Kawasaki disease epidemic: the dilemma of evaluating clinical models

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To the Editor,

Following the outbreak of the coronavirus 2019 disease (Covid-19) pandemic, some authors have highlighted a link between severe forms of Covid-19 disease and the so-called cytokine storm, with increased levels of ferritin (1), characterized by an abnormal activation of the patient's immune system with the release of numerous inflammation mediators such as IL-1, IL-6, TNF and numerous chemokines.

This scenario is very heterogeneous. Some patients with Sars-Cov-2 infection develop secondary lymphohistiocytic hemophagocytosis (sHLH), while others, do not meet the criteria of sHLH but show some characteristics similar to hyperferritinemic syndrome (2).

In the pediatric field, a new multisystem inflammatory disease similar to Toxin Shock Syndrome (TSS) and atypical Kawasaki disease (KD) with exposure or suspected or proven SARS-CoV 2 infection has been reported in the UK (3), while an increase in the frequency of KD-like has been reported in Italy (4).

Evaluating clinical models it is clear that:

-Kawasaki disease (KD) is a rare acute pediatric vasculitis with coronary artery aneurysms as its main complication. The diagnosis is based on the presence of persistent fever, exanthema, lymphadenopathy, conjunctival injection, and changes in the mucosae and cutaneous extremities of hands and feet (5).

-Toxic Shock Syndrome (TSS) is a disease caused by toxins produced by Staphylococcus Aureus but also related to group A Streptococcus, is characterized by fever, diffuse macular erythroderma, peeling 1–2 weeks after getting the rash, hypotension and multisystem implication of three or more of the following organ systems: gastrointestinal, muscular, mucous, renal, hepatic, haematological, central nervous system (6). However, isolation in biological samples of one of the bacteria mentioned above is necessary to make the diagnosis. It is possible to hypothesize that SARS-CoV2, alone or in combination, may trigger or facilitate TSS.

-Secondary Hemophagocytic lymphohistiocytosis (sHLH) is a severe systemic inflammatory syndrome that can be fatal, often triggered by infection. The diagnosis is based on a number of clinical signs and laboratory findings, five out of the following nine diagnostic criteria must be met: fever, splenomegaly, cytopenias (affecting two or more of three lineages in the peripheral blood), hypertriglyceridemia, hypofibrinogenemia, elevated ferritin, hemophagocytosis in bone marrow/spleen/lymph nodes, low or absent natural killer (NK)-cell activity, or elevated soluble CD25 (7).

The pediatric cases described during the Covid 19 pandemic, labeled as atypical KD or hyperinflammatory syndrome, have clinical features and laboratory tests that are reminiscent of both KD, TSS and sHLH, but do not fully meet any of the clinical criteria for these diseases.

It is possible to hypothesize that there is a new pediatric pathological entity characterized by a state of hyperinflammation and manifested by fever, systemic involvement, gastrointestinal symptoms mostly abdominal pain, cardiogenic shock due to severe myocarditis and acute kidney injury. Numerous definitions have been proposed of which pediatric inflammatory multisystem syndrome (PMIS) temporally associated with SARS-CoV-2 (8).

PMIS appears to be a postinfectious inflammatory process, suggested by the fact that it is delayed after the COVID peak, by the negativity of the nasopharyngeal swab and by the antibody positivity. The characteristics that allow us to distinguish PMIS from KD are: the different age group affected, as PIMS mostly affects children with an average age of 8-10 years including adolescents. Another element of difference lies in the geography of the affected areas given the less frequent Chinese cases, despite being the country most affected at the beginning of the pandemic.

From available clinical data and reports, differences between PMIS and KD are evident: in KD involvement of the gastrointestinal and renal systems are uncommon. In addition, to the laboratory tests, it is possible to find some major analogies between PIMS and sHLH for example hyperferritinemia, D-dimer increase, and to the cytokine storm of TSS (9).

Patients have improved coincident with IVIG with or without steroids, suggesting that this kind of therapy, in KD, TSS and in this new inflammatory syndrome is effectively modulating cytokine activation.

It is necessary to collect further factors that allow us to better understand this emerging new hyperinflammatory pathology (PMIS) and its overlap with other inflammatory disorders (Figure 1). In the meantime strict medical surveillance is pivotal in order to maintain low the transmission of Sars-CoV-2 in childhood .

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Not applicable

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