

COVID-19 associated Paediatric Inflammatory Multisystem Syndrome (PIMS) in children

Klučka J.¹, Kratochvíl M.¹, Dominik P.¹, Homola L.², Horák O.³, Nečas J.⁴, Jabandžiev P.⁴ and Štourač P.¹

¹Department of Paediatric Anaesthesia and Intensive care medicine, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic

²Department of Children's Infectious Diseases, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic

³Department of Paediatric Neurology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic

⁴Department of Paediatric, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic

ABSTRACT

The clinical course of the SARS-CoV-2 virus infection (COVID-19 disease) in paediatric patients is predominantly mild. However, in a small percentage of paediatric patients, the COVID-19 could lead to the development of with the Paediatric Inflammatory Multisystem Syndrome (PIMS) presenting as high fever, gastrointestinal symptoms, neurological symptomatology and even as multiorgan dysfunction. These three cases represent the first published report of critically ill paediatric patients with PIMS in the Czech Republic.

KEYWORDS

COVID-19 – inflammatory syndrome – paediatric patient

SOUHRN

Klučka J., Kratochvíl M., Dominik P., Homola L., Horák O., Nečas J., Jabandžiev P. a Štourač P.: Covid-19 u dětí spojený s dětským zánětlivým multisystémovým syndromem (PIMS)

Průběh infekce virem SARS-CoV-2 (onemocnění covid-19) je u většiny pediatrických pacientů mírný. U malého procenta dětských pacientů může po překonání covid-19 infekce dojít k rozvoji multisystémového zánětlivého syndromu (PIMS), který se prezentuje horečkou, gastrointestinálním diskomfortem často napodobujícím náhlou příhodu břichu, a neurologickou symptomatologií v kombinaci s multiorgánovým selháním. Tři uvedené kazuistiky pediatrických pacientů s PIMS představují první publikované případy kriticky nemocných pacientů v České republice.

KLÍČOVÁ SLOVA

covid-19 – zánětlivý multisystémový syndrom – pediatrický pacient

Epidemiol Mikrobiol Imunol, 2021;70(4):281–284

INTRODUCTION

During 2020, the SARS-CoV-2 pandemic has led to almost 100 million confirmed cases of COVID-19 and 2 million deaths. In the majority of reported paediatric patients infected with COVID-19, the disease had only mild symptomatology, presented predominantly as upper respiratory tract infection [1]. However, in the spring of 2020, a rising number of paediatric patients with Kawasaki-like syndrome were reported, with high fever, maculopapular rash, conjunctivitis, gastrointestinal symptoms, cardiac or even multiple organ dysfunction [2]. In majority of these patients (> 85%), the association with COVID-19 was confirmed by high anti-SARS-CoV-2 antibodies [3]. The condition was classified initially as Multiple Inflammatory Syndrome in Chil-

dren (MIS-C). However, the term COVID-19 associated with Paediatric Inflammatory Multisystemic Syndrome (PIMS) is currently preferred. We would like to present three cases of critically ill paediatric patients with PIMS.

CASES PRESENTATION

Case 1

A previously healthy 13-year-old patient with six days course of upper respiratory tract symptoms and high fever (up to 40.0 °C) treated by a paediatrician with cefuroxime orally was admitted to the paediatric intensive care unit (PICU) in septic shock, after cardiac arrest (initial rhythm ventricular fibrillation, the return of spontaneous circulation in 15 minutes). The patient

was not previously tested for SARS-CoV-2 nor had a risk contact (information from mother). He remained in severe circulatory shock despite fluid resuscitation (noradrenalin 0.7 µg/kg/min), with severe acute respiratory distress syndrome (ARDS with P/F ratio 47 mmHg on positive-end-expiratory pressure – PEEP 12 cm H₂O) and bleeding disorder (oral and nasal cavity). The macular rash was present on both hands, with subsequent desquamation and bilateral non-purulent conjunctivitis. Admission cardiac troponin I (c-Tn-I) was highly elevated (3.92 ng/mL, normal range 0.0–0.4 ng/mL). Inflammatory markers (C-reactive protein – CRP 311 mg/L, normal range 0–10 mg/L, procalcitonin – PCT over 50 ng/mL, normal range < 0.05 ng/mL presepsin 5 899 pg/mL, normal range < 320 pg/mL) and D-dimers (over 35 mg/L, normal range < 0.5 mg/L) were elevated with thrombocytopenia ($99 \times 10^9/L$, normal range $150\text{--}450 \times 10^9/L$) were present at admission. The X-ray revealed left-sided lobar pneumonia, antibiotic therapy with meropenem and vancomycin was initiated. Reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nasopharyngeal swabs were negative both on admission and at control after 48 hours. No causative pathogen was found on the microbiology and PCR testing during the whole PICU stay. The patient's condition gradually improved and he was weaned from mechanical ventilation and extubated on day 5. During the PICU stay, the blood cultures, blood PCR screening, sputum (cultivation and PCR) were all negative. Serology was positive for IgM (5.61 PI – positivity index, < 1.1 neg, ≥ 1.1 positive) and IgG (> 400 AU/mL, <12 AU/mL neg., 12–15 unclear, >15 positive) anti-SARS-CoV-2 antibodies (chemiluminescent immunoassay method testing) during the hospital stay (on 22nd day after admission).

Magnetic resonance imaging (MRI) of the brain was performed due to qualitative disorder of consciousness with the findings of hyperintensity (FLAIR sequence) of basal ganglia (n. caudatus and putamen). The condition was gradually improving over the hospital stay.

Case 2

A healthy 11-year-old boy was admitted to a regional hospital after a 7-day course of high fever, elevated CRP (205–190 mg/L) and signs of acute abdomen. The patient was tested negative (PCR) for SARS-CoV-2 15 days before initial symptoms, with PCR positive mother in the same household. At admission, he had tachypnea (25–30/min), tachycardia (130/min) and appeared toxic. Antibiotic treatment was initiated and, the patient was transferred to PICU at the University Hospital. COVID-19 antigen test was negative. At the admission, he was hypotensive (noradrenaline – NRA up to 0.41 µg/kg/min) despite fluid resuscitation, inflammatory markers were elevated (CRP 164 mg/L, procalcitonin 16.64 ng/mL, presepsin 2 226 pg/mL), with thrombocytopenia ($35 \times 10^9/L$), lymphopenia

($0.59 \times 10^9/L$), elevated D-dimers (9.66 mg/L) and hyponatremia (129 mmol/L). After initial assessment and partial stabilization, an appendectomy was performed, with the appendix without macroscopical signs of inflammation. The nasopharyngeal swab for SARS-CoV-2 and Rapid antigen test on day 3 were both negative; however, serology on day 6 revealed positive anti-SARS-CoV-2 IgM (2.03) and IgG (105 AU/mL) antibodies together with positive anti-*Mycoplasma pneumoniae* IgM antibodies. His condition gradually improved, and after eight days he was transferred to the standard ward.

Case 3

11-year-old boy without comorbidities was admitted to the regional hospital with a three-day history of fever, abdominal discomfort and severe headache. There were no reported epidemiologic risk contact and no previous SARS-CoV-2 tests performed before admission. Laparoscopic appendectomy was performed with ulcero-phlegmonous appendicitis findings and antibiotics (ATB) therapy (piperacillin-tazobactam, gentamicin, metronidazole) was initiated. His condition gradually worsened over the next three days, accompanied by a high fever, severe headache, positive meningeal signs with progressive tachypnoea and hypotension. Computed tomography (CT) of the brain was without pathology, CT of the abdomen revealed ileitis and mesenteric lymphadenopathy, lumbar puncture revealed monocytosis in cerebrospinal fluid (CSF). Both SARS-CoV-2 antigen and RT-PCR were negative. Due to progressive multiorgan dysfunction, the patient was transferred to PICU at the University Hospital on the 6th day after initial symptoms. At admission, he was haemodynamically compromised, on norepinephrine (up to 0.3 µg/kg/h), tachypnoeic (30/min), somnolent with high inflammatory markers (CRP 238 mg/L, PCT 4.64 ng/mL, presepsin 1 796 pg/mL), coagulopathy (International Normalized Ratio – INR 1.7) and elevation of D-dimers (3.08 mg/L). Abducens nerve paresis and bilateral conjunctivitis were present. On imaging, bilateral pleural effusions were found with pericardial effusion and slightly depressed myocardial function (ejection fraction – EF 55%). Acyclovir was initiated due to possible herpetic central nervous system infection. After obtaining initial microbiology samples, including CSF, antibiotics were empirically escalated to meropenem and vancomycin (for potential nosocomial septic shock syndrome). A stress dose of hydrocortisone due to circulatory failure was administered, and negative fluid balance was targeted. The blood screening was positive for IgG (77.9 AU/mL) anti-SARS-CoV-2 antibodies, with negative IgM, CSF was negative for common neuropathogens (was not tested for SARS-CoV-2). The patient condition gradually improved over time, and on day 10 (after initial presentation), he was transferred to a secondary hospital for further treatment.

DISCUSSION

Here, we present three cases of patients who have been admitted with similar clinical symptoms – gastrointestinal discomfort, hypotension, headache and fever. The differential diagnosis of these symptoms should raise suspicion on sepsis unknown origin (possible abdominal), central nervous system infection, and recently defined Multisystemic Inflammatory Syndrome in Children (MIS-C) or Paediatric Inflammatory Multisystem Syndrome (PIMS). There are currently several PIMS definitions (World Health Organization – WHO, Royal College of Paediatrics and Child Health – RCPCH and Centers for Diseases Control and Prevention – CDC) [1, 2, 3]. According to the WHO definition, MIS-C could be defined by the combination of fever ≥ 3 days in the patient between 0–19 years and elevated markers of inflammation (CRP, PCT, erythrocyte sedimentation rate), clinical presentation (at least 2 symptoms): skin rash or conjunctivitis, hypotension or shock, myocardial dysfunction (ECHO, troponin, BNP), gastrointestinal symptomatology, coagulopathy, lacking an alternative diagnosis, and relation to COVID-19 infection or exposure [1, 2, 3]. Other reported clinical symptoms related to PIMS are encephalopathy (lethargy, confusion, seizures), respiratory failure, polyserositis [4]. The typical laboratory findings are elevated inflammatory markers (CRP, PCT, presepsin, IL-6) with neutrophilia and lymphopenia together with hypertriglyceridemia and elevated lactate dehydrogenase. Depressed left ventricle systolic function (up to 90% of PIMS cases), elevated cardiac enzymes (troponin) and elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP [4] are further findings. PIMS typically manifest 3–4 weeks after COVID-19 acute infection (PCR positivity) [5] and is associated with positive serum anti-COVID-19 IgG antibodies in the majority of patients [6]. Initial clinical presentation patients with PIMS could be very similar to septic shock. There is an urgent need for clinical approach standardization. All patients should be clinically evaluated according to the ABCD approach (A – airway, B – breathing, C – circulation, D – disability = neurology), and wide infection screening should be initiated (blood cultures, nasopharyngeal swabs for PCR, blood for PCR, sputum and urine cultures, laboratory – CRP, PCT, full blood count, coagulation tests with D-dimer) together with diagnostic imaging (chest radiography, abdominal ultrasound, chest ultrasound and echocardiography). Complete COVID-19 screening – PCR, antigen testing blood antibodies levels could be helpful to distinguish PIMS and acute COVID-19 infection (PIMS has positive IgG anti-COVID-19 antibodies in majority of patients). Broad-spectrum antibiotic therapy according to the local protocol for sepsis/septic shock should be initiated, and in case of high suspicion on PIMS the intravenous immunoglobulins (2 g/kg) should be admini-

stered (although based only on observational data) [3, 4]. In patients with organ dysfunction or shock, methylprednisolone (1–2 mg/kg/day i. v. or 10–30 mg/kg/day in the refractory state – persistent organ dysfunction) should be administered according to the recently published guidelines [7]. In patient refractory to IVIG and corticosteroids, anakinra (interleukin-1 receptor blocker) should be considered. Previously highlighted Tocilizumab is not further recommended for MIS-C treatment due to lack of evidence-based data benefit and long-lasting effect of treatment (long-lasting immunosuppression) [7]. Overall reported mortality of patients with PIMS is up to 1.7%, significantly higher than acute COVID-19 in children (0.09%) [3, 8]. The alarming mortality in combination with a higher incidence of coronary artery aneurysms (up to 7.1%) in PIMS patients compared to Kawasaki disease (1.3%) [3,9] should raise the suspicion on PIMS in every paediatric patient presenting with signs of sepsis or septic shock. For secondary cardiac prevention, low-dose aspirin (3–5 mg/kg/d) should be administered in all patients with MIS-C (except patients with high risk of bleeding, low platelet count $< 80 \times 10^9$) until ≥ 4 weeks from diagnosis and negative echocardiography findings (coronary arteries) [7]. Although immunoglobulin and especially corticoid administration (immunosuppression in possible active infection) should be administered with extreme caution in patients with septic shock or cardiac dysfunction, early aggressive immunomodulatory therapy could lead to early recovery of patients with PIMS. Reported three PIMS cases, represent the first critically ill patients admitted to PICU at University Hospital in Brno and has immediately led to urgent PIMS local protocol formation. At the time of admission, there were only observational data referring to PIMS patients, and no definitive treatment was established. Case 1 was the first-ever PIMS case in PICU, and the positive anti-SARS-CoV-2 antibodies were obtained from the excessive followed laboratory investigations performed at neurologic standard ward after patient's condition stabilization. These factors could explain that corticosteroid treatment and intravenous immunoglobulins were not administered in reported cases. They, however, became standard of care in all following patients, together with acute anti-SARS-CoV-2 antibodies screening in patients presented with PIMS symptoms. In conclusion, during the actual COVID-19 pandemic, PIMS should be considered (ruled out) as a possible diagnosis in all critically ill paediatric patients.

REFERENCES

1. Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr*, 2020;174(9):882–889.

2. Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine*, 2020;26:100527.
3. Whittaker E, Bamford A, Kenny J, et al. PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA*, 2020;324(3):259–269.
4. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. 2021-5-1 [cit.2021-6-30]. Available at: www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19.
5. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. 2020-05-15 [cit.2021-6-30]. Available at: www.who.int/publicationsdetail/multisystem-inflammatory-syndrome-in-children-and-adolescents-withcovid-19.
6. COVID-19: Multisystem inflammatory syndrome in children (MIS-C) clinical features, evaluation, and diagnosis [online]. 2021-4-02 [cit.2021-6-30]. Available at: https://www.uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-clinical-features-evaluation-and-diagnosis?search=coronavirus-disease-2019-covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-clinical-features-e%E2%80%A6&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
7. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2. *Arthritis Rheumatol*, 2021;73(4):e13–e29.
8. Feldstein LR, Rose EB, Horwitz SM, et al. Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med*, 2020;383(4):334–346.
9. Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 paediatric patients: A systematic review. *EClinicalMedicine*, 2020;24:100433.
10. Kil HR, Yu JW, Lee SC, et al. Changes in clinical and laboratory features of Kawasaki disease noted over time in Daejeon, Korea. *Pediatr Rheumatol Online J*, 2017;15(1):60.

Acknowledgements

The work was supported by a Specific University Research provided by MŠMT MUNI/A/1178/2020), supported by MH CZ - DRO (FNBr, 65269705) and supported by funds from the Faculty of Medicine MU to the junior researcher (Jozef Klučka, Martina Kosinová, ROZV/28/LF/2020).

Conflict of interest

None declared.

Authors' contributions

JK, MK, PD, LH, OH, PJ and PS have all contributed to the final text. All authors critically reviewed the manuscript and accepted the last version of it.

Do redakce došlo dne 28. 1. 2021.

Adresa pro korespondenci:
MUDr. Lukáš Homola, Ph.D.
Fakultní nemocnice a LF MU
Jihlavská 20
625 00 Brno
e-mail: Homola.Lukas@fnbrno.cz