yr. 42%: 6-12 yr. 26%: > 12 yr.	52% (51/93)	8% (15)	29% (29)	NT-proBNP : 90% (89) Troponin I: 71% (71)	32% (32/93)	7
Whittaker et al. 2020	58	9 yr.(5.7-14)	31% (18)	14% (8)	50% (29)	NT-proBNP: 83% (24/29) Troponin I: 68% (34/50)	-	6
Belhadger et al. 2020	35	10 yr.	<30%: 28%(10) 30-50%: 72% (25)	17% (6)	68% (24)	100% (35)	8% (3)	16
Toubiana et al. 2020	21	7.9 yr (3.7-16.6)	76% (16)	24% (5)	67% (14)	NT-proBNP: 78% (14/18) Troponin I: 81% (17/21)	57% (12)	5
Matsubara et al. 2020	28	11.4 yr.	42% (median EF: 47%)	4% (1)	85% (24)	61% (17)	39% (11)	24
Verdoni et al. 2020	10	7.5 yr.	60% (6)	20% (2)	20%(2)	NT-proBNP: 100% (10) Troponin I: 50% (5)	30% (3)	3

Data are median (interquartile range) or n (%), where the number is the total number of patients with available data. LVEF- left ventricle ejection fraction, NT-proBNP: N-terminal-pro hormone brain-type natriuretic peptide,

Schlapbach et al. proposed a management guideline based on the similarities of clinical presentation of PIMS with other hyperinflammatory syndromes [27]. In all cases, the first line of therapy is represented by a single dose of Immunoglobulin G. If patients present with signs of shock similar to *toxic shock syndrome* and require ICU admission, in addition to Immunoglobulin, they recommend an initial pulse corticosteroid therapy with Methylprednisolone (10 mg/kg/day), followed by a slow wean (2 mg/kg/day). If patients do not present with clinical improvement in 24-36 hours and other possible diagnoses were excluded, clinicians should consider other treatments (Anakinra or Tocilizumab). Additionally, prophylactic anticoagulation with unfractionated Heparin and/or antiplatelet therapy with Aspirin should be used associated with broad-spectrum antibiotics. If patients present with clinical characteristics similar to *KD*, in addition to Immunoglobulin, they recommend antiplatelet therapy with Aspirin in low dose. According to the same protocol, corticosteroid therapy (Prednisolone) should be considered in selected cases (patients that associate coronary abnormalities, age below one year, or patients that present a resistance for Immunoglobulin) associated with fractionated Heparin in specific cases. If PIMS presents like a multiinflammatory syndrome that does not resemble either of the two syndromes mentioned above, they recommend a multidisciplinary approach and administration of a single dose of Immunoglobulin in selected cases, low dose of corticosteroid, prophylactic anticoagulation with fractionated Heparin and antiplatelet therapy. It is important to mention that if clinical symptoms do not improve and hyper inflammation is present, Schlapbach et al. recommend initiation of pulse corticosteroid therapy or a second dose of Immunoglobulin.

In patients with cardiovascular involvement, the management should be guided by echocardiographic findings and cardiac enzymes. If the myocardial injury is documented on cardiac imaging, the patients may benefit from heart failure therapy. Fur-

thermore, if patients are hemodynamically unstable and present with signs and symptoms of shock, they may require inotropic or ventilation support.

During follow-up, clinical improvement was seen in most cases. As stated above, after immunomodulation, in most cases cardiac dysfunction improves or even normalizes. Because medium- and long-term effects are still unknown, we emphasize the importance of cardiac evaluation in all patients with PIMS. Serial echocardiography should be performed to evaluate cardiac function and the state of coronary arteries. The optimal time between echocardiography assessments should be specified in each case during hospitalization. There are recommendations that serial echocardiograms should be performed every 2-3 days in patients with acute myocardial injury. If cardiac dysfunction is present during hospitalization, echocardiography should be repeated at 5-7 days or at the time of the discharge. Furthermore, due to an increased risk of arrhythmias, an electrocardiogram should be repeated every 48 h. Long-term follow-up should include serial echocardiography an electrocardiogram at discharge and every 6 months. Repeated magnetic resonance imaging could be considered in patients that presented with ventricular dysfunction [26]. Laboratory testing should be performed to monitor the evolution of the inflammation markers and cardiac enzymes.

CONCLUSION

Infection with SARS COV-2 virus in children has a mild course. However, several cases exhibit pediatric multi-inflammatory syndrome associated with Covid-19 infection. Despite the low incidence and mortality, most patients present with myocardial injury and are prone to develop acute heart failure. Early diagnosis and treatment lead in most cases to a favourable outcome. However, our understanding of the medium and long-term outcomes is limited, therefore we emphasize the importance of constant cardiac evaluation in all patients after PIMS.

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