Coronavirus Disease 2019 (COVID-19) in Children: Lessons from Pediatric Rheumatology

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The clinical presentation and outcomes of coronavirus disease 2019 (COVID-19) are characterized by exceptional variability in manifestations, which depend on many factors, one of which is the patient's age. One of the severe life-threatening manifestations in adults is acute respiratory distress syndrome (ARDS), in some cases accompanied by the development of multiple organ failure (MOF). During the first two to three months of the COVID-19 pandemic, the global medical community was inclined to think that this infection is rather mild and not fatal in children. However, with the accumulation of new information, it became clear that there is a growing recognition of multisystem inflammatory syndrome (MIS-C) developing in children chronologically associated with SARS-CoV-2, and usually leading to serious consequences. The article presents the most essential epidemiological, clinical and laboratory characteristics of the syndrome, as well as discusses MIS-C pathogenesis and differential diagnosis aspects with a number of other acute conditions associated with imbalance of cytokines, and available pharmacotherapies.

Keywords: COVID-19, multisystem inflammatory syndrome in children (MIS-C), Kawasaki disease
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КОРОНАВИРУСНАЯ БОЛЕЗНЬ 2019 (COVID-19) У ДЕТЕЙ: УРОКИ ПЕДИАТРИЧЕСКОЙ РЕВМАТОЛОГИИ

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Клиническая картина и исходы коронавирусной болезни 2019 (coronavirus disease – COVID-19) зависят от многих факторов, одним из которых является возраст пациента. Одним из тяжелых жизнеугрожающих проявлений у взрослых является острый респираторный дистресс-синдром (ОРДС), в ряде случаев сопровождающийся развитием полиорганной недостаточности. В течение первых месяцев пандемии COVID-19 сложилось мнение, что у детей это заболевание, как правило, протекает в легкой форме и не приводит к летальному исходу. Однако по мере накопления новых сведений стала очевидной возможность тяжелого течения COVID-19 у детей, приводящего к развитию патологии, получившей название «мультисистемный воспалительный синдром» (Multisystem inflammatory syndrome in children – MIS-C). В статье обсуждаются эпидемиологические, клинические и лабораторные характеристики MIS-C, подходы к дифференциальной диагностике с другими воспалительными заболеваниями у детей, предполагаемые механизмы иммунопатогенеза и перспективы фармакотерапии.

Ключевые слова: коронавирусная болезнь 2019 (COVID-19), мультисистемный воспалительный синдром у детей, болезнь Кавасаки
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The 2019 coronavirus disease (COVID-19) pandemic, which is etiologically related to the SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus-2), has reawakened professional interest to new clinical and fundamental problems in the immunopathology of human diseases in adults [1] and children [2] in general, and systemic autoimmune rheumatic diseases (SARDs) in particular [3]. In adults, the clinical presentation of COVID-19 infection varies from asymptomatic carriage to development of the acute respiratory distress syndrome (ARDS), microvascular coagulopathy, macro-thrombosis, and multiple organ failure associated with high mortality [1]. The first months of the COVID-19 pandemic produced an impression that this disease is usually mild and very rarely fatal in children. Available statistics from Asia, Europe and North America on COVID-19 prevalence indicates that 2.1–7.8% out of all confirmed cases can be attributed to pediatric practice [2]. However, due to the asymptomatic or mild course of infection, data regarding the true spread of COVID-19 among children is still uncertain. In the Russian Federation, children account for about 7% of reported COVID-19 cases [4]. True causes for COVID-19 uncommonness in childhood are not fully clear [5,6]. Potential explanations include low expression of angiotensin-converting enzyme (ACE) 2 on the respiratory epithelial cells which is used by SARS-CoV-2 as a receptor for invasion, differences in underlying essential immunological mechanisms, in particular, enhanced protection of the Th2 immune response, synthesis of cross-reacting antibodies to other coronaviruses, as well as lower prevalence of comorbidities in children, etc.

The course of COVID-19 infection in children can vary from asymptomatic to clinically manifested severe disease [4], including acute respiratory viral infection, viral pneumonia without

respiratory failure, pneumonia with acute respiratory failure, and ARDS. However, recently attention has been drawn to the specific feature defined as "multisystem inflammatory syndrome in children" (MIS-C) [2,7,8] (Table 1), or "pediatric inflammatory multisystem syndrome" (PIMS) associated with acute coronavirus infection [9]. To a certain extent, this syndrome resembles some emergencies a pediatric rheumatologist has to face [2, 10], in particular, Kawasaki disease (KD) with associated severe damage to the cardiovascular system [11, 12] and macrophage activation syndrome (MAS) [13].

Epidemiology of MIS-C

About 1,000 cases of MIS-C were registered worldwide during the first 6 months in 2020 [2]. According to EM Dufort et al. [14], the incidence of laboratory confirmed SARS-CoV-2 infection was 322 per 100,000 children and adolescents, and incidence of MIS-C was 2 per 100,000. MIS-C cases have been reported in Europe, South America, Canada, and the United States, but have not been reported in children in China and other Asian countries [2]. The documented mean age in children developing MIS-C was 8–11 years, and the majority of them (more than 70%) were initially healthy. Obesity and bronchial asthma were the most common comorbidities. In three published large series of observations 25–45% of patients were black, 30–40% were Hispanic, 15–25% were Caucasians, and 3-28% were Asian [15–17]. There were no significant gender differences.

Clinical manifestations

MIS-C develops 2–4 weeks after infection with SARS-CoV-2 [15]. Clinical manifestations are characterized by a wide variety of signs and symptoms [16–22] (Table 2). According to EM Dufort et al. [14] a third of cases in the United States, did not meet the diagnosis of MIS-C according to the CDC (The Centers for Disease Control and Prevention) criteria, because they did not have a PCR-based laboratory confirmation of SARS-CoV-2 infection, although all clinical and laboratory signs were similar to those observed in confirmed SARS-CoV-2 cases.

MIS-C clinical course is divided hypothetically into initial and fool blown disease based on distinctive clinical features (Table 3). S Godfred-Cato et al. [23] conducted one of the largest studies in the United States involving 570 children [23]. Patients' mean age was 8 years (from 2 weeks to 20 years), 55.4% were boys; 40.5% were Hispanic, 33.1% were black, and 13.2% were non-Hispanic white. Obesity as the most common co-morbidity was documented in 30.5% of Hispanics, 27.5% of blacks, and 6.6% of Caucasians. Abdominal pain (61.9%), vomiting (61.8%), skin rash (55.3%), diarrhea (53.2%), hypotension (49.5%), and conjunctival injection (48.4%) were the most common presenting signs and symptoms. The majority of patients had gastrointestinal (90.9%) cardiovascular (86.5%), and dermatological (70.9%) symptoms. Severe complications, including cardiac dysfunction (40.6%), shock (35.4%), myocarditis (22.8%), coronary artery dilation or aneurysm (18.6%), and acute kidney injury (18.4%) were documented in a significant number of MIS-C patients. More than half of these patients (63.9%) were admitted to the intensive care unit due to concern for rapid deterioration. Positive PCR test or antibodies to SARS-CoV-2 (anti-SARS-CoV-2) were found in by far the majority of patients (99.1%), 46.1% had only anti-SARS-CoV-2, and 25.8% had only positive PCR tests. Four or more organ systems were affected in 86% of patients. Three main variants (classes) of MIS-C were identified based on clinical manifestations. Class 1 included 203 (35.6%) patients with the highest number of involved organ systems (48.8% were children with 6 or more organ systems involved), including the cardiovascular system (100.0%) and gastrointestinal tract (97.5%) pathology. Class 1 patients had higher prevalence of abdominal pain, clinical presentation of shock, myocarditis, and lymphopenia, and significantly increased concentrations of C-reactive protein (CRP), ferritin, troponin, and NT-proBNP (N-terminal brain natriuretic pro-peptide). Anti-SARS-CoV-2 with or without positive PCR results were detected in almost all patients of this group (98.0%). These cases fulfilled the MIS-C criteria. Class 2 included 169 (29.6%) patients with clinically significant respiratory system involvement (pneumonia and ARDS) in 76.3%, meeting the criteria of COVID-19 or COVID-19 accompanied with MIS-C. SARS-CoV-2 PCR positivity only predominated and was established in a significantly higher (84%) proportion of these patients. This group has the highest mortality rate (5.3%). Class 3 included 198 (34.7%) patients with the youngest mean age (6 years) as compared to class 1 (9 years) or class 2 (10 years) patients. The highest incidence of skin rashes (62.6%) and mucosal lesions (44.9%) were two specific features in children of this group. Aneurysm and dilatation of the coronary arteries detection rates (18.2%) were higher than in class 2 patients (15.8%), but lower than in class 1 patients (21.1%). At the same time, patients from this group were more likely to meet the criteria for KD (6.6%) compared to patients of class 1 (4.9%) and class 2 (3.0%), had the lowest incidence of comorbidities, and were less likely to have such complications as shock and myocarditis. Anti-SARS-CoV-2 only were detected in the majority of children (63.1%), while anti-SARS-CoV-2 and positive PCR were found in 33.8%. These data indicate a significant heterogeneity of MIS-C, which is suggestive of potential

Table 1. Preliminary criteria of multisystem inflammatory syndrome in children (MIS-C), recommended by WHO [7]*

I. Children and adolescents with febrile fever lasting ≥3 days	
II. At least 2 out of the following features:	1. Signs of dermal and mucosal damage (rash, involvement of oral mucosa, swelling of hands and feet) or bilateral non-suppurative conjunctivitis
	2. Arterial hypotension or shock
	3. Signs of myocardial dysfunction, pericarditis, valvulitis, or coronary artery disease (based on Echo-CG data or elevated troponin/NT-proBNP levels)
	4. Laboratory signs of coagulopathy (elevated D-dimer levels, increased PT, PTT)
	5. Acute GIT disorders (vomiting, diarrhea, unexplained abdominal pain
III. Elevated acute phase reactants (ESR, CRP, procalcitonin)	
IV. Exclusion of other obvious causes of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes	
V. Verification of COVID-19: a positive SARS-CoV-2 PCR test, a positive test for antigen or serological tests, or probable contact with COVID-19 infected individuals	

Note. *The diagnosis is confirmed when criteria from all 5 categories are present.

Table 2. Clinical and laboratory features of MIS-C

Clinical signs	In the majority of patients:
	Shortness of breath
	Arterial hypotension
	In some patients:
	Confused mental state
	Head ache
	Vomiting
	Syncope
	Abdominal pain
	Diarrhea
	Conjunctivitis
	Cough
	Dyspnea / laborious breathing
	Rash
	Lymphadenopathy
	Mucosal changes
	Cervical stiffness
	Sore throat
	Swelling of hands and feet
Laboratory signs	In all patients:
	Decreased fibrinogen levels
	Increased CRP
	Increased D-dimer
	Hyperferritinemia
	Hypoalbuminemia
	Lymphopenia
	Normal or increased neutrophil count
	Any other potential cause of these abnormalities should be ruled out
	In some patients:
	Anemia
	Coagulopathy
	Acute kidney injury
	Increased IL-10 levels
	Increased IL-6 levels
	Proteinuria
	Increased creatin kinase levels
	Increased LDH levels
	Increased troponin
	Elevated triglycerides
	Elevated transaminases
	Thrombocytopenia
Instrumental data	Echo-CG and ECG: Signs of myocarditis, valvulitis, pericardial effusion, dilatation of the coronary arteries.
	Thoracic X-ray: Symmetrical inhomogeneous infiltrates, signs of pleurisy.
	Abdominal ultrasound: Lymphadenopathy, hepatosplenomegaly, ascites, signs of colitis, ileitis.
	Computed tomography: Signs of pleurisy, pulmonary infiltrates, and coronary arteries involvement after contrast enhancement.

MIS-C "overdiagnosis" based on "accidental" detection of anti-SARS-CoV-2 with further spread of COVID-19 pandemic and increasing number of SARS-CoV-2 infected children.

It is also obvious that the pathology, which is defined as MIS-C, requires differential diagnosis with diseases and complications that accompany other infectious, hematological diseases and SARDs. As for systemic autoimmune rheumatic diseases attention should first be paid to KD, hemophagocytic lymphohistiocytosis (HLH), bacterial sepsis, infectious toxic shock, systemic onset juvenile idiopathic arthritis (sJIA), systemic lupus erythematosus, and systemic vasculitis. Despite some similarities in clinical manifestations, the supposed association between MIS-C and infectious toxic shock was not confirmed, since blood cultures were negative in the majority of MIS-C patients. However, significant proportion of MIS-C patients (30–70%) show clinical and laboratory signs that are typical for toxic shock, therefore caution is needed not to miss secondary bacterial infection.

Table 3. Clinical and laboratory characteristics of multisystem inflammatory syndrome in children (MIS-C) stages

Manifestations	Rate, %
Initial signs	
Persisting fever (average duration of 4–6 days)	100
Gastrointestinal symptoms (vomiting, diarrhea, abdominal pain)	60–100
Rash	45–76
Conjunctivitis	30–81
Mucosal involvement	27–76
CNS involvement	29–58
Respiratory signs (dyspnea, laborious breathing)	21–65
Cervical pain	10–16
Myalgia	8–17
Hands/feet stiffness	9–16
Lymphadenopathy	6–16
Clinical manifestations of full-blown disease	
Clinical picture of shock	32–76
Meeting full clinical criteria for complete KD	22–64
Myocarditis (Echo-CG criteria, elevated troponin/BNP)	51–90
Arrythmia	12
Acute respiratory failure	28–52
Acute kidney injury	8–52
Serositis	24–57
Hepatitis/hepatomegaly	5–21
CNS involvement	6–7
Laboratory signs of full-blown disease	
Lymphopenia	80–95
Increased neutrophil counts	68–90
Moderate anemia	70
Thrombocytopenia	31–80
Elevated CRP	90–100
Increased ESR	75–80
Increased D-dimer level	67–100
Increased ferritin level	55–76
Increased procalcitonin level	80–95
High IL-6 serum levels	80–100
Low serum albumin	48–95
Elevated transaminases	62–70
Increased LDH level	10–60
Hypertriglyceridemia	70
Instrumental exams findings in full-blown disease	
Impaired left ventricular function according to EchoCG	31–58
Coronary arteries dilatation/aneurisms based on US findings	8–38
Pleural effusions, mass lesions, atelectasis, ground glass opacities based on X-ray and MSCT findings	Data not specified
Free liquid, ascites, inflammation of mesenterium and intestinal wall, including terminal ileitis, mesenterial lymphadenopathy	Data not specified

Shared clinical features of KD and MIS-C require special clinical attention [11, 12, 24]. KD is considered currently as a systemic vasculitis with predominant involvement of small and medium-sized arteries with highest prevalence in children under 5 years of age and being the leading cause of cardiac pathology in pediatric patients in developed countries with low incidence of group A β-hemolytic Streptococcus infection and acute rheumatic fever [25, 26]. In contrast, in most cases, MIS-C develops in initially healthy older children and adolescents. According to the American Heart Association criteria [25], the diagnosis of complete KD includes high grade fever lasting for 5 or more days and at least four of five main clinical signs (bilateral conjunctivitis; involvement of oral and lip mucosa manifesting in hyperemia, redness of the mouth – "raspberry/strawberry" tongue or cracked lips; swelling of hand and feet with red and flaky skin; polymorphic rash; cervical lymphadenopathy). The incomplete form of KD is characterized by unexplainable fever ($\geqslant$ 5 days) in combination with 2–3 main clinical and laboratory signs or features of heart damage. KD-like changes were detected in 22–64% of patients with MIS-C, with echocardiographic signs of reduced LV function in 58% of them. Increased signal intensity in T1- and T2-weighted MRI images was indicative of diffuse myocardial edema. Dilatation of the coronary arteries was found in 8–38% of patients. As shown in recent studies moderate and transient dilatation of coronary arteries in children with MIS-C [27] strongly resembles the patterns observed

Table 4. Comparative characteristics of MIS-C and Kawasaki disease (KD)

	MIS-C	KD
Mean age	9 (5,7–14)	2,7 (1,4–4,7)
Ethnicity	African/Hispanic origin	Asian origin
GIT symptoms (abdominal pain)	+++ (49–80%)	Rare
Signs of kidney injury	++	Very rare
Myocardial dysfunction/myocarditis	+++	Very rare
ARDS	Rare (1.5–10%)	Very rare
Propensity to developing shock	+++ (0–76%)	Rare
Leukocytes	↑↑	↑
Lymphocytes	↓	Normal
Hemoglobin	↓	↓ or normal
Platelets	↓	↑↑
CRP	↑↑↑	↑
Ferritin	↑	↑ (non-significantly)
Albumin	↓	↓ or normal
NT-pro-BNP	↑↑↑	↑ or normal
Troponin	↑	Normal
D-dimer	↑↑↑	↑

in other "febrile" conditions in children, including JIA with systemic onset [28]. However, available preliminary autopsy data do not confirm the inflammation of coronary arteries in adult patients with COVID-19 [29,30] and in children with MIS-C [31].

The dilation of the coronary arteries in MIS-C is considered to be associated primarily with endothelial dysfunction (without morphological changes), induced by "proinflammatory" cytokines. Therefore, the pathology of coronary arteries in MIS-C is strikingly different from specific coronary pathology in KD, which is characterized by pronounced dilation and aneurysms, often leading to myocardial infarction, rupture of the aneurysm and sudden death [25]. Certain similarities of clinical and laboratory manifestations are immediately obvious when comparing MIS-C and KD, but specific differences are also there (Table 4). In this regard the study of L Verdoni et al. [32] which was conducted in the epicenter of coronavirus infection in Italy and showed clear differences between MIS-C and KD both in terms of clinical manifestations and laboratory parameters is of great interest. The difference in racial and ethnic background in individuals with similar clinical picture interpreted as a "KD-like syndrome", suggests that MIS-C develops as a consequence of SARS-CoV-2 infection in a population with a genetic predisposition distinct from that leading to KD [24, 33, 34]. Hyperproduction of proinflammatory cytokines in patients with MIS-C can contribute to the development of similar clinical and laboratory manifestations in patients not only with KD, but also with the "cytokine storm" syndrome (CSS) in COVID-19 [35, 36] and with other SARDs [37, 38] due to underlying "thromboinflammation" as the key pathogenetic mechanism of a wide range of infectious and inflammatory diseases [39, 40].

Intermittent fever, heart, liver and kidney damage, cytopenia, hyperferritinemia, increased concentrations of C-reactive protein (CRP), triglycerides, lactate dehydrogenase, and D-dimer are the clinical and laboratory signs associated with both – the MIS-C and the CSS. Keeping in mind the similar pathogenetic background of CSS in both – MIS-C and MAS, a characteristic complication of sJIA and a very rare phenomenon in other SARDs, other potential origins of excessive inflammation should be ruled out before confirming MIS-C (Table 5)

Table 5. Comparative characteristics of primary and secondary HLH and MIS-C criteria

Criterion	Presence in MIS-C
Primary hemophagocytic lymphohistiocytosis (HLH 2004 y) (5 out of 8 criteria are required)	
Fever (>38 °C)	+
Splenomegaly	+/-
2- or 3-germ lines cytopenia (leukocytes <1,0×10^9/l, Hb <90 g/L or platelets <100×10^9/l)	Thrombocytopenia, anemia; normal leukocyte count is often associated with lymphopenia
Elevated triglycerides (>3,0 mmol/L) *or* low fibrinogen ≤1,5 g/L	+
Presence of hemophagocytosis in the bone marrow aspirates	No data
Hyperferritinemia (>500 μg/L)	+
High levels of soluble CD-25 >2400 U/ml	+
Decreased NK activity	+
MAS in systemic onset juvenile arthritis (first 2 criteria and 2 out of the following 4 are required)	
Fever (>38 °C)	+
Hyperferritinemia (>684 ng/ml)	+
Low platelets count <181×10^9/ml	+
AST elevation > 48 U/l	+
Elevated triglycerides > 156 mg/dl (>1,75 mmol/L)	+
Decreased fibrinogen ≤ 360 mg/dl (3,6 g/L)	+
MAS in systemic lupus erythematosus (not less than 1 clinical and 2 laboratory criteria are required, bone marrow biopsy is needed only in questionable cases)	
Fever (>38 °C)	+
Hepatomegaly (≥3 cm from the lower edge of the rib cage)	+
Splenomegaly (≥3 cm from the lower edge of the rib cage)	+/-
Hemorrhagic manifestations	In some cases
CNS involvement (excitability, disorientation, drowsiness, headache, convulsions, coma)	Often
2- or 3-germ lines cytopenia (leukocytes <4,0×10^9/L, Hb <90 g/L or platelets <150×10^9/L)	Thrombocytopenia, anemia; often, normal leukocyte count can be associated with lymphopenia
AST elevation (>40 units/L)	+
LDH elevation (>567units/L)	+
Hypofibrinogenemia (<1.5 g/L)	+
Hypertriglyceridemia (>178 mg/dl)	+
Hyperferritinemia (>500 μg/L)	+
Presence of hemophagocytosis in the bone marrow aspirates	No data

[13, 41, 42]. All this taken together suggests that MIS-C, as a complication of SARS-CoV-2 infection, to a certain extent resembles secondary HLH associated with infectious etiological factors, primarily with such viral infections as Epstein–Barr virus, cytomegalovirus, herpes simplex virus, parvovirus B-18, and HIV [43, 44].

Immunopathological mechanisms

Development of symptoms 2–4 weeks after contracting SARS-CoV-2 virus, more often in patients with anti-SARS-CoV-2, indicates that MIS-C is a post-infectious complication,

Table 6. Preliminary guidelines for the treatment of multisystem inflammatory syndrome in children (MIS-C)

Drug names	Recommended dosing regimens	Notes
IVIG	When KD criteria are present – 2 g/kg body weight. When MAS/HLH criteria are present – 1–2 g/kg body weight.	With extreme caution if kidney function is impaired
Acetylsalicylic acid	When KD criteria are present 30–50 mg/kg/day, and dose de-escalation to 3–5 mg/kg/day in >48 hours after the resolution of fever	With extreme caution in severe thrombocytopenia
Glucocorticoids*	Treatment regimen in accordance with the recommendations for KD, when necessary criteria are present. Treatment regimen in accordance with the recommendations for HLH, when required criteria are present.	With caution in patients having positive PCR test in view of simultaneous viral infection
Anakinra*	2–6 mg/kg/day i/v, treatment duration depends on patient's response and status	
Tocilizumab*	12 mg/kg i/v in patients weighing <30 kg, and 8 mg/kg in patients weighing > 30 kg	

Note. * Sepsis should be ruled out.

and not a manifestation of acute infection [34]. Meanwhile, MIS-C pathogenetic mechanisms are far from being clear [2, 33, 45]. It has been established that IgG anti-SARS-CoV-2 can be detected approximately 2 weeks after contracting SARS-CoV-2 infection, although synthesis of antibodies is not always associated with recovery. It is noteworthy to mention that high titers of IgG and IgA antibodies to SARS-CoV-2 S (spike) protein are detected in children with MIS-C and negative SARS-CoV-2 – PCR tests [46], moreover these titers in children with MIS-C are higher than in adults with severe COVID-19 [47]. At the same time, a decrease in the neutralizing activity of anti-SARS-CoV-2 in patients with MIS-C is indicative of a defect in protective antiviral immunity [48]. In contrast to COVID-19 course in adults [49], the role of specific T-cell immune response to SARS-CoV-2 that potentially contributes to recovery or progression of the disease is not clear in children. Available evidence suggests that SARS-CoV-2 S protein can directly activate T cells. This potential is associated with "superantigen-like" motif in S-protein structure which is equivalent to staphylococcal endotoxin B [50], and, therefore it can eventually induce hyperproduction of proinflammatory cytokines. Quite remarkable is the fact that higher concentration of antibodies against the receptor-binding-domain (RBD) of SARS-CoV- 2 S protein is found in patients with severe MIS-C [51] vs moderately severe disease, and higher titers usually correlate with more severe inflammation. The RBD is involved in viral binding to ACE-2 in the cells expressing this enzyme. Presumably anti-SARS-CoV-2 induce a proinflammatory phenotype of immune response in MIS-C triggered by antibody-dependent enhancement (ADE) mechanisms [52], as it had been observed with dengue fever, direct cellular cytotoxicity, formation of "pathogenic" immune complexes (IC), "hyperimmune" activation of macrophages or catalytic antibody activity (abzyme), modifying ACE-2 performance. Another study showed that detection of neutralizing anti-SARS-CoV-2 in MIS-C is associated with excessive production of proinflammatory cytokines such as interleukin (IL) 18, IL16, with increased chemotaxis of myeloid cells, activation of lymphocytes, monocytes, and natural killer cells, and overexpression of ICAM-1 (intercellular adhesion molecule 1) and Fc-γ receptor 1 on surfaces of neutrophils and macrophages [53]. Abundant data on a wide range of autoantibodies that bind to endothelial, interstitial, and immune cells is of particular importance, hypothetically allowing to consider MIS-C as a kind of virus-induced autoimmune disease. Additionally, serum of patients with MIS-C was found to contain circulating immune complexes consisting of antibodies to the S-protein and the protein itself which triggered macrophage activation [54]. MJ Carter et al. [55] reported increased serum concentrations of proinflammatory cytokines including IL1β, IL6, IL8, IL10, IL17, interferon (IFN)-γ, alongside with T- and B-cell lymphopenia in the acute phase of MIS-C, which is very similar to laboratory findings in patients with severe COVID-19 complicated by CSS [56]. Additionally, MIS-C cases were associated with increased expression of CD64 (Fc γ receptor involved in the activation of proinflammatory M1 macrophages) on the membrane of neutrophils and monocytes, and HLA-DR (activation marker) on the membrane of γσ T cells and $CD4^+CCR7^+$ T-cell. Moreover, recovering patients tended to gradually normalize the above-mentioned immune disorders. Another study showed that the range of "hyperinflammation" biomarkers in patients with MIS-C is distinct from that detected in adult COVID-19 cases and children with KD, mostly because of the Th17 type of immune response predominance in KD [57]. Preliminary data on the features of cytokine hyperproduction profiles in patients with MIS-C, KD, MAS and CSS in COVID-19 were obtained by other authors [58, 59].

Principles of therapy

The goals of MIS-C treatment include suppression of systemic inflammation and reduction of persistent organ and system failure risk, but guidelines and recommendation for MIS-C therapy are under development [60–63]. It should be emphasized that, fortunately, the mortality rates in children with MIS-C are relatively low (about 6%), which is significantly lower than in adults with severe COVID-19, especially when complicated by the CSS. Taking into account the recentness of this challenge, current preliminary recommendations are based on the results of open studies [14, 32, 64–73] and the opinion of experts who extrapolated the experience from management of pathogenetically and clinically similar conditions, primarily KD, MAS, HLH, and the CSS syndrome in COVID-19 (Table 6). These recommendations generally envisage administration of intravenous immunoglobulins (IVIG), glucocorticoids (GCs), aspirin, and direct anticoagulants. IVIG with a wide range of immunomodulatory, antiviral and antibacterial effects, is not only the most efficient therapy for KD [74, 75], but also readily used in severe exacerbations of SARDs, sepsis [76], and COVID-19 [77–79]. It is noteworthy to mention that some IVIG preparations contain antibodies that cross-react with SARS-CoV-2 [80]. Plasma of recovered COVID-19 patients is believed to produce positive effect in critically ill not only due to the content of antiviral neutralizing antibodies, but also due to immunomodulatory effects similar to those of IVIG [81]. Rheumatology has accumulated an immense positive experience with GCs in management of "critical" SARDs complications [82] relying on extremely broad spectrum of anti-inflammatory and immunomodulatory effects of these drugs [83, 84]. Potentially GCs can block synthesis of a wide range of proinflammatory mediators (including IL-1α/β, IL6, IL12, IL17, IFN-γ, TNF-α, etc.) [84], which may have pathogenetic significance in development

of KD, MIS-C and COVID-19. Results of the RECOVERY (Randomised Evaluation of COVid-19 thERapY) study demonstrate a drop in mortality following administration of dexamethasone in severe COVID-19 patients [85]. Therapeutic relevance of biologics, including inhibitors of IL1, IL6 and TNF-α is substantiated by immune mechanisms underlying MIS-C [45]. According to S Godfred-Kato et al. [23], 80.5% of children with MIS-C received IVIG, 62.8% – systemic GCs, 58.6% – antiplatelet agents, 44.2% – anticoagulants, 41.9% – vasoactive drugs, 22.6% – biologics, and 38.1% of children required oxygen support. Preliminary results suggest IL1 inhibitors to be the most effective therapy for patients resistant to IVIG and GCs, as Anakinra proved high efficacy in children with systemic JIA [86, 87], MAS [88, 89], secondary HLH [90, 91], septic shock [92], as well as in adults with COVID-19 complicated by CSS [93–101]. It is hoped that accumulation and integration of the results from open studies, especially from the pediatric segment of the RECOVERY study, will allow us to better understand the mechanism and predictors of disease progression to MIS-C and find best solutions in terms of effective and safe therapies for pediatric patients.

Conclusion

Currently important data have been obtained supporting recognition of SARS-CoV-2 role in the pathogenesis of a wide range of "hyperinflammatory" syndromes not only in adults [35, 36], but also in children. MIS-C presumably can be considered as a post-viral (autoimmune?) syndrome, induced by SARS-CoV-2 infection [53, 57]. The role of autoimmune mechanisms is evidenced by data confirming presence of a wide range of autoantibodies in the serum of MIS-C patients that react with antigenic determinants of cardiac, vascular, and gastrointestinal cells [53, 57], also including endoglin, a vascular endothelial glycoprotein involved in maintaining the integrity of the vascular wall. Hyperproduction of a wide range of anti-nuclear autoantibodies documented in adult patients correlated with the severity of COVID-19 [102–105]. However, many questions concerning immunopathological mechanisms and specific features differentiating MIS-C from KD, toxic shock syndrome, HLH, and MAS remain unanswered. Genetic predisposition is an important risk factor for KD and HLH, however, such genetic (or epigenetic) mechanisms that may be involved in MIS-C pathogenesis are not yet established. Further research is needed to develop safe and most effective pharmacotherapeutic strategy for MIS-C with due regard for its clinical and pathogenetic heterogeneity.

Research transparency

The study was not sponsored. Authors are fully responsible for submitting the final version of the manuscript for press.

Declaration on financial and other relationships

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