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A new multisystem inflammatory syndrome temporally associated with SARS-CoV-2 in a 6-year-old boy

Nowa wieloukładowa choroba zapalna o możliwym związku z zakażeniem SARS-CoV-2 u 6-letniego chłopca

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Abstract

In December 2019, China reported cases of infections caused by a new zoonotic coronavirus, which gradually developed into a pandemic. The disease was initially believed to be mild in children. In April 2020, a possible relationship between a new paediatric multisystem inflammatory syndrome and SARS-CoV-2 was found. In May, the Royal College of Paediatrics and Child Health published the criteria for the diagnosis of this new disease. We present a case of a 6-year-old boy retrospectively diagnosed with SARS-CoV-2-related multisystem inflammatory syndrome based on medical history, physical examination, laboratory and imaging findings, as well as the available literature.

Keywords: multisystem inflammatory syndrome, COVID-19, paediatric population

Streszczenie

W grudniu 2019 roku w Chinach odnotowano przypadki zachorowań na nowego odzwierzęcego koronawirusa, które stopniowo przybrały postać pandemii. Początkowo sądzono, że zachorowania u dzieci mają łagodną postać. W kwietniu 2020 roku stwierdzono możliwy związek nowej wieloukładowej choroby zapalnej u dzieci z SARS-CoV-2. W maju Royal College of Paediatrics and Child Health opublikowało kryteria konieczne do rozpoznania nowej jednostki chorobowej. W pracy przedstawiono przypadek 6-letniego chłopca, u którego na podstawie danych z wywiadu, badania przedmiotowego, wykonanych badań laboratoryjnych i obrazowych oraz w odniesieniu do dostępnych publikacji autorki rozpoznały retrospektywnie wieloukładową chorobę zapalną o możliwym związku z zakażeniem SARS-CoV-2.

Słowa kluczowe: wieloukładowa choroba zapalna, COVID-19, populacja pediatryczna

INTRODUCTION

Coronaviruses are a large family of viruses that are common in animals, but many also infect humans. In the recent years, new coronaviruses responsible for severe respiratory infections have emerged.

Cases of infections caused by the new zoonotic coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were first reported in December 2019 in China. In the months that followed, rapid spread of infections, initially in China's neighbouring countries and then worldwide, was observed. In mid-March 2020, the World Health Organization (WHO) announced the SARS-CoV-2 pandemic⁽¹⁻³⁾.

A total of 23,424,844 cases and 808,716 deaths due to SARS-CoV-2 infection (coronavirus disease 19, COVID-19) had been reported by August 24 this year.

Until now, children have rarely been affected by COVID-19. The disease has been milder in children than in adults, and asymptomatic cases have been frequently reported^(1,4,5). Symptomatic cases in paediatric patients usually manifest as acute respiratory infection with fever and cough. Unlike adults, children are more likely to present with extrapulmonary symptoms in the form of diarrhoea and vomiting^(4,6). Gastrointestinal symptoms occur due to the presence of angiotensin-converting enzyme 2 (ACE2) receptors not only in lung cells, but also in intestinal epithelial cells. The presence of the virus in patient's intestinal biopsy samples and stool is evidence for the possible tropism to the gastrointestinal tract⁽³⁾.

Xu et al. investigated the presence of SARS-CoV-2 nucleic acid in rectal swabs from 10 children with COVID-19, and found that the time from the initial positive result to testing negative was up to 51 days compared to 7 days for a throat swab in the same patients. This study showed that rectal swabs may be more useful than nasopharyngeal swabs in the assessment of treatment efficacy and the time of infection resolution in children. However, there is no direct evidence for viral transmission by the faecal-oral route^(3,7).

In April 26, 2020, the North Central London Clinical Commissioning Group and the Paediatric Intensive Care Society warned about the possible relationship between a new form of multisystem inflammatory syndrome and SARS-CoV-2 infection. The reported cases of young patients with the new disease resembled Kawasaki disease, macrophage activation syndrome (MAS) or toxic shock syndrome (TSS). Some of these patients were confirmed to be SARS-CoV-2-positive^(2,5).

In May 2, 2020, the Royal College of Paediatrics and Child Health (RCPCH) published guidelines for the diagnosis and management of a suspected multisystem inflammatory syndrome temporally associated with COVID-19, based on the analysis of reported cases⁽⁵⁾.

We present a case of multisystem inflammatory syndrome apparently related to infection with SARS-CoV-2 in a 6-year-old boy. The diagnosis was established

retrospectively based on the analysis of available literature reports.

CASE REPORT

On April 22 this year, a 6-year-old boy was admitted to the Department of Paediatrics and Gastroenterology of the Medical University of Lublin. Abdominal pain, an episode of vomiting and a fever of up to 40°C persisting for two days and poorly responding to antipyretic drugs were the direct reasons for admission.

Previously, the child was healthy, vaccinated according to the vaccination schedule. The boy lived only with his mother, who showed no alarming symptoms at the time of her son's admission to the hospital or during his hospital stay.

On admission, the boy's overall condition was moderate. On physical examination, no abnormalities were found other than tenderness on palpation of the right hypochondrium and middle abdomen. Laboratory workup performed on day 1 revealed increased inflammatory markers, leukopenia with lymphocytosis, minor microcytic anaemia, increased activity of aminotransferases and gamma-glutamyl transpeptidase, reduced total protein and albumin, increased D-dimers, with normal fibrinogen levels despite the inflammatory reaction.

Abdominal ultrasound (US) performed after hospital admission showed the gallbladder surrounded by hypodense oedema up to 5 mm thick and a slightly enlarged spleen. Chest radiography was unremarkable.

On day 2 of hospital stay, the patient developed a coarse, confluent rash on the skin of the face, trunk and, to a lesser extent, the limbs and perineal area, as well as palmar erythema. The skin lesions persisted for 3 days, changing their morphology from macular to garland-like during this period; the rash was not haemorrhagic. Furthermore, bilateral non-purulent conjunctivitis was observed during the first days of hospital stay. On day 3, the boy developed oedema, mainly in the hands and feet, as well as had very low albumins. Similar symptoms and albumin levels persisted despite repeated administration of 20% albumins.

Fever of up to 40°C persisted despite antibiotic therapy and antipyretics. The clinical picture and laboratory findings raised a suspicion of Kawasaki disease. A rheumatological and neurological consultation was ordered. The rheumatologist examining the boy did not find a sufficient number of criteria confirming the disease. Echocardiography (ECHO) showed no significant heart pathology.

Due to the persistent pancytopenia and suspicion of MAS, a haematologist consultation was ordered, followed by bone marrow biopsy. Myelogram showed no abnormalities.

Nasopharyngeal swab for SARS-CoV-2 was negative. Due to the lack of availability of serological tests that could confirm infection with the new coronavirus, such a test was not performed.

Diagnostic serology for influenza virus, parvovirus B19, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes



Fig. 1. Abdominal US. A gallbladder surrounded by oedema

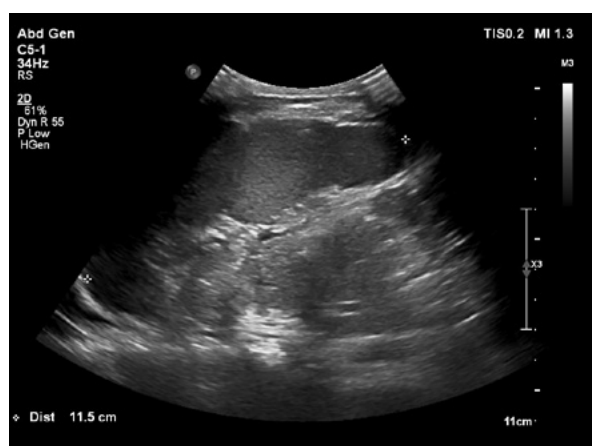


Fig. 2. Abdominal US. Enlarged spleen

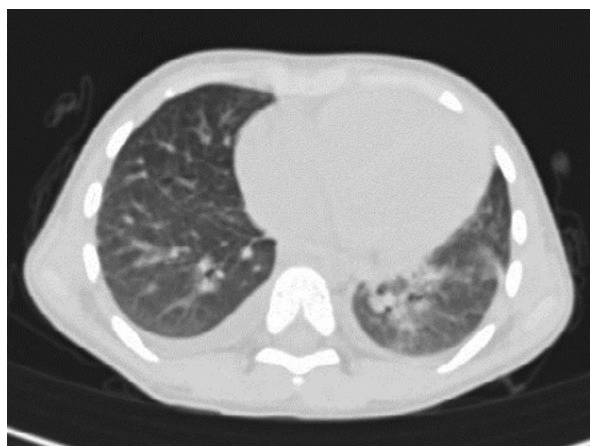


Fig. 3. A CT image. Fluid in both pleural cavities and minor parenchymal densities in the lower lung segments

simplex virus (HSV), and human herpes virus type 6 (HHV6) did not confirm infection with any of these infectious agents. Blood cultures collected on day 1 showed no growth. Due to the child's severe condition, high fever and persistent abdominal pain, abdominal computed tomography (CT) was performed on day 4 of hospital stay. It revealed an increased amount of fluid in the peritoneal cavity and

a slightly enlarged spleen. The CT also partially covered the chest, showing fluid in both pleural cavities and small parenchymal densities in the lower segments of the lungs.

Empirical antibiotic therapy (Augmentin), which was started on admission, was switched to broad-spectrum (meropenem, vancomycin) antibiotic therapy due to lack of improvement in the child's condition and deteriorating laboratory values. The boy received a single intravenous infusion of immunoglobulins on day 3 of hospital stay.

The child's vital signs were constantly monitored during hospitalisation, with no significant deviations. Fluid balance was performed, persistent hypoalbuminaemia was corrected with intravenous albumin infusions, and diuretics were administered due to oedema.

The treatment resulted in a gradual improvement in the clinical condition and normalisation of laboratory parameters. The boy was discharged home in good overall condition after 2 weeks of hospital stay.

The course of the disease in the described patient was not severe, no decompensation was observed, possibly as a result of treatment with intravenous immunoglobulins. The disease in the child was treated as a severe infection of unknown aetiology. It did not fully meet the criteria for Kawasaki disease or MAS. The similarity of the symptoms in the presented patient and laboratory findings allowed to retrospectively establish a likely diagnosis of a multisystem inflammatory disease temporarily associated with SARS-CoV-2 infection (Figs. 1–3, Tab. 1).

DISCUSSION

Since last December, infection with a new zoonotic coronavirus, known as severe acute respiratory virus 2 (SARS-CoV-2), has been the subject of many clinical observations and literature reports. The disease that develops as a result of infection with the SARS-CoV-2 is referred to as COVID-19^(1,3,6).

Due to the mass scale of infections, the WHO announced the SARS-CoV-2 pandemic on 11 March 2020. There had been 23,424,844 cases of SARS-CoV-2 infection reported by 24 August 2020.

Coronaviruses are enveloped viruses whose genome of about 30 kb is positive-sense single-stranded RNA. Depending on the genomic structure, there are four types of coronaviruses: α , β , γ and δ , with α and β coronaviruses infecting mammals only. Human coronaviruses such as 229E and NL63 are responsible for respiratory infections and belong to the group of α coronaviruses. The human Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 are classified as β coronaviruses⁽⁸⁾.

It was observed during the pandemic that infection with SARS-CoV-2 in adults varies from asymptomatic forms, through symptoms of upper respiratory tract catarrh, to severe respiratory failure requiring treatment in intensive care units. There are probably many reasons for the varied course of COVID-19, such as genetic predisposition,

Laboratory parameters	Reference range	On admission	Week 1 of stay	Week 2 of stay	At discharge
C-reactive protein [mg/dL]	0–0.5	5.63	13.24–3.56	1.54–0.38	Not performed
Erythrocyte sedimentation rate [mm/h]	2–15	27	Not performed	44	Not performed
Procalcitonin [ng/mL]	<2	2.940	12.590–0.350	0.124–0.085	Not performed
White blood cells [thousand/mm ³]	3.4–9.5	2.55	3.08–11.19	11.39–7.87	6.9
Lymphocytes [thousand/mm ³]	1–3.6	0.38	0.51–2.62	3.29–4.43	4.37
Thrombocytes [thousand/mm ³]	140–420	101	68–147	410–878	842
Lactate dehydrogenase [U/L]	0–764	473	430	Not performed	Not performed
Ferritin [ng/mL]	4–67	642	639.1–562.6	339.8	Not performed
Lactates [mmol/L]	0.5–2.2	3.7	3.1–2.0	Not performed	Not performed
Fibrinogen [g/L]	2.00–4.00	2.40	2.89–2.47	Not performed	Not performed
D-dimers [ng/mL]	<500	7,456	6,832–5,520	2159	Not performed
Alanine aminotransferase [U/L]	0–39	167	127–37	28	31
Aspartate aminotransferase [U/L]	0–52	252	142–44	32	Not performed
Gamma-glutamyl transpeptidase [U/L]	<26	117	106–74	62–41	35
Total protein [g/mL]	6.0–8.0	4.85	3.99–4.43	5.61–7.37	Not performed
Albumins [g/mL]	3.8–5.4	3.01	2.36–3.23	3.72–4.21	Not performed

Tab. 1. Laboratory findings

differences in the expression of ACE2 molecules or dipeptidyl peptidase-4 (DPP4) receptors, which enable the virus to enter cells, or earlier exposure to another coronavirus⁽⁹⁾. According to literature data and media reports, children are less likely to contract SARS-CoV-2, and if infected, they present milder manifestations^(2,8,10,11).

The lower prevalence and generally milder course of SARS-CoV-2 in children may be explained by the hypothesis on its molecular mechanism, which is based on the affinity of the virus to the ACE2 receptor. The action of the human coronavirus depends mainly on the interaction between its transmembrane spike glycoprotein (S-protein) and specific angiotensin-converting cellular receptors (ACE2). The angiotensin 2 converting enzyme has been identified as a functional receptor for SARS-CoV-2. It has been shown that the expression of this enzyme begins to increase later in childhood, which may protect children from the most aggressive course of infection⁽⁶⁾.

In addition to differences in ACE2 expression levels between adults and children, it has been shown that ACE2 expression may also depend on gender. The ACE2 gene is located on chromosome X. Circulating ACE2 levels are higher in males than in females, which may partly account for the differences in the severity and mortality between the two groups, both in adults and children/adolescents.

The qualitative differences in response to the SARS-CoV-2 virus between children and adults may also result from the immune developmental stage. With age, continuous antigenic stimulation and thymic involution alter the distribution in the T cell pool from naïve T cells to central memory T cells, effector T cells and memory T effector cells. This process is accompanied by loss of expression of co-stimulatory molecules, such as CD27 and CD28, which increases susceptibility to infections. In the early postnatal period, CD4+ T cells are unable to produce Th1-mediated

proinflammatory cytokines to the benefit of Th2 cells. CD8+ T cells reduce the expression of cytotoxic and inflammatory mediators. The reduced ability of T cells to destroy microbes early after birth may explain the susceptibility of infants to SARS-CoV-2. The third possibility is that the simultaneous presence of other viruses in the lungs and airways, which is common in young children, may force the SARS-CoV-2 virus to compete with them and, consequently, limit its growth⁽⁸⁾.

During the pandemic, attention was drawn to the possible association between SARS-CoV-2 infection in children and a new multisystem inflammatory syndrome. The first reports on this relationship appeared in the last week of April this year, and were based on cases among paediatric patients in Great Britain. This fact was reported by the North Central London Clinical Commissioning Group and the Paediatric Intensive Care Society. Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PMIS) is the working name of the disease. According to the data, the course of PMIS may be similar to that seen in Kawasaki disease, MAS or TSS^(1,2,5,9).

This comparison between SARS-CoV-2 infection and hyperferritinemic syndromes is based on the similar proinflammatory cytokine profile, the so-called cytokine storm, high ferritin levels, lymphopaenia, reduced number and activity of NK cells, coagulopathy and abnormal liver parameters⁽⁹⁾. It is likely that the level of ferritin plays a key role in monitoring patient's condition – high levels clearly correlate with the severity of the disease. The H subunit of ferritin shows proinflammatory activity, inducing the expression of many inflammatory mediators, and the iron released from ferritin additionally promotes a procoagulant state by producing a hydroxyl radical. Therefore, the use of deferoxamine, an iron chelator, is currently being investigated in patients with severe COVID-19 infection⁽⁹⁾.

The similarity in molecular mechanisms underlying hyperferritinic syndromes and PMIS support the concept of using anti-inflammatory and immunomodulating drugs, such as inhibitors of interleukins IL-1, IL-6, IL-18, glucocorticosteroids, cyclosporin, intravenous immunoglobulins, as well as plasmapheresis. There are ongoing studies assessing the efficacy of tocilizumab⁽⁹⁾.

A milder course of COVID-19 has been noted in some patients undergoing immunosuppressive therapy for other indications, including organ transplantation and rheumatic diseases. A register of such patients is kept by the Italian Society of Rheumatology and the European League Against Rheumatism⁽⁹⁾.

Despite the relatively small number of cases of PMIS compared to the number of patients with COVID-19, the RCPCH published guidelines for the diagnosis and treatment of PMIS in early May 2020^(1,5,12).

According to the RCPCH, PMIS can be diagnosed in a child with a persisting fever, dysfunction of one system (urinary, cardiovascular, respiratory, neurological, or gastrointestinal) or multiple systems (shock syndrome). The clinical symptoms include lymphadenopathy, hepatic and/or splenic enlargement, and a change in the pattern of skin lesions. A child suspected of this disease presents with elevated levels of inflammatory parameters, neutrophilia accompanied by lymphopaenia, as well as thrombocytopenia, elevated ferritin and triglyceride levels, decreased fibrinogen levels, increased D-dimers, increased activity of aminotransferases, lactate dehydrogenase, hypoalbuminaemia, hyponatraemia and, in some cases, renal dysfunction markers. Infectious aetiology of the disorders should be excluded in a patient suspected of having PMIS. Confirmation of SARS-CoV-2 infection is not necessary.

Diagnostic imaging of the respiratory tract usually shows heterogeneous, symmetrical infiltrates accompanied by pleural effusion. Children with PMIS require hospitalisation and an assessment by an infectious disease specialist, rheumatologist and cardiologist in order to diagnose myocarditis or coronary vessel pathologies in a timely manner. It is necessary to monitor patient's vital signs; treatment in an intensive care unit may be necessary if the patient's condition worsens^(1,5,11).

The Royal College of Paediatrics and Child Health recommends symptomatic treatment of PMIS after resuscitation of the patient, if needed. Empirical antibiotic therapy is routinely used after sampling blood for culture. Children meeting the Kawasaki disease criteria should be treated with an intravenous infusion of immunoglobulins. Virological and bacteriological tests should be performed, if possible, before the administration of immunoglobulins. The Royal College of Paediatrics and Child Health recommends collecting patient's serum and plasma samples for research purposes. Specialist treatment – antiviral or immunomodulating – can only be used in specialised centres, following the decision reached during a medical case conference held by doctors of many specialties^(1,5,12).

In Bergamo (Italy), Verdoni et al. observed a 30-fold higher incidence of Kawasaki disease at the peak of the pandemic compared to the last 5 years. The authors also described a group of 10 paediatric patients hospitalised during the coronavirus pandemic, half of whom met the full criteria for Kawasaki disease and half of whom met part of the criteria. Five of the described patients presented symptoms of shock requiring fluid therapy, and 2 patients were administered positive inotropic medications. Two of the described children had a positive polymerase chain reaction (PCR) swab, while 8 had positive serology. However, since these tests were not performed during the presence of disease symptoms, it is difficult to clearly confirm the relationship between SARS-CoV-2 infection and the symptoms presented by patients⁽¹³⁾.

Belhadjer et al. described a group of 35 patients aged 2–16 years with persistent fever and symptoms suggesting Kawasaki disease. None of the patients presented with the full symptomatology. Signs of left ventricular dysfunction (ejection fraction <50%) were confirmed based on laboratory findings [elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP)] and diagnostic imaging (ECHO) in all patients. Some patients developed cardiogenic shock. Infection with SARS-CoV-2 was confirmed based on nasopharyngeal swab using PCR or serological examination in 88.5% of patients. Infection with SARS-CoV-2 was not confirmed in the other patients. The authors suggested a possible mechanism of cardiac and pulmonary damage in the described patients, assuming that it was caused by a cytokine storm triggered by an abnormal response of pro-inflammatory cells and T cells⁽¹¹⁾.

Waltuch et al. described cases of PMIS in 4 children serologically positive for COVID-19. The authors pointed to typical laboratory abnormalities in patients: increased C-reactive protein, erythrocyte sedimentation rate, procalcitonin, ferritin, D-dimers, and lactate dehydrogenase activity. Furthermore, high levels of IL-6, IL-8 and tumour necrosis factor α (TNF- α) were also found in the described patients. The patients were treated, among other things, with tocilizumab – an anti-IL-6 antibody. According to Waltuch et al. the release of proinflammatory cytokines (cytokine storm) in the course of PMIS may be responsible for increased vascular permeability, multiorgan failure and decompensation in the patient⁽²⁾.

Symptoms observed in PMIS, most likely resulting from immune disorders accompanying SARS-CoV-2 infection, are also emphasised by other authors. Dolinger et al. described a case of PMIS in an adolescent with Crohn's disease. The girl developed symptoms of a multisystem inflammatory disease, a fever lasting 5 days, skin rash, drops in blood pressure resistant to fluid therapy and severe abdominal pain. Laboratory workup showed increased activity of liver enzymes, increased inflammatory parameters, and an increased profile of proinflammatory cytokines (IL-6, IL-8, TNF- α) than is usually observed in inflammatory

bowel diseases. Treatment of exacerbations of Crohn's disease with infliximab (anti-TNF- α antibody) led to improvement of the patient's general condition within a few hours, which suggests a possible therapeutic role of anti-TNF- α preparations in inhibiting the inflammatory cascade in COVID-19⁽¹⁴⁾.

CONCLUSIONS

Considering the available scientific reports and clinical case reports published to date, multisystem inflammatory syndrome temporally associated with COVID-19 should be suspected in all children with the symptoms of severe infection of unknown aetiology.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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