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Giuseppe CALCATERRA, Jawahar MEHTA, Vassilios FANOS, Pier Paolo BASSAREO

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Insights on Kawasaki disease and multisystem inflammatory syndrome; Relationship with COVID-19 infection

Giuseppe CALCATERRA [1], Jawahar L. MEHTA [2], Vassilios FANOS [3], Pier Paolo BASSAREO [4]

[1] Post graduate medical School, University of Palermo, Palermo, Italy

[2] Division of Cardiology, University of Arkansas for Medical Sciences and the VA Medical Center, Little Rock, AR, USA

[3] Neonatal Intensive Care Unit, Azienda Ospedaliera Universitaria, University of Cagliari, Monserrato, Cagliari, Italy

[4] University College of Dublin, Mater Misericordiae University Hospital, Dublin, Republic of Ireland

Corresponding author:

Pier Paolo Bassareo MD, PhD, MSc, FESC
University College of Dublin
Mater Misericordiae University Hospital
Eccles St, Inns Quay, Dublin 7, D07 R2WY
Dublin, Republic of Ireland
Telephone: +35314096083
Mail: piercard@inwind.it

Abstract

At the beginning of coronavirus disease 2019 (COVID-19) children seemed to be less affected and with milder symptoms than adults. Afterward, however, a warning was released regarding the possible association between COVID-19 and Kawasaki disease (KD) or Kawasaki-like disease. Thereafter, labels of Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) in Europe and Multisystem Inflammatory Syndrome in Children (MIS-C) in the USA were coined to refer to this new disease entity. The reality is that PIMS-TS/MIS-C resembles certain KD complications such as toxic shock syndrome and macrophage activation syndrome than to classic KD. PIMS-TS/MIS-C and KD share the viral origin (however just supposed for KD) and consequent dysregulated innate immune system inflammatory reaction. PIMS-TS/MIS-C symptoms occur about 2-4 weeks after the onset of COVID-19 or having been exposed to somebody positive for COVID-19, rather than in the acute phase of the infection. Clinically PIMS-TS/MIS-C affects older children than KD and presents more often with gastrointestinal symptoms, shock, and multi-organ dysfunction. myocarditis is more common in PIMS-TS/MIS-C than coronary artery aneurysms formation seen in KD. There are also differences in laboratory tests and immunology responses in KD and PIMS-TS/MIS-C.

Thus PIMS-TS/MIS-C seems to be a new and multifaceted entity, distinct from KD, notwithstanding some common features in both. The dysregulated innate immune system reaction is responsible for PIMS-TS/MIS-C onset and outcome. A multidisciplinary approach, involving paediatric intensivists, paediatric cardiologists, infectious disease specialists, immunologists, and rheumatologists, is needed for the treatment of these children.

Keywords: COVID-19, SARS-CoV-2, Kawasaki disease, PIMS-TS, MIS-C, innate immune system

Introduction

The coronavirus disease 2019 (COVID-19), responsible for the present pandemic of a severe acute respiratory distress syndrome, is the third spillover of an animal coronavirus (SARS-CoV-2) to humans resulting in a major epidemic, and the second pandemic event over last two decades **[1,2].** COVID-19 is dramatically putting healthcare systems under intense pressure worldwide **[3,4].**

Initial reports suggest that the severe illness caused by SARS-CoV-2 is associated with mortality ranging from 3% to 12% of confirmed cases. Certain populations like older men with pre-existing comorbidities such as hypertension, diabetes, cancer, heart failure as well as lung diseases or immuno-compromised subjects are more likely to die **[5-7].**

Conversely, children, and adolescents younger than 18 years seemed to be largely spared from the adverse outcomes of SARS-CoV-2 infection, particularly in terms of mortality **[8,9]**. This is probably due to the fact that ACE2 receptors are genetically under-expressed on the epithelial cells of the respiratory tree and other body systems in children **[10].**

Many reports, initially from Europe and later from the US, have appeared of *COVID-19 infection* in children, who developed a more serious inflammatory syndrome, often leading to hospitalization and occasionally requiring intensive care. A warning as to a possible connection between COVID-19 and Kawasaki disease (KD) or Kawasaki-like disease was released from Italy in May 2020 **[11].** In fact, physicians from northern Italy (Bergamo, Pope John XXIII hospital), one of the world's hardest-hit areas during the pandemic, noticed that a large number of children under the age of 9 years presented with a syndrome mimicking KD, with an incidence up to 30-fold than usual. The majority of the these children had an incomplete or atypical KD with resistance to aspirin and i.v. immunoglobulins as well as a tendency to develop macrophage activation syndrome (MAS), i.e. a severe KD complication requiring aggressive treatment and often admission to paediatric intensive care unit **[11]**. Shortly afterwards, the National Health Service (NHS) in the UK noted a rise in the number of children of all ages presenting with a multi-system inflammatory state requiring admission to intensive care unit across London and other British regions. These children were presenting with severe symptoms similar to those found in two rare conditions: KD and toxic shock syndrome **[12].** Soon thereafter, physicians from Stanford University in the United States published a case report describing a 6-month-old infant who tested positive for COVID-19 and was diagnosed with KD **[13].** On May 8th, 2020, the US Centers for Disease Control (CDC) released an alert as to the occurrence of a new entity associated with COVID-19 and termed it as Multisystem Inflammatory Syndrome in Children (MIS-C) **[14].**

Because of these cases sharing clinical features which are in part similar and in part distinct from KD and toxic shock syndrome, some authors still use the term “Kawasaki” or “Kawasaki-like” when referring to this new emerging entity **[15].** Conversely, the official European and British authorities prefer using the definition of paediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 (PIMS-TS), while the American CDC and the World Health Organisation (WHO) refer to it as MIS-C **[16,17].** All these definitions seem to be somewhat interchangeable.

Based on these considerations and for the sake of scientific clarity, we believe that a few things should be pointed out.

KD, named after the Japanese Paediatrician Tomisaku Kawasaki described it in 1967, is an acute self-limiting inflammatory disorder. KD is believed to be the commonest cause of acquired heart disease in children aged under 5 years with male preponderance (85%) in developed countries. It usually presents with persistent fever, rash, conjunctivitis, lymphadenopathy, mucosal (redness and cracking of the lips) and peripheral erythema and oedema in hands and feet. In severe cases, KD presents with systemic vasculitis, affecting predominantly medium-sized arteries, particularly the coronary arteries, resulting in the formation of coronary artery aneurysms in 15–25% of untreated patients **[18].** The first historical report of coronary artery aneurysms at autopsy in a boy with likely previous vasculitis appeared back in 1871 **[19].**

The cause of KD is unknown and its pathogenesis remains undefined, leading to uncertainties regarding its diagnosis and treatment. KD can damage the heart and the main complication is the development of coronary artery aneurysms. Although it is widely believed that KD is caused by an infectious agent, there is evidence that ethnicity factors play a role in determining susceptibility and severity of the disease. Evidence for host susceptibility comes from epidemiological data. The incidence of KD is highest in male children of Asian ethnicity, with over 10 times the incidence rate compared to children of European and North American descent under 5 years of age. The incidence in Japan is 138/100 000 in children younger than 5 years, whereas in the USA it is 17/100 000, and in the UK/EU 8/100 000. This increased incidence persists in children of Japanese migrants living in low-incidence countries. Notably, the incidence is high in first degree relatives of KD patients **[20].**

The widely leading thought is that KD is not a "disease" in the classic sense, but an inflammatory reaction that occurs in genetically susceptible individuals in whom viral pathogens or environmental agents trigger an aberrant innate immune response **[21]**. It would not be totally surprising if COVID-19 infection results in a similar disorder in susceptible children. It is possible that infection with not yet identified pathogen/s is associated with classic KD. More data will be needed to verify this hypothesis **[22].**

The classification of KD with its subtypes and complications has been reported in Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: Scientific Statement for Health Professionals From the American Heart Association **[23].** Here we summarize the manifestation of KD and PIMS-TS/MIS-C in **Tables 1 and 2.**

In our opinion, there are important differences between KD and PIMS-TS/MIS-C (see also *Table 2*). The PIMS-TS/MIS-C is more similar to atypical KD, toxic shock syndrome, and macrophage activation syndrome than to classic KD. The PIMS-TS/MIS-C seems to affect older children than KD (average age 9 years old versus 4 years in classic KD) and presents more often with abdominal pain and other gastrointestinal symptoms (50–60%) as well as conjunctivitis, rash, irritability and, in some cases, shock, usually of myocardial origin, or multi-organ dysfunction. In addition, PIMS-TS/MIS-C appears to affect a higher proportion of African and Caribbean children, while KD affects Asian children predominantly. Other differences are present in laboratory tests as well (see *Table 2*). Kawasaki and PIMS-TS/MIS-C have also overlapping features such as persistent fever and inflammation **[11,12,24].**

As to pathogenesis, some studies suggest that the underlying cause of KD may be an undefined infection: seasonal peaks during winter and spring, outbreaks with a clear geographical epicentre, the peak incidence is in children aged 1-2 years, while infants less than 3 months are protected, perhaps reflecting a protective role of transplacental antibodies. The disease is extremely rare in adults, as a possible consequence of a previous exposure and subsequent acquired immunity. Clinically, KD is similar to other infectious diseases **[25]**. Notably specific infective agent/s as cause of KD has not been identified. A viral origin of KD was proposed, but not proven. Other possible causes (i.e. bacteria, drugs) have also been proposed **[26-28]**. Children with this new entity, possibly COVID-19-related syndrome, may or may not test positive for COVID-19, but the link with SARS-CoV-2 is clear. In fact, the disease usually occurs in children and adolescents about 2-4 weeks after the onset of COVID-19 symptoms or having been in touch with someone positive for COVID-19,

rather than in the acute phase of the SARS-CoV-2-induced disease **[29].** This is one of the main differences between KD and PIMS-TS/MIS-C. In KD the trigger or the triggers are still unknown, while in PIMS-TS/MIS-C the trigger is known (i.e. SARS-CoV-2) and universally accepted by the scientific community. Coronary artery dilatation and/or aneurysms, which are the most dreaded complication of KD, can develop also in PIMS-TS/MIS-C, as a result of the cytokine storm and high levels of IL-6, although myocarditis is more frequent **[30].**

Immunology is different as well in subjects with KD and PIMS-TS/MIS-C, as shown in the recent Cactus study, involving Italian and Swedish researchers. The authors found that the inflammatory response in PIMS-TS/MIS-C differs from the cytokine storm of severe acute COVID-19 while there are some common features. The differences are related to T-cell subsets and IL-17A (owing to an IL-17A mediated hyperinflammation in KD, but not in PIMS-TS/MIS-C). Lastly, autoantibody profiling suggests multiple autoantibodies (vs endoglin and Rpbj proteins) that may be involved in the pathogenesis of PIMS-TS/MIS-C by disrupting myocardial and vascular tissue. These autoantibodies are absent in KD and released by T-cells **[31].** These findings have important implications in clinical practice, in terms of developing specific tests for an early diagnosis and ad hoc treatments. In PIMS-TS/MIS-C, high dose of i.v. immunoglobulins may be capable of hampering autoantibodies response, and inteleukin-1 receptor antagonist anakinra should block IL-1 receptors, whilst corticosteroids are effective against endothelial inflammation. Administering Tocilzumab vs IL-6 and TNF-alpha blockers is not recommended. For the first time, the potential efficacy of Secukinumab, a monoclonal antibody which binds to the protein interleukin IL-17A, has been suggested **[31].**

Although we are learning much about COVID-19 and its manifestations every day, it is clear that prompt evaluation and appropriate treatment of children with symptoms of PIMS-TS/MIS-C due to an aggressive immune system hyperinflammatory reaction is the key to prevent a permanent body's organs injury **[32].** Infection and inflammation are two sides of the same coin. Inflammation is an essential part of an effective immune system response, since an infection cannot be removed without an appropriate inflammatory reaction. Pathogens entering the human body cause the recruitment of immune cells, which in turn eliminate pathogens and ultimately lead to tissue repair and homeostasis restoration **[33].** However, a persistent excess in inflammation represents a disease itself. Since the beginning of COVID-19 outbreak, SARS-CoV-2 has been shown induce multiple types of vasculitides, such as Henoch-Schonlein purpura, systemic lupus erythematosus, and juvenile dermatomyositis in different children of different ethnic origin. This suggests that

SARS-CoV-2 infection facilitates endotheliitis because of the virus entering the endothelial cells and inducing a local inflammatory response, as suggested by the presence of viral elements within these cells **[34,35]**.

Although reports of COVID19 infection in children are growing, there is still much to learn about the novel coronavirus. Apart from the classic respiratory symptoms, less obvious manifestations, sometimes called "COVID toes" due to 'erythema pernio', chilblains, and other skin ailments have been reported **[36**].

To the best of the current knowledge, it is not clear whether recovery from the disease gives a short-lasting or permanent immunity against COVID-19 or not. This represents a major issue, along with the current lack of a vaccine **[37].**

On balance, PIMS-TS/MIS-C seems to be a new and multifaceted entity, clinically distinct from KD, - notwithstanding having more than a few features in. Laboratory tests results are quite different in KD and PIMS-TS/MIS-C. We suggest that KD and PIMS-TS/MIS-C may represent a metonymy*, a word which comes from the Greek μετωξυμία/μετωνυμία and Latin *metōnymía*, which means "a change of name". Different infectious agents (including coronavirus) are likely to trigger a final similar pathway made up of a dysregulated innate immune system reaction, thus causing KD or PIMS-TS/MIS-C in genetically predisposed and immunologically susceptible individuals **[38].**

A multidisciplinary approach, involving paediatric intensivists, paediatric cardiologists, infectious disease specialists, immunologists, and geneticists, is needed for appropriate diagnosis and treatment. With the upcoming school reopening and consequent risk of clusters, we do need to be careful and put our children's health first during the global COVID-19 pandemic **[39].** It is not just a casualty that in the US, during the week ending September 10th 2020, a peak of COVID-19 was registered, along with a steady upward trend in the number of cases over the preceding weeks, with the cases involving children encountering for more than 10% of all cases now **[40].**

* (from μετά, *metá*, "after, beyond", and -ὄνομα/ὄνυμα, *ónoma*, "name")

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Table 1.

Kawasaki disease classification [23]

Classic or typical Kawasaki disease features

- Fever ≥ 5 days (major criterium)
- At least 4 of the following minor criteria:

1. Bilateral not exudative conjunctival injection
2. Changes of the mucosae of the oropharynx, including injected pharynx, injected and/or dry fissured lips, or strawberry tongue
3. Changes in the peripheral extremities (at least one), such as oedema and/or erythema of hands and/or feet, desquamation usually beginning at periungal skin
4. Polymorphous, but non-vesicular, rash
5. Not suppurative cervical lymphadenopathy greater than 1.5 cm

The symptoms cannot be explained by the presence of other concomitant diseases
The cases with fever coming to a standstill at day 5 should be included as well

Incomplete Kawasaki disease features

- Fever ≥ 5 days (major criterium)
- Less than 4 of the above stated minor criteria

It is more common in children aged less than 12-24 months and should be suspected in each child under 6 months with persisting fever and signs of systemic inflammation, without any other illnesses as a possible cause of the symptoms

Atypical Kawasaki disease

Patients have fever lasting for at least 5 days, with different signs and symptoms than classic Kawasaki disease (for example, meningitis, seizures, facial palsy, acute abdomen, acute pancreatitis, cholestatic jaundice, arthritis, renal injury, pneumonia)

Kawasaki disease shock syndrome

It is a complication of Kawasaki disease which put at risk patients' life. Patients present with systolic hypotension for age or a sustained decrease in systolic blood pressure from baseline more than ≥20% compared to healthy individuals of the same age. In this setting, raises in troponin and pro-BNP are signs of myocarditis and heart failure.

Macrophage activation syndrome

It is a rare, but potentially fatal complication of Kawasaki, with activation of cytotoxic cells, hypersecretion of pro-inflammatory cytokines (INF-γ, IL-10, IL-6, IL-8, IL-18, TNF-α), and multisystem organ damage. Patients develop resistance to i.v. immunoglobulins therapy. Macrophage activation syndrome clinical presentation is acute, sometimes dramatic, with rapid evolution to organ damage. Fever and splenomegaly are always present. One third of children have central nervous system dysfunction with dizziness, hallucinations, ataxia. Around 20% of patients have haemorrhage. Those with the involvement of two or more organs or systems are more likely to have a worse prognosis with need to be admitted to paediatric intensive care unit.

Table 2. Comparison between Kawasaki disease and PIMS-TS/MIS-C

	Kawasaki	**PIMS-TS/MIS-C**
Aetiology	unknown	viral
Time between acute infection and onset of symptoms	unknown	2-4 weeks
Averaged age of onset	4 years	9 years
Clinics	fever, mucosal and cutaneous signs, coronary artery aneurysms	fever, gastro-intestinal symptoms, shock, myocarditis
Recurrence	very rare	unknown, though with most coronaviruses immunity wanes and infections recur lifelong
Ethnicity	mainly African-Caribbean	mainly Asian
Cardiovascular complications	coronary artery aneurysms; thrombosis is limited within aneurysms	myocarditis more frequent than coronary aneuryms; generalised clots formation
Laboratory	anaemia for age, increased platelet count after day 7 of fever, hypoalbuminemia, elevated WBC and ALT	increased ferritin, normal or reduced platelet count, hypoalbuminemia, normal or reduced

			WBC
Immunology		increased IL-6 and TNF-α	*increased IL-17, T cells*

Acronyms: *WBC: white blood cells; ALT: alanine aminotransferase; IL: interleukin;* TNF-α*: tumour necrosis alpha*