HOT TOPIC REVIEW

Pediatric Inflammatory Multisystem Syndrome (PIMS) – Potential Role for Cytokines Such Is IL-6

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Summary

COVID-19 is a transmissible respiratory disease caused by coronavirus SARS-CoV-2, which is similar to SARS or MERS. Its increased severity was noted in aged patients usually over 65 years of age. Children and young people have an asymptomatic or mild course of the disease. Unfortunately, the number of children with problems after mild or asymptomatic COVID-19 recovery is increasing and their troubles resemble Kawasaki disease, although the laboratory findings seem to be different. This condition is called pediatric inflammatory multisystem syndrome (PIMS), and it is a new disease seen in children directly influenced by previous SARS-CoV-2 infection. The literature reports that PIMS typically follows 2–4 weeks after SARS-CoV-2 infection. The clinical symptoms of the affected children are extremely complex, ranging from gastrointestinal to cardiovascular problems with frequent skin and mucosal manifestations, and without intensive treatment they can be fatal. The exact causes of PIMS are recently unknown, however, it is explained as hyperactivation of immunity. In this minireview, we summarize data on the prominent role of the IL-6–IL-6R–STAT3 axis in PIMS aetiopathogenesis. Therapeutic manipulation of IL-6 or IL-6 receptor could be an approach to the treatment of children with severe PIMS.

Key words

SARS-CoV-2 • COVID-19 • IL-6 • Hyperinflammation • Cytokine storm • PIMS • Kawasaki-like disease

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Introduction

COVID-19 is a transmissible respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In 2020, COVID-19 rapidly reached the extent of pandemics, however, a significant part of the infected patients were asymptomatic or experienced a very mild disease course. The increased severity of this infection was more frequently observed in aged people. In the elderly, the disease can often be fatal, probably due to the presence of comorbidities. These patients die from severe respiratory distress with respiratory and heart failure, but damage occurring in other organs is not rare (Gavriatopoulou *et al.* 2020). It seems to follow the expression of angiotensin-converting enzyme 2 (ACE2), which is also a receptor for virus entry. However, ACE2 is also expressed elsewhere (*Tissue expression of ACE2 - Summary - The Human Protein Atlas*, accessed 20/02/2021), and the infection of cells in different tissues and organs is possible (Bao *et al.* 2021). Therefore, the symptomatology can be variable. Many people suffer

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from multiple severe health issues even long after the viral infection cure and require extensive medical care and rehabilitation to achieve complete recovery. The published analysis demonstrated that severe COVID-19 is associated with a hyperactivated immune response. IL-6 is a hallmark of this cytokine storm (Smetana *at al.* 2020). Moreover, IL-6 even has a predictive biomarker role (Han *et al.* 2020).

On the other hand, the level of IL-6 in severe COVID-19 is lower than in non-COVID-19 cytokine release syndrome, respiratory distress syndrome and sepsis (Leisman *et al.* 2020). Kaye and Siegel (2020) presented clinical evidence suggesting that an increase of IL-6 in COVID-19 patients stimulates blood vessel permeability, cytokine release, activation of macrophages, neutrophilia, lymphopoenia, and fibrin formation. From this point of view, the applicability of the IL-6 level as a prognostic biomarker in COVID-19 patients and anti-IL-6 targeted therapy requires closer discussion (Chen *et al.* 2021, Salama *et al.* 2021).

COVID-19 in children

SARS-CoV-2 can also infect children, however, the course of the disease in childhood is frequently mild or even asymptomatic (Bhuiyan *et al.* 2021, de Souza *et al.* 2020, Naja *et al.* 2020, She *et al.* 2020). Nevertheless, as the pandemic continued since the spring 2020, pediatricians around the world started to report on pediatric patients with peculiar severe hyperinflammatory disease with multi-organ involvement. The novel syndrome was termed Pediatric Inflammatory Multisystem Sydrome (PIMS) or Multisystem Inflammatory Syndrome in Children (MIS-C). There is robust evidence of the association of PIMS to SARS-CoV-2 infection in the recent history of the sick children. The causal effect of the virus seems to be confirmed (Carbajan *et al.* 2020, Feng *et al.* 2020), and it is broadly accepted that PIMS represents an immune-mediated post-infectious complication of SARS-CoV-2 (Malviya *et al.* 2021). The diagnosis of PIMS is based on the clinical symptoms and recent SARS-CoV-2 infection confirmed by PCR, serology, or COVID-19 exposure within the last four weeks before the symptoms (Malviya *et al.* 2021).

The clinical course in children with PIMS may differ from very mild to very severe, requiring immediate admission to a pediatric intensive care unit (PICU). The most common symptoms include fever (99 %), gastrointestinal problems (85 %) with abdominal pain, vomiting and diarrhoea, acute myocarditis-like presentation (80 %) with ventricular dysfunction (tachycardia, decreased left ventricular ejection fraction, hypotension), respiratory problems (50 %), and Kawasaki-like disease (23 %) with or without coronary aneurysms or pericardial effusions (Pouletty *et al.* 2020, Hoste *et al.* 2021).

Laboratory tests reveal very high inflammatory biomarkers such as C-reactive protein, procalcitonin or erythrocyte sedimentation rate with neutrophilia, lymphopenia and thrombocytopenia, but without positive evidence of bacterial infection in haemoculture (Malviya *et al.* 2021, Verdoni *et al.* 2020, Viner and Whittaker, 2020). Hyponatremia and/or hypoalbuminemia have been described (Schvartz *et al.* 2020), together with elevated D-dimers due to coagulopathy and hyperferritinemia as a marker of macrophage activation syndrome (Loomba *et al.* 2020). Many of laboratory findings in children with PIMS mirror the results of laboratory observations in adult COVID-19 patients with a severe course of the disease (Kaye and Siegel 2020).

Therapy in children with PIMS is based on clinical manifestation and requires a multidisciplinary approach. Severely affected children with PIMS are treated in PICUs. Intravenous immunoglobulins, glucocorticoids, inhibitors of interleukin-1 (anakinra), interleukin-6 (tocilizumab) or TNF-α (infliximab) were reported as a possible approach to immunomodulatory treatment in children. Ionotropic therapy and non-invasive or mechanical ventilation are used in children with heart failure according to the local standards (Hoste *et al.* 2021). Antiplatelet and/or anticoagulation therapy were used in some children. It has been well documented (de Souza *et al.* 2020, Naja *et al.* 2020, She, Liu and Liu 2020) that SARS-CoV-2 can infect children, however, the disease is frequently asymptomatic or presents only a very mild course (Bhuiyan *et al.* 2021). Surprisingly, an increased number of children with pleomorphic problems resembling Kawasaki disease (Patel and Shulman 2015) were reported even in the early phase of COVID-19 pandemics from various countries (Akca *et al.* 2020, Rehman *et al.* 2020). This Kawasaki disease-like condition usually appears several weeks (2–4) after SARS-CoV-2 infection, typically in the convalescent phase (Malviya and Mishra 2021). There is robust evidence of the association of these symptoms to SARS-CoV-2 in the history of the sick children.

The symptoms may include mucocutaneous inflammatory rash, strawberry tongue and non-purulent

conjunctivitis like in classical Kawasaki disease. However, there are also musculoskeletal pain, cardiovascular problems (including severe hypotension and shock), coagulopathy (usually with elevated ferritin and D-dimers), gastrointestinal manifestations (diarrhoea, vomiting, pain) – all this is less frequently present in the Kawasaki disease. Children typically exhibit high inflammatory markers such as CRP (C-reactive protein) without further evidence of bacterial infection. The syndrome is also associated with neutrophilia and lymphopoenia (Bhat *et al.* 2020).

Role of cytokines in PIMS

From the differential diagnostic point of view, PIMS differs from the Kawasaki syndrome by the presence of higher levels of inflammatory markers highly potent to stimulate immune response such as CRP, IL-1b, IL-6, IL-8, TNF-α, CCL3, CCL4, CCL19, CXCL10. (Calò Carducci *et al.* 2020, Feng *et al.* 2020, Godfred-Cato *et al.* 2020, Gruber etal. 2020, Gupta *et al.* 2020, Niño-Taravilla *et al.* 2020, Sood *et al.* 2021, Yasuhara *et al.* 2021). Although the published data slightly differs, IL-6 seems to be in the intersection of all published results.

Role of IL-6 in PIMS

Based on the available data, the level of IL-6 in PIMS-affected children ranges in the interval from 50–738 pg/ml, while the normal value is usually lower than 7 pg/ml (Calò Carducci *et al.* 2020, Feng *et al.* 2020, Godfred-Cato *et al.* 2020, Gruber *et al.* 2020, Gupta *et al.* 2020, Niño-Taravilla *et al.* 2020, Sood *et al.* 2021, Yasuhara *et al.* 2021). This widely described elevation of the serum level of IL-6 in PIMS-affected children suggests a possible role in the etiopathogenesis of the disease. IL-6 was identified as a 26 kD protein that stimulates B cells to produce immunoglobulins. Later, the pleiotropic effects of this cytokine on different cell types were defined, also depending on the type of receptor that recognizes IL-6 (Kang *et al.* 2019). Many cell types such as macrophages, osteoclasts, dendritic cells, lymphocytes, endothelial cells, epithelial cells (including airway epithelium and pneumocytes), smooth muscle cells, hepatocytes, and cancer-associated fibroblasts produce IL-6 (*Cell type atlas - IL6 - The Human Protein Atlas*, accessed 20/02/2021, Kang *et al.* 2019, Lacina *et al.* 2019, Brábek *et al.* 2020).

IL-6 is a cytokine causally responsible for initiation of the immune response and angiogenesis. It is also involved in differentiation of Th17 lymphocytes (Kang *et al.* 2020). Therefore, it is not surprising that it represents one of the fundamental mediators in autoimmune inflammations such as osteoarthritis, where its targeting is a promising approach to the therapy of this disease. For example, Siltuximab that targets IL-6 and Tocilizumab directed against the IL-6 receptor are clinically employed (Wiegertjes *et al.* 2020). IL-6 is upregulated in the course of ageing, where its high increase was observed pre-mortally (Lacina *et al.* 2019, Brábek *et al.* 2020). IL-6 also represents one of the most important molecules of the cancer microenvironment. In this context, it participates in the crosstalk between cancer-associated fibroblasts and cancer cells (Brábek *et al.* 2020, Novotný *et al.* 2020). In cancer patients and late elderly, IL-6 has a pronounced systemic effect. It affects the metabolism of hepatocytes, adipocytes and striated muscle cells. All those effects finally result in cachexia (Flint *et al.* 2016, Zimmers *et al.* 2016, White 2017).

The IL-6 signalling was thoroughly summarized in reviews in the latest years (Kang *et al.* 2019, Lacina *et al.* 2019, Gharibi *et al.* 2020). In inflammatory conditions, production of IL-6 is stimulated via activation of Toll-like receptor 4 and receptors for a broad spectrum of cytokines, including IL-1, IL-6, TNF-α. IL-6 is recognized by specific receptors that form a complex with glycoprotein 130 (gp130). This heterogeneous complex is docked in the cell membrane. It can be consequently cleaved by ADAM17 protease at the transmembrane site. After such shedding, the receptor remains capable of ligand binding and activation. When binding IL-6 as its high-affinity ligand, the IL-6 receptor heterogeneous complex via signal transducer pg130 phosphorylates STAT3. Phosphorylated STAT3 is consequently translocated to the cell nucleus, where it affects gene expression. The target gene products are proteins essential in controlling inflammation. The list includes, but is not limited to, IL-6, IL-10, IL-17, IL-23, IFN-γ, TNF-α, CRP, RANTES, VEGF-A, HGF, bFGF. The central position of the IL-6 – STAT-3 axis is demonstrated in the Fig. 1 after analysis by software of the String Consortium (*IL6 protein (human) - STRING interaction network*, accessed 20/02/2021), where many factors upregulated in PIMS (Calò Carducci *et al.* 2020, Gruber *et al.* 2020) have been included. Interestingly, the ferritin heavy chain, which is also elevated in PIMS-

affected children, seems not to be influenced by the mentioned axis.

As documented earlier in cancer, COVID-19 and ageing, IL-6 is also involved in functions not directly associated with the initiation of the immune reaction. Based on the summarized data, we conclude that IL-6 plays a prominent role in children affected by PIMS after SARS-CoV-2 infection. This cytokine seems to be a key player in the inadequate hyperactivation of immunity with severe pleomorphic symptoms accompanied by a risk of serious cardiovascular problems such as coronary aneurysms in the affected children. From this point of view, the therapy of PIMS targeted to IL-6 or IL-6 receptor complex can be rational and promising in the indicated cases, and several approved drugs for this therapy are available.

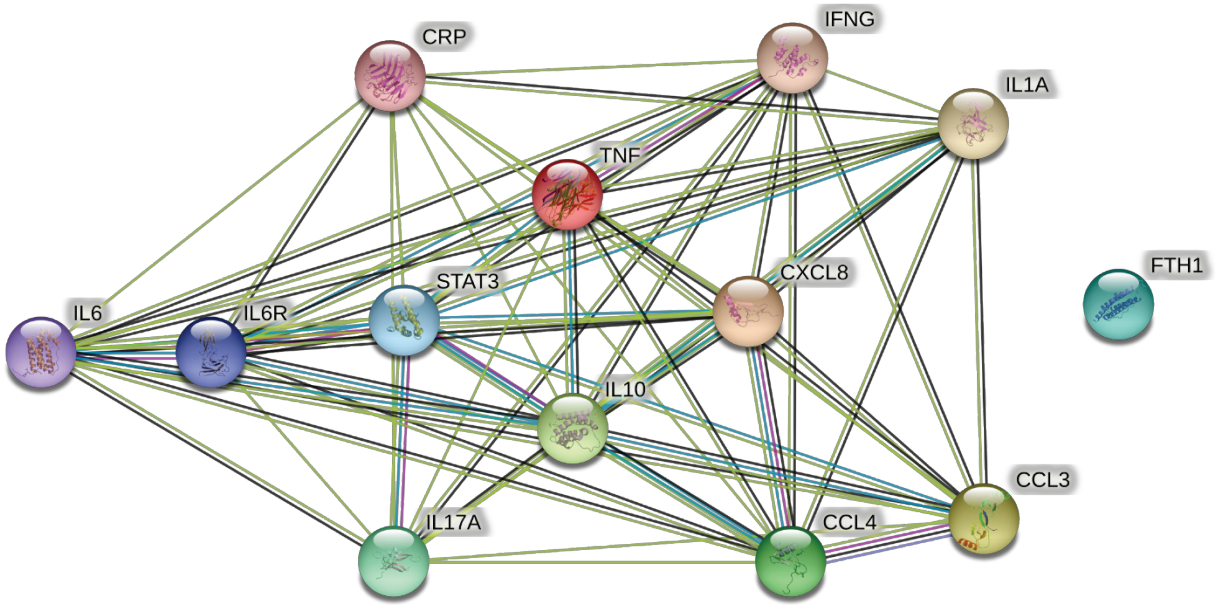

Fig. 1. Network of cytokines dependent on the IL-6 – IL-6R – STAT3 axis. The names of proteins are given in generally accepted terms. For better explanation, CRP is C-reactive protein, IFNG is interferon-γ, TNF is tumor necrosis factor-α. FTH1 (ferritin heavy chain) has not been included by the STRING (https://string-db.org/) software to the interactive system.

Conclusions

PIMS is a serious pediatric disease that is associated with previous infection of SARS-CoV-2, even asymptomatic. The affected children have complex symptoms from gastrointestinal to cardiovascular problems, including formation of large aneurysms in coronary arteries. The skin and mucosa are also frequently affected. This etiopathogenesis of the disease is not fully clear, but it seems to be induced by delayed hyperactivation of the immune response against SARS-CoV-2. This event is similar to cytokine storm, a serious and frequently fatal complication of COVID-19 in adults. The key role in PIMS, similarly to the cytokine storm in adults, is played by enhanced production of IL-6, when interaction of this cytokine with the IL-6 receptor and activation of STAT3 induces production of a panel of cytokines that are responsible for PIMS initiation (Brábek *et al.* 2020, Hoste *et al.* 2021). In addition to immunosuppressive therapy, targeting of the IL-6–IL-6 receptor axis can, therefore, be a good strategy for severe PIMS treatment.

Conflict of Interest

There is no conflict of interest.

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