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Pediatric Inflammatory Multisystem Syndrome; Unusual Presentation of COVID-19 in Children: About Thirty Cases

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Abstract

Pediatric inflammatory multisystem syndrome PIMS is a new entity of systemic inflammatory disease in children that appeared in the epidemic context of COVID-19 infection in April 2020. The pathophysiological mechanisms of PIMS are poorly understood and the hypothesis of a maladaptive hyperactive immune response, notably involving cytokines, is described in the literature. In our study, we report our experience regarding the clinical presentation, diagnosis, management and outcome of patients who presented with pediatric inflammatory multisystem syndrome *post* COVID-19.

Keywords

COVID-19, Inflammation, Kawasaki Like, Myocarditis, Immunoglobulins

1. Introduction

Pediatric inflammatory multisystem syndrome is a rare pediatric systemic inflammatory vasculopathy that can occur following SARS-CoV-2 infection. PIMS usually occurs two to six weeks after suspected or confirmed SARS-CoV-2 infection.

Symptoms of PIMS identified in 17 systematic reviews included abdominal pain, vomiting, rash (any type), hemodynamic shock or hypotension, conjunctivitis, diarrhea, other cardiac abnormalities (pericardial effusion, myocarditis), oral cavity changes (dry/cracked lips, raspy tongue), and swelling of the extremities.

Preventive measures to reduce the risk of transmission of SARS-CoV-2 infec-

tion can be combined to mitigate the risk of PIMS in children. This approach includes ventilation, universal mask use in indoor public spaces, vaccination, mask use in high-risk areas, and communication about the importance of wearing a mask with good fit and filtration capacity to protect the wearer and others. Individuals most at risk of severe disease (those with compromised immune systems and those in racialized or low-income populations), those who are ineligible for vaccination (children under five years of age), and those whose academic activities are disrupted (those who cannot attend class because they are infected or symptomatic) may benefit from population-based interventions.

In addition, PIMS is a recognized disease associated with COVID-19. It has been described as a post-viral systemic inflammatory vasculopathy in children who have been infected with SARS-CoV-2, with a clinical presentation similar to that of Kawasaki disease.

This syndrome typically appears two to six weeks after suspected or confirmed SARS-CoV-2 infection, and the disease is attributed to an enhanced immune response, rather than active viral replication and acute infection [1].

2. Objective

To report the experience of Pediatrics Department A, University hospital center Mohamed VI, Marrakech Morocco regarding the clinical and paraclinical diagnosis and therapeutic management of patients with pediatric inflammatory multisystem syndrome post COVID-19.

3. Method

Prospective study carried out in the department of pediatrics a *university hospital center* Mohammed VI Marrakech, Morocco, during the period from July to December 2021.

Thirty patients were included in our study who presented clinical criteria (fever, signs of shock, digestive or neurological signs) and biological criteria (inflammatory syndrome, coagulation disorders) and echocardiographic criteria (myocarditis) of pediatric inflammatory multisystem syndrome according to Swiss recommendations.

The data collection was made from an exploitation form filled in at the admission of the patient to our department specifying the age of the patient, the vaccination status, the history of infection by COVID-19 in the entourage, the delay between the infection and the appearance of the symptoms, the different symptoms presenting the patient as well as the biological and radiological abnormalities allowing to retain or to exclude the PIMS.

4. Results

Thirty patients were included in our study, male gender predominated with a percentage of 67%, mean age was 7 years with extremes ranging from 1 to 15 years, mean time from onset of symptoms to consultation was 7 days, a history

of COVID-19 infection within 4 to 6 weeks after symptoms was reported in 14 cases, two cases were vaccinated against COVID-19.

The clinical presentation of the multisystem inflammatory syndrome was variable in our patients: Twenty patients, or 66%, presented a KAWASAKI like with a complete clinical picture (prolonged fever, cervical adenopathy, skin rash, mucosal involvement, conjunctivitis). Four patients (14%) presented cardiogenic shock requiring initial hospitalization in the pediatric intensive care unit, one patient presented severe sepsis with a sub-occlusive picture, three patients (10%) presented variable general signs (prolonged fever, abdominal pain, diarrhea, vomiting, skin rash), two patients were operated on for appendectomy, the surgical exploration was normal (**Table 1**) [2].

The inflammatory balance was disturbed in all our patients with major hyperleukocytosis in 93% of cases, neutropenia in 66%, thrombocytosis in 90% and coagulation disorders in 86%.

COVID IGG serology was positive in all our patients.

As part of the screening for cardiac complications, a cardiac ultrasound was performed in all our patients, revealing dilated cardiomyopathy with profound alteration of the ejection fraction in three cases, 10%, an aneurysm of the left coronary artery in one case 3%, and minimal dilation of the right coronary artery in one case, and normal in twenty-five cases 83%.

Regarding the therapeutic management we applied the therapeutic recommendations of the Swiss companies [3] [4] [5] [6] [7], 87.5% of the cases received immunoglobulins at the dose of 2 g/kg/12h during the first week of their hospitalization, corticosteroids at the dose of 2 mg/kg/day for 4 weeks associated with anticoagulants 100 IU/kg/day and antiplatelet 5 mg/kg/day have been prescribed to all our patients to all our patients, and broad spectrum antibiotic therapy were indicated in 12 cases in view of clinical signs of infection (**Figure 1**).

Twenty-nine of our patients had a favorable evolution with regression of clinical signs and normalization of the biological balance after one month.

Only one patient died one week after admission to the pediatric intensive care unit following a rupture of a coronary aneurysm despite the administration of two doses of immunoglobulin, a corticosteroid bolus and an antiplatelet agent.

The criteria for discharge of our patients were essentially based on clinical

Table 1. Clinical presentation of PIMS.

Clinical presentation	Number	Percentage
KAWASAKI LIKE	20	66%
Cardiogenic shock	4	13%
Atypical presentation	3	10%
Pseudo-chirurgical symptoms	2	6%
Sepsis	1	3%

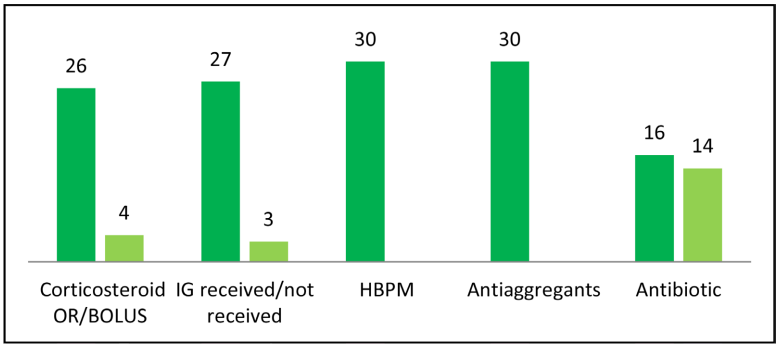

Figure 1. Treatment protocol.

improvement and normalization of the biological workup with a normal cardiological control.

Regular clinical examination was performed in 20 of our patients or 66% every two weeks, with monthly cardiac ultrasound.

5. Discussion

The current COVID-19 pandemic has resulted in many surprises, including the emergence of PIMS, which has clinical features distinct from those of classic Kawasaki disease. Although the proportion of children infected with SARS-CoV-2 who subsequently develop symptoms of PIMS is small, most of them require early clinical management because of the severity of the disease.

Preliminary case definitions of this new inflammatory condition have been published by the UK Royal College of Paediatrics and Child Health (RCPCH), the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). Both the CDC and WHO have named this condition "multisystem inflammatory syndrome in children" (MIS-C), while the Anglo-Saxons and Europeans refer to it as *pediatric inflammatory multisystem syndrome* (PIMS).

In the various series in the literature, the French series is to date the largest published series of PIMS, with more than 100 cases.

Myocarditis and KAWASAKI like syndrome were the most common clinical presentations with a percentage of 70% and 61% of cases respectively. Seritis and macrophagic activation syndrome (MAS) were also found with a frequency of 23%, in comparison with our series KAWASAKI like syndrome predominated with a percentage of 67% of cases, while cardiac involvement was low described in 21% of cases.

The severity of PIMS remains in the cardiac involvement, some patients develop a shock by myocardial failure in the 3 to 5 days of the beginning of the fever requiring the realization of a cardiac echography in all these children having a PIMS, this examination was practiced in all the patients of our series. Complementary examinations typically show lymphopenia, thrombocytosis, thrombocytosis and a major inflammatory syndrome, coagulation disorders and signs of myocardial distress, which is consistent with our results [8] [9] [10] [11].

Hospitalization in the intensive care unit was indicated in 67% of the cases in the French series, whereas only 17% of the cases required this procedure in our series.

The therapeutic management was a major subject of debate between the various learned societies, but they were in favor of combining corticosteroid therapy and immunoglobulin infusion.

In our series, 90% of our patients were put on corticosteroids, immunoglobulins, antiplatelet agents and anticoagulants according to Swiss recommendations with good clinical and biological improvement. 10% of patients did not receive immunoglobulins due to lack of means.

The follow-up of children with PIMS with cardiac complications was essential; the different series reported late complications, especially cardiac ones, whereas in our series no later complications were reported with a follow-up of 5 months.

The various literature reviews concluded that PIMS in children is generally characterized by anosmia, fatigue and shortness of breath.

Since the majority of studies focused on white children, more studies with racialized communities are needed. Johnson *et al.* (2020) Recognized that racialized communities are most affected by COVID-19, case prevalence and economic hardship [12] [13] [14] [15] [16].

Although Black race membership has been identified as a risk factor for MSP, it remains to be determined whether this risk is based on biological or social factors, or both. Rubens *et al.* (2021) noted that "… ethnic and racial differences can represent vulnerabilities in viral transmission related to occupational exposures, housing conditions and the need to use public transit.

These factors, in addition to limitations in access to health care and systemic inequities, contribute to the disparities highlighted during the COVID-19 pandemic".

A March 30, 2021, news article indicated that about 50% of Toronto's population belonged to a racialized group, yet this group accounted for 77% of all COVID-19 cases.

The authors reported that The Hospital for Sick Children in Toronto treated approximately 130 patients with PMI, of whom only 20% were white.

Prevention strategies to reduce the transmission of SARS-CoV-2 can be combined to mitigate the risk of SMPS in children.

This combined approach includes ventilation, wearing masks indoors in public places, vaccination, instructions for wearing masks in high-risk locations, and communication of the importance of wearing a mask that provides a good fit and filtration capability to protect the wearer and others. Those most at risk for severe illness, those who are not eligible for vaccination (c children under the age of five) and those whose academic activities are disrupted (people who cannot attend their classes because they are infected or symptomatic) can benefit from population-wide interventions [17]-[22].

Its prevalence in children (less than 10%) is lower than the estimated prevalence in the adult population, which may reflect the relatively benign nature of

the disease in children.

The clinical aspects of PIMS are better described and most patients experience gastrointestinal, cardiovascular, mucocutaneous and dermatological symptoms. The risk of PIMS is higher in racialized communities, especially among black children [23] [24] [25].

In our study, the delay in patient consultation, the non-availability of immunoglobulins during the first week of hospitalization were the two elements influencing the evolution of our patients.

In addition, the irregular follow-up of some of our patients did not allow us to have a clear idea on the evolution of all our patients.

6. Conclusions

As pediatric inflammatory multisystem syndrome is still a recently described condition, it is essential that all children who have developed it benefit from a specific follow-up, the frequency of which will be adapted according to the severity of the clinical presentation and the existence or risk of complications.

Other measures should be taken to improve the management of these children, develop standardized definitions of PIMS symptoms and separate diagnostic criteria, conduct additional research on risk factors associated with the development of PIMS, identify co-factors Basic pre-infection morbidity in patients and controls; helping to distinguish them from the sequelae of COVID-19 or other conditions; whether SARS-CoV-2 persists in children and contributes to the development of PIMS; determine the duration of the sequelae or symptoms of the PIMS, determine the biological and physiological processes contributing to the PIMS, determine whether the PIMS differs among variants of concern, because most studies were conducted prior to the emergence of the Delta and Omicron variants, determine if vaccination status affects the development and severity of PIMS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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