СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted*

ISSN Online 2406-0895

Case Report / Приказ болесника

Ružica Kravljanac[1,2,♣], Nataša Stajić[1,2], Vladislav Vukomanović[1,2], Gordana Petrović[1], Miloš Kuzmanović[1,2]

Severe neurological complications in a child with multisystem inflammatory syndrome in children after asymptomatic COVID-19

Тешке неуролошке компликације код детета са мултисистемским инфламаторним синдромом код деце после асимптоматског ковида 19

[1]Dr. Vukan Čupić Institute for Mother and Child Healthcare of Serbia, Pediatric Clinic, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Received: October 26, 2023
Revised: March 30, 2024
Accepted: March 31, 2024
Online First: April 4, 2024
DOI: https://doi.org/10.2298/SARH231026030K

♣Correspondence to:
Ružica KRAVLJANAC
Faculty of Medicine, University of Belgrade, Pediatric Clinic, Dr. Vukan Čupić Institute for Mother and Child Healthcare of Serbia, Radoja Dakića 6–8, 11070 Belgrade, Serbia
E-mail: **ruzica.kravljanac@gmail.com**

Severe neurological complications in a child with multisystem inflammatory syndrome in children after asymptomatic COVID-19

Тешке неуролошке компликације код детета са мултисистемским инфламаторним синдромом код деце после асимптоматског ковида 19

SUMMARY

Introduction Coronavirus disease-2019 (COVID-19) usually leads to a mild infectious disease course in children, but serious neurological complications were described in association with both, acute infection and the multisystem inflammatory syndrome in children (MIS-C). Cerebrovascular disorders (CVD) in children are rare complication of MIS-C, and various potential mechanisms of CVD in MIS-C were hypothesized.

Case outline In an eight-year old girl, diagnosis of MIS-C was made according to clinical features of prolonged fever, circulatory shock, heart and renal insufficiency, skin abnormalities, conjunctival hyperemia, and stomach pain associated with laboratory findings (increased CRP, D-dimers, pro BNP, troponins, IL-6), supported by positive contact with SARS-CoV2 one month before the disease onset and increased IgG and IgM anti -SARS-CoV2-antibodies. From the second day of hospitalization, left side hemiplegia was observed and using brain CT and MR, CVD was diagnosed. Together with cardiovascular support, corticosteroids and IVIG were administered. On fourth day of hospitalization, diagnosis of cerebral salt wasting syndrome (CSWS) was made according to severe dehydration, polyuria, hyponatremia, increased natriuria, and increased urine: serum osmolality ratio. CSWS had very severe course lasting more than one month. The girl was discharged with stable vital signs, normal diuresis and hemiparesis.

Conclusion This is the first case in the literature presenting association of severe CSWS and CVD in a child with MIS-C after COVID-19.

Keywords: COVID-19; MIS-C; cerebrovascular disease; cerebral salt wasting syndrome

САЖЕТАК

Увод Болест изазвана вирусом короне (ковид 19) најчешће има благи клинички ток болести код деце, међутим описане су тешке неуролошке компликације које су удружене, како са акутном инфекцијом, тако и са мултисистемским инфламаторним синдромом код деце (*multisystem inflammatory syndrome in children – MIS-C*) после ковида 19. Цереброваскуларна болест код деце је ретка компликација *MIS-C* и постоје различите претпоставке о потенцијалним механизмима који до ње доводе.

Приказ болесника Код осмогодишње девојчице је постављена дијагноза *MIS-C* на основу: клиничке слике која је обухватала пролонгирану фебрилност, циркулаторни шок, срчану и бубрежну недовољност, промене на кожи, коњуктивалну хиперемију и болове у стомаку; резултата лабораторијских анализа (повишени *CRP*, *D-dimeri*, *proBNP*, тропонини, *IL*-6); података о контакту са вирусом месец дана пре почетка болести и повишених вредности *IgG* и *IgM* антитела на *SARS-CoV*2. Од другог дана хоспитализације запажа се левострана хемипареза, а применом компјутеризоване томографије и *MR* ендоканијума је доказана цереброваскуларна болест. Поред кардиоваскуларне потпоре, примењени су кортикостероиди и интравенски имуноглобулини. Четвртог дана хоспитализације постављена је дијагноза синдрома церебралног губитка соли на основу тешке дехидрације, полиурије, хипонатријемије, повишене натриурије и повишеног односа осмолалности урина и серума, који је имао тежак клинички ток и трајање од преко месец дана. Девојчица је пуштена стабилних виталних знакова, нормалне диурезе и хемипаретична.

Закључак Удруженост тешког синдрома губитка соли и цереброваскуларне болести код детета са *MIS-C* после ковида 19 није до сада описана, тако да је ово први приказ у литератури.

Кључне речи: *COVID*-19; *MIS-C*; цереброваскуларна болест; синдром губитка соли

INTRODUCTION

Coronavirus disease-2019 (COVID-19) usually leads to a mild infectious disease course in children, but serious neurological complications were described in association with both acute infection and multisystem inflammatory syndrome in children (MIS-C) [1]. The criteria for MIS-C are fever, evidence of inflammation, at least two organs involved, no other active

infection that could explain condition, associated with plausible epidemiologic link to SARS-CoV-2 through a positive laboratory test (PCR, antigen or antibody) or confirmed exposure [2]. Cerebrovascular disorders (CVD) in children are rare complication of MIS-C, while various potential mechanisms of CVD in MIS-C were hypothesized.

This is the first case in the literature with the association of CVD and long-lasting life-threatening cerebral salt wasting syndrome (CSWS) in a child with MIS-C after COVID-19.

CASE REPORT

In an eight-year-old girl, MIS-C after asymptomatic COVID-19 was complicated by CVD and life-threatening cerebral salt wasting syndrome lasting for more than four weeks.

The onset of disease was 8 days before admission, with everyday fever (up to 39.8°C) and vomiting. Three days after fever onset, the girl felt severe stomach pain. Two days before admission the girl became very exhausted and had submandibular and auricular exanthema followed by target-skin changes on limbs. Ceftriaxone was administered intravenously. In history, we found out that the father had suffered from COVID-19 with positive PCR test SARS CoV-2 one month before, while our patient was asymptomatic and PCR negative at the same period. The girl was healthy before current disease with normal psychomotor development, regularly vaccinated according to the schedule.

At the admission at the Institute, the girl was in poor condition, exhausted, with Glasgow coma score of 14, she was answering the questions and complaining on severe stomach pain, HR was 132/min, BP was 73/35 mmHg, she had poor capillary filling, gallop heart rhythm and systole murmur of 2/6. The breathing rate was of 28/min, SpO was 97%, with normal auscultator finding. Erythema multiform on the neck, palms, dorsal side of feet and gluteal regions was present. Lips and tongue were „strawberry-like" and conjunctive was hyperemic. No visceromegaly was present. Edema of dorsal side of feet and distal part of the legs was observed. The girl was dehydrated with oliguria during the first day of hospitalization. No lateralization in neurological finding was observed at the admission. Abnormal laboratory findings included: C-reactive protein 44.2 mg/l; Plt 133; Gly 8.3 mmol/l; urea 32 mmol/l; Cr 97 mmol/l; tCO2 13 mmol/l; potassium 2.8 mmol/l; sodium 122 mmol/l; chlorine 87 mmol/l; uric acid 609 mcmol/l; gamma GT 9 IJ/L; NT-proBNP 1244 pg/ml (increased); troponin I 0.689 (normal < 0.3); troponin T 0.127 (normal < 0.1); proBNP 22742 (normal < 125); IL-6: 11.6 pg/ml (normal < 7); D dimers 1970 (normal < 230); serology for SARS-CoV2: IgM 44 (positive), IgG 84 (positive), PCR negative.

Heart ultrasound on admission showed damaged function of left ventricle with ejection fraction of 45%. During heart ultrasound follow-up, the recovery of heart function was observed within the next seven days. The renal function was normalized on the second day after admission.

Diagnosis of MIS-C was made according to clinical features of prolonged fever, circulatory shock, heart and renal insufficiency, skin abnormalities, conjunctival hyperemia, and stomach pain associated with laboratory findings (increased CRP, D-dimers, pro BNP, troponins, IL-6), supported by positive contact with SARS-CoV2 one month before the disease onset and increased IgG and IgM anti -SARS-CoV2-antibodies.

The initial treatment of MIS-C included: parenteral hydration and electrolyte disturbances correction, inotropic stimulation (dopamine), decongestive therapy (spironolactone and furosemide), antibiotics (ceftriaxone), high dosages of methyl-prednisolone and fraxiparine.

The day after admission, the girl became somnolent with left side hemiparesis. Brain native computerized tomography (CT) scan was done urgently (Figure 1). Anti-Aquaporin-4 Ab, anti-MOG-Ab, anti-NMDA-Ab were negative.

On the seventh day after hemiplegia appearance, MR (Figure 2) and MR angiography (Figure 3) of the brain were done. Intravenous immunoglobulins were introduced seven days after the onset of hemiparesis in dosage of 0.4 g/kg/day, for five days. The administration of low-molecular heparin was stopped on the eleventh day of hospitalization and acetylsalicylic acid was introduced. In further course, the girl was treated by Prednisone 2 mg/kg per day. Five days' cure of methyl-prednisolone in dosage of 500mg/m^2/day was repeated after three weeks from the first cure. Four weeks after the first treatment of IVIG, the one-day infusion of 1g IVIG was given. The improvement of severe left side hemiparesis was very slow during the first four weeks of disease, while cognitive functions were normal all the time.

From the fourth day of hospitalization, severe dehydration was observed due to polyuria associated with hyponatremia, increased natriuria > 100 mmol/l, increased ratio of urine: serum osmolality (Osmolality: urine 604 mOsm/kg, serum 294 mOsm/kg). Since renal and endocrinology causes for polyuria were excluded, diagnosis of cerebral salt wasting syndrome (CSWS) was made. With the increased intake of sodium, fluids and low dosage of mineralocorticoids, the balance was hardly achieved. The managing of CSWS was frustrating, with duration for more than four weeks with diuresis up to 10mg/kg/h, and fluid intake up to 6

liters per day. Any decrease of fluid intake led to severe dehydration. The girl was discharged with stable vital signs, normal diuresis and hemiparesis.

The subject's parents' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent institutional ethics committee (No 8/131), and conforms to the legal standards.

DISCUSSION

Cerebrovascular disorder in children is a rare complication of either COVID-19 or MIS-C after COVID-19 [3]. The results of studies from the early pandemic showed the risk of stroke in children and adolescents from 0.29% to 0.62%. The prevalence of SARS-CoV-2 infection among children with arterial ischemic stroke tested by PCR or serology was 6.1% and 6.9% [3]. Our patient suffered CVD after asymptomatic SARS-CoV-2 infection. Similarly, it was described by Beslow et al. that 13 of 23 cases with stroke had asymptomatic SARS-CoV-2 infections, and among the patients with symptoms, there was a broad range of periods between viral symptom onset and stroke [3].

The inflammatory-mediated thrombosis has been identified as a mechanism for SARS-CoV-2-associated with stroke. The children with elevated inflammatory markers or MIS-C may be at particularly high risk of stroke [3]. The use of fraxiparine as soon as diagnosis of MIS-C was established, did not prevent CVD in our patient. O'Loughlin L et al. reviewed published cases of pediatric patients with severe neurological issues and a coexisting positive SARS-CoV-2 test. MIS-C was diagnosed in 65 out of 159 cases with severe neurological manifestations, while in 38 cases CVD was diagnosed. [4]. In some of the cases with stroke associated with COVID-19, underlying disorders had existed, while our patient was healthy, with normal neurodevelopment before current disease.

The underlying pathophysiology of neurological complications of MIS-C is cytokine storm, characterized by high levels of tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-12, and interferon gamma (INFγ) [5]. The hyperinflammatory state contributes to a pro-coagulable state: initial vasculitis causes the disruption of vascular integrity, the exposure of thrombogenic basement membrane and, finally, the activation of the clotting cascade [1].

The mechanism of CVD in our case is unclear. Inflammatory-mediated mechanism is supposed, since the elevated inflammatory markers, presence of MIS-C and very early appearance (on the same day as hemiparesis occurred) of neuroimaging finding of huge ischemic lesion and cerebral edema, suggested considering that vessels occlusion is not the

only mechanism. Clinical signs of cytokine storm including cardio-circulatory shock together with increased inflammatory biomarkers (CRP, IL-6, D-dimmers) which preceded the neurological abnormalities, strongly suggested the role of inflammation in CVD in our case.

The preferred treatment strategy has to be more aggressive at the diagnosis of MIS-C, to block the cytokine cascade [6]. Maggio et al. described favorable prognosis in 22 children with MIS-C treated by IVIG and steroids as the first-line treatment pointing that this approach could explain the favorable prognosis [6]. Despite the same treatment in our case, neurological complications were happening. Recovery rates, including occurrence and resolution of coronary artery aneurysms, were similar for primary treatment with intravenous immunoglobulin when compared to glucocorticoids or intravenous immunoglobulin plus glucocorticoids [7].

Clinical and laboratory findings after admission of our patient presented prerenal type of acute renal impairment with signs of acute tubular damage due to dehydration and renal involvement of MIS-C. Two days later, global renal function was normalized including tubular function. In further course, extreme polyuria and dehydration dominated with normal renal function, low uric acid in serum and relatively decreased urine osmolality suggested cerebral salt wasting syndrome. N-terminal pro-brain natriuretic peptide (NT-proBNP), plays vital roles in regulation of volume status. There is no data if the increased level of brain natriuretic peptide in children with MIS-C might be a contributing factor in CSWS associated with MIS-C and CVD, so further investigations are necessary to explain this possibility. Despite early recognition and treatment of CSWS in our case, the duration of CSWS was very long and additionally complicated the recovery of the patient.

MIS-C has a wide range of clinical symptoms including neurological symptoms and prognosis [8, 9]. In the study of de Faries et al. death occurred in 21.5% children with COVID and MISC, reporting that the mortality was associated with higher levels of vasoactive inotropic-score, presence of acute respiratory distress syndrome, higher levels of erythrocyte sedimentation rate, and thrombocytopenia [10].

There is no literature data about CSWS associated with CVD in MIS-C. Our case with severe CSWS and CVD shows that COVID-19 might be associated with life-threatening neurological complications in children, even if the acute illness is asymptomatic.

Conflict of interest: None declared.

REFERENCES

1. Lin JE, Asfour A, Sewell TB, Hooe B, Pryce P, Earley C, Shen MY, Kerner-Rossi M, Thakur KT, Vargas WS, Silver WG, Geneslaw AS. (2021) Neurological issues in children with COVID-19. Neurosci Lett 19; 743:135567. doi: 10.1016/j.neulet.2020.135567. Epub 2020 Dec 19. PMID: 33352286; PMCID: PMC7831718.)
2. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020. https://www.who.int/newsroom/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and adolescents-with-covid-19. Accessed March 23, 2023.
3. Beslow LA, Agner SC, Santoro JD, Ram D, Wilson JL, Harrar D, et al. International Prevalence and Mechanisms of SARS-CoV-2 in Childhood Arterial Ischemic Stroke During the COVID-19 Pandemic. Stroke 2022; 5:101161STROKEAHA121038250. doi: 10.1161/STROKEAHA.121.038250. Epub ahead of print. PMID: 35380052
4. O'Loughlin L, Alvarez Toledo N, Budrie L, Waechter R, Rayner J. A Systematic Review of Severe Neurological Manifestations in Pediatric Patients with Coexisting SARS-CoV-2 Infection. Neurol Int 2021;13(3):410-427. doi: 10.3390/neurolint13030041. PMID: 34449704; PMCID: PMC8396020.
5. Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological involvement in COVID-19 and potential mechanisms: a review. Neurocritical Care 2020; 34(3):1062-1071. https://doi.org/10.1007/s12028-020-01049-4
6. Maggio MC, Giordano S, Failla MC, Campione MG, Alaimo A, Corsello G. Ten-month follow-up of patients with covid-19 temporally related multi-system inflammatory syndrome in children: the experience of the children hospital of Palermo. Ital J Pediatr. 2023; 49(1):37. doi: 10.1186/s13052-023-01416-9. PMID: 36959663.
7. Channon-Wells S, Vito O, McArdle AJ, Seaby EG, Patel H, Shah P, et al. Immunoglobulin, glucocorticoid, or combination therapy for multisystem inflammatory syndrome in children: a propensity-weighted cohort study. Lancet Rheumatol 2023; 5(4):e184-e199. doi: 10.1016/S2665-9913(23)00029-2. Epub 2023 Feb 14. PMID: 36855438; PMCID: PMC9949883.
8. Hoseininasab A, Sinaei R, Bagheri MM, Ahmadipour M, Derakhshan R, Najafzadeh MJ, et al. Multisystem inflammatory syndrome in children (MIS-C) post-COVID-19 in Iran: clinical profile, cardiac features, and outcomes. BMC Pediatr. 2024 Mar 13;24(1):179. doi: 10.1186/s12887-024-04652-y. PMID: 38481221.
9. Lampidi S, Maritsi D, Charakida M, Eleftheriou I, Farmaki E, Spyridis N, et al. Multisystem inflammatory syndrome in children (MIS-C): A nationwide collaborative study in the Greek population. Eur J Pediatr. 2024 Jan 12. doi: 10.1007/s00431-023-05383-5. Epub ahead of print. PMID: 38214810.
10. de Farias ECF, Pavão Junior MJC, de Sales SCD, do Nascimento LMPP, Pavão DCA, Pinheiro APS, et al. Factors associated to mortality in children with critical COVID-19 and multisystem inflammatory syndrome in a resource-poor setting. Sci Rep. 2024 Mar 6;14(1):5539. doi: 10.1038/s41598-024-55065-x. PMID: 38448485; PMCID: PMC10918095)

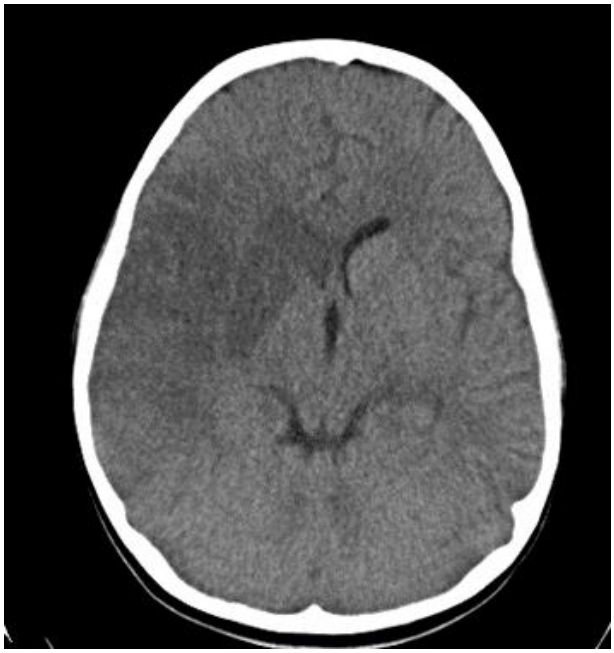

Figure 1. Computerized tomography showed a huge zone of non-homogenous hypodensity of the brain parenchyma involving cortex and white matter in the right frontal-parietal-temporal regions, nucleus caudate, putamen and globus pallidus; involved zones are edematous with compression to the right ventricle

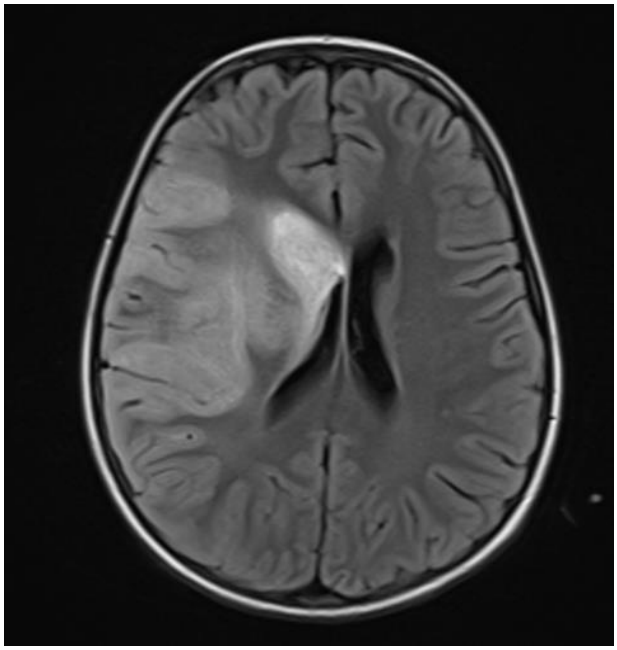

Figure 2. Seven days after the left-side hemiplegia onset, brain MR showed a huge zone of inflammation with cytotoxic edema involving grey and white matters of the right hemisphere involving lateral aspect of the inferior, and the entire middle frontal gyrus, right temporal gyrus, insula, capsule external and internal, part of corticospinal tract, and the right basal ganglia

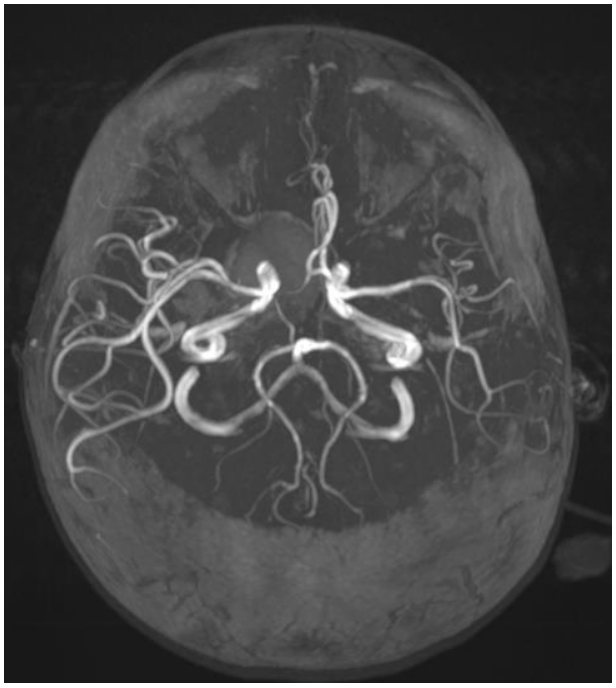

Figure 3. Brain MR angiography done seven days after left-side hemiplegia onset showed decreased signal flow through the A1 segment of the right anterior cerebral artery

