CASE REPORT

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Neonatal multisystem inflammatory syndrome during acute SARS-CoV-2 infection

Multisistemski zapaljenski sindrom kod novorođenčadi tokom akutne infekcije SARS-CoV-2

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Abstract

Introduction. During the development and spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, a new inflammatory response syndrome arose in newborns, defined as the multisystem inflammatory syndrome (MIS) in neonates (MIS-N). **Case report.** A term infant girl with a fever diagnosed with SARS-CoV-2 infection was admitted to the hospital. In laboratory findings, the values of lactate dehydrogenase, ferritin, interleukin-6, and D-dimer were elevated. Upon admission, dual parenteral antibiotic therapy (ceftazidime, vancomycin), and one day later, low molecular weight heparin (LMWH) therapy, was commenced. After five days of hospitalization and febrility, with negative results of microbiological analyses and further deterioration of laboratory findings, intravenous immunoglobulin (IVIg) was administered at a dose of 2 g/kg for one day and methylprednisolone at a dose of 1 mg/kg/day for four days, after which the reduction of corticosteroid therapy was continued with prednisone. One day after IVIg dministration, the newborn became afebrile, with the gradual normalization of laboratory findings. The newborn was discharged after 16 days of hospitalization. Ten days after discharge, prednisone therapy was discontinued. Two weeks after discharge, the administration of heparin was discontinued. Seven days later, the D-dimer value increased significantly, and the anticoagulant therapy was reinstated. After one month, the D-dimer value completely normalized, and the LMWH therapy was discontinued. **Conclusion.** After the applied therapy for MIS in children, there was a cessation of febrility and gradual normalization of values of the laboratory parameters. This confirms that the newborn, in this case, probably had MIS-N. The prolonged elevated D-dimer value was most probably a consequence of the MIS.

Key words:
covid 19; diagnosis; fibrin fragment d; heparin, low-molecular-weight; immunoglobulins, intravenous; infant, newborn; inflammation; syndrome.

Apstrakt

Uvod. Tokom razvoja i širenja epidemije izazvane *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), pojavio se novi sindrom zapaljenskog odgovora kod novorođenčadi koji je označen kao multisistemski zapaljenski sindrom (MZS) kod novorođenčadi (MZS-N). **Prikaz bolesnika.** Terminsko novorođenče, devojčica, primljeno je u bolnicu zbog povišene telesne temperature i dijagnostikovane infekcije SARS-CoV-2. U laboratorijskim nalazima nađene su povišene vrednosti laktat dehidrogenaze, feritina, interleukina-6 i D-dimera. Po prijemu, započeta je dvojna antibiotska terapija (ceftazidim, vankomicin) parenteralno, a dan kasnije, i terapija heparinom niske molekulske mase (HNMM). Nakon pet dana hospitalizacije i febrilnosti, pri čemu su nalazi mikrobioloških analiza bili negativni, a zbog daljeg pogoršanja vrednosti laboratorijskih nalaza, primenjena je terapija intravenskim imunoglobulinom (IVIg) u dozi od 2 g/kg jedan dan i metilprednizolonom u dozi od 1 mg/kg/dan četiri dana, nakon čega je nastavljeno postepeno smanjenje terapije kortikosteroidima primenom prednizona. Jedan dan nakon primene IVIg-a, novorođenče je postalo afebrilno, uz postepenu normalizaciju laboratorijskih nalaza. Dete je otpušteno posle 16 dana hospitalizacije. Deset dana posle otpusta, prekinuta je terapija prednizonom. Dve nedelje nakon otpusta, prekinuto je davanje heparina. Sedam dana kasnije, vrednost D-dimera je značajno porasla i terapija

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antikoagulansom je ponovo započeta. Mesec dana kasnije, vrednost D-dimera se potpuno normalizovala, i terapija HNMM-om je prekinuta. **Zaključak.** Nakon primenjene terapije za MZS kod dece, došlo je do prestanka febrilnosti i postepene normalizacije vrednosti laboratorijskih parametara, što ukazuje da je novorođenče u ovom slučaju imalo MZS-N. Povišena vrednost D-dimera tokom produženog vremenskog perioda je najverovatnije bila posledica MZS.

Ključne reči:
covid 19; dijagnoza; d dimer; heparin, niskomolekulski; imunoglobulini, intravenski; novorođenče; zapaljenje; sindrom.

Introduction

In the latter half of April 2020, a new syndrome in children and adolescents associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was described for the first time and was named the multisystem inflammatory syndrome (MIS) in children (MIS-C) [1, 2]. The World Health Organization has developed a case definition for MIS-C, which includes children up to 19 years of age with clinical signs of elevated body temperature that persists for more than three days, involving two or more organ systems (digestive system, skin and mucous membranes, cardiovascular system), elevated markers of inflammation, and evidence of the existence of SARS-CoV-2 infection without another microbiologically proven cause of inflammation [3]. This syndrome is relatively rare but potentially a severe and life-threatening complication of SARS-CoV-2 infection [4, 5]. This syndrome also occurred in newborns and was named MIS in neonates (MIS-N). There is no clear agreed definition of MIS-N, as well as no guidelines and protocols for the diagnosis and treatment of this complication [5].

Case report

A term infant girl became ill on the day of admission to the hospital, on day eight after birth, with the appearance of elevated body temperature and secretion from the nose. This was a child from normal pregnancy, which ended with a vaginal delivery without complication, Apgar score 9/10. The newborn was breastfed since birth.

On admission to the hospital, the baby was awake, eupneic, and tachycardic. Body temperature measured rectally was 38.2 °C (normal temperature measured rectally is 36.5 °C–37.5 °C). In the physical findings, only the yellow discoloration of the skin stood out. Upon admission, a nasopharyngeal swab was performed: the reverse transcriptase-polymerase chain reaction test for SARS-CoV-2 for the child and the mother was positive. The mother had suffered from nasal discharge, cough, and fever, which started two days before the child was admitted to the hospital. Until then, the mother had no confirmed COVID-19 infection and did not receive the vaccine against COVID-19. Initial laboratory analysis was performed (Table 1). Chest X-ray, ultrasound of the central nervous system and abdomen, and echocardiographic findings were normal. Furthermore, upon admission to the hospital, blood culture, urine culture, and stool were sampled; after that, dual empirical parenteral antibiotic therapy (ceftazidime, vancomycin) was commenced. Dual empirical antibiotic therapy was started because of suspected late neonatal sepsis and was applied until sepsis was ruled out. Due to elevated D-dimer value (> 2,500 ng/mL, reference range 0–230 ng/mL), low molecular weight heparin (LMWH) was introduced at a dose of 100 IU/kg/day. Febrility persisted with a further increase in lactate dehydrogenase, ferritin, interleukin-6 (IL-6), and persistence of elevated D-dimer values (Table 1) without the involvement of other organ systems.

After five days of hospitalization and febrility, with negative results of the blood and urine culture and further deterioration of laboratory findings, intravenous immunoglobu-

Table 1

Laboratory results

Parameter	Reference range	Days of hospitalization				
		1	3	5*	11	18
C reactive protein (mg/L)	0–5	0.72	0.78	0.76	0.46	0.3
Albumin (g/L)	38–60	/	33	/	29.79	33.85
GGT (IU/L)	13.8–132	184.8	119.88	125.04	76.2	78.6
LDH (IU/L)	180–433.2	544.2	522	696	683.4	381
Interleukin-6 (pg/mL)	0–6.4	/	64.9	104	23.7	3.0
D-dimer (ng/mL)	0–230	/	>2,500	>2,500	1,620	540
Ferritin (μg/L)	5–204	/	863	1,582	/	781
High-sensitivity troponin I (ng/L)	**	/	35.6	41.5	/	28.3
CK-MB (ng/mL)	**	/	10.7	7.5	/	2.7
Bilirubin (mmol/L)	0.01–21	256	/	82.84	/	32
Indirect bilirubin (mmol/L)	0.01–16	242.9	/	74.64	/	29

GGT – gamma-glutamyl transpeptidase; LDH – lactate dehydrogenase; CK–MB – creatine kinase- myoglobin binding.
***On this day, a decision was made to begin therapy with intravenous immunoglobulins due to further deterioration of the values in the laboratory findings.**
****In the laboratory where CK-MB and high-sensitivity troponin I analyses were performed, reference values for the pediatric population were not specified.**

lin (IVIg) therapy was administered at a dose of 2 g/kg for one day. Then, parenteral corticosteroid therapy (methylprednisolone) was started at a dose of 1 mg/kg/day for four days, after which the reduction of corticosteroid therapy was performed with oral corticosteroid (prednisone). One day after IVIg administration, the newborn became afebrile, with gradual normalization of laboratory findings (Table 1). The newborn was discharged after 16 days of hospitalization to continue treatment with prednisone and LMWH at home. Ten days later, prednisone therapy was discontinued. Two weeks after the discharge, the administration of LMWH was stopped (at the D-dimer value of 410 ng/mL). Seven days later, the D-dimer value increased significantly (2,358 ng/mL). The child was hospitalized, and anticoagulant therapy was reinstated. Results of additional laboratory analyses (C-reactive protein, complete blood count, fibrinogen, indicators of kidney and liver function, IL-6, ferritin, and hemostasis parameters) were normal, as well as the findings of radiological and cardiovascular examinations (abdominal and cranial ultrasound, echocardiographic examination). After one month, the D-dimer value completely normalized, and the LMWH therapy was stopped.

Discussion

There is limited knowledge about cases of MIS in the neonatal population. Although the incidence of MIS-N is not known, this entity is rare. In a systematic review that included 27 studies, only 104 cases of neonates with MIS-N were described [5]. The pathophysiological mechanisms of MIS-N have not been fully elucidated. Maternal SARS-CoV-2 infection during pregnancy can cause a hyperinflammatory response in the newborn by transplacental transfer of IgG that binds to the spike protein of the virus. These antibodies cross the placenta to provide passive immunity to the newborn. The patient's mother also had a current COVID-19 infection. As it had happened during the pandemic, some people had COVID-19 infection several times. We had no information if the mother initially had an infection during pregnancy. For technical reasons, an IgG test was not performed for the mother. Postnatally, IgA antibodies are transmitted to the newborn *via* breast milk, which may also play a role in the body's defense against infection [6–9]. In children with a genetic predisposition, antibodies bind to receptors on neutrophils and macrophages, causing the activation and secretion of proinflammatory cytokines responsible for the development of MIS [10, 11]. According to More et al. [12], MIS-N can be divided into early MIS-N, which occurs in the first 72 hours of life due to the transplacental transfer of maternal antibodies, and late MIS-N, which occurs after 72 hours of life as a consequence of the secondary production of antibodies, as part of the current infection of the newborn, but it can also be caused by transplacental transfer of maternal antibodies. The diagnosis of MIS-N in our patient was made on day 12 of life, which, according to these criteria, would correspond to late MIS-N. Given the specificity of the neonatal age, the question arises of the possibility of applying the proposed MIS-C criteria [13]. In our case, the newborn met the following criteria for the diagnosis of MIS-C: febrile for longer than five days without other signs of infection and pathological values of laboratory findings. Despite negative microbiological analyses (blood, urine, and stool culture for bacteria and fungi) and the applied broad-spectrum empirical antibiotic therapy, the parameters of inflammation continued to increase, which made us consider the MIS-N diagnosis in our case.

The American College of Rheumatology has issued guidelines for MIS-C diagnosis and treatment without special recommendations for the treatment of MIS-N [14]. The treatment strategy mainly follows the treatment standards for Kawasaki disease due to the overlapping features. Although both diseases are systemic inflammatory diseases, they differ in their diagnostic criteria. For the treatment of MIS-C, high doses of IVIg (1–2 g/kg) and corticosteroids 1 mg/kg are generally recommended, which was applied during the treatment of the newborn in our case summary [15–17].

Conclusion

After the applied therapy, there was the cessation of febrility and gradual normalization of laboratory parameters, which implies that the newborn in question probably had MIS-N. In this case, prolonged administration of LMWH was required. Since the presence of deep vein thrombosis was ruled out by supplementary testing, we believe that the prolonged elevated D-dimer value is a consequence of inflammation as part of a multisystem inflammatory response. Currently, there is no widely accepted standard for the treatment of MIS-N, but only recommendations based on case series, reports, and experience in the treatment of MIS-C. There is a need for further research in this field because as much as MIS-N resembles MIS-C, it remains significantly different.

Conflict of interest

The authors declare no conflict of interest.

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