DOI: https://doi.org/10.2298/SARH231026030K
UDC: 616.98-06:578.834

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

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

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**SUMMARY**
**Introduction** Coronavirus disease-2019 (COVID-19) usually leads to a mild infectious disease course in children, but serious neurological complications have been 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 have been 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 intravenous immunoglobulin were administered. On the 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

## INTRODUCTION

Coronavirus disease-2019 (COVID-19) usually leads to a mild infectious disease course in children, but serious neurological complications have been 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 have been 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 CSWS lasting for more than four weeks.

The onset of the disease was eight 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 the medical history, we found out that the father had suffered from COVID-19 with positive PCR test for SARS CoV-2 one month earlier, while our patient was asymptomatic and PCR-negative at the same period. The girl was healthy before her current disease, with normal psychomotor development, regularly vaccinated according to the schedule.

On admission to the Institute, the girl was in poor condition, exhausted, with Glasgow coma score of 14, she was answering questions and complaining on severe stomach pain, heart rate was 132 beats/minute, blood pressure was 73/35 mmHg, she had poor capillary filling, gallop heart rhythm and systole murmur of 2/6. The breathing rate was 28 breaths/minute, SpO was 97%, with normal auscultator finding. Erythema multiform on the neck, palms,

**Received • Примљено:** October 26, 2023
**Revised • Ревизија:** March 30, 2024
**Accepted • Прихваћено:** March 31, 2024
**Online first:** April 4, 2024

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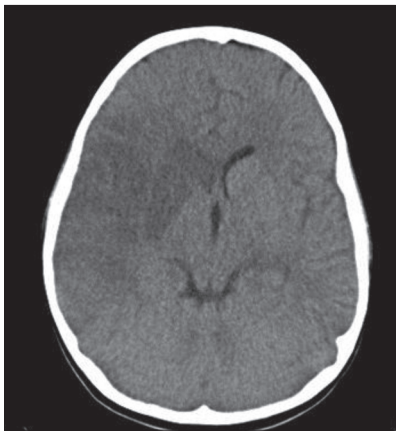

**Figure 1.** Computerized tomography showed a huge zone of non-homogenous hypodensity of the brain parenchyma involving cortex and white matter in the right frontal-parietal-temporal regions, nucleus caudate, putamen, and globus pallidus; involved zones are edematous with compression to the right ventricle

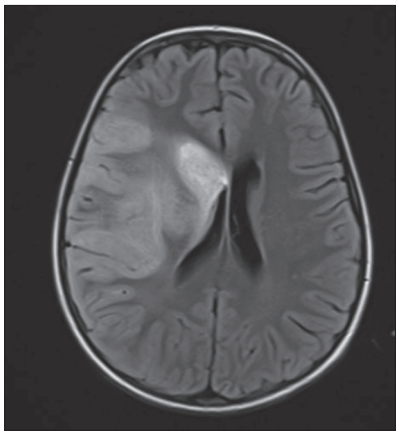

**Figure 2.** Seven days after the left-side hemiplegia onset, brain MR showed a huge zone of inflammation with cytotoxic edema involving grey and white matters of the right hemisphere involving lateral aspect of the inferior, and the entire middle frontal gyrus, right temporal gyrus, insula, capsule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

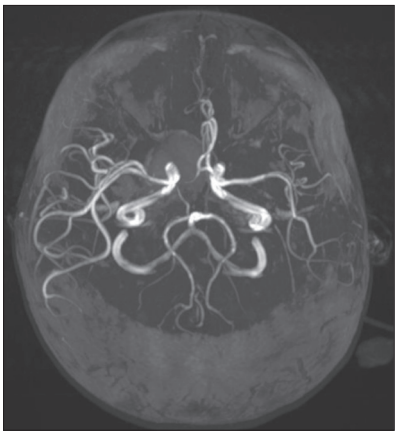

**Figure 3.** Brain MR angiography done seven days after left-side hemiplegia onset showed decreased signal flow through the A1 segment of the right anterior cerebral artery

dorsal side of the 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 on admission. Abnormal laboratory findings included the following: C-reactive protein 44.2 mg/l; platelet count 133; Gly 8.3 mmol/l; urea 32 mmol/l; Cr 97 mmol/l; $tCO_2$ 13 mmol/l; potassium 2.8 mmol/l; sodium 122 mmol/l; chlorine 87 mmol/l; uric acid 609 mcmol/l; gamma-glutamyl transferase 9 IJ/l; NT-proBNP 1244 pg/ml (increased); troponin I 0.689 (normal < 0.3); troponin T 0.127 (normal < 0.1); proBNP 22,742 (normal < 125); IL-6: 11.6 pg/ml (normal < 7); D-dimer 1970 (normal < 230); serology for SARS-CoV2: IgM 44 (positive), IgG 84 (positive), PCR negative.

Heart ultrasound on admission showed damaged function of the left ventricle with ejection fraction of 45%. During heart ultrasound follow-up, the recovery of the 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, proBNP, 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 the following: parenteral hydration and electrolyte disturbances correction, inotropic stimulation (dopamine), decongestive therapy (spironolactone and furosemide), antibiotics (ceftriaxone), high doses of methyl-prednisolone and Fraxiparine (Aspen Notre-Dame-de-Bondeville, Notre-Dame-de-Bondeville, France).

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 the dosage of 0.4 g/kg/day, for five days. The administration of low-molecular heparin was stopped on the 11th day of hospitalization and acetylsalicylic acid was introduced. In the further course, the girl was treated with prednisone 2 mg/kg per day. Five days' cure of methyl-prednisolone in the dosage of 500 mg/m$^2$/day was repeated after three weeks from the first cure. Four weeks after the first treatment of intravenous immunoglobulin (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 the 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 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 the duration of more than four weeks, with diuresis up to 10 mg/kg/h, and fluid intake of up to six 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 the 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%, respectively [3]. Our patient suffered CVD after asymptomatic SARS-CoV-2 infection. Similarly, it was described by Beslow et al. [3] 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.

The inflammatory-mediated thrombosis has been identified as a mechanism for the SARS-CoV-2-associated stroke. The children with elevated inflammatory markers or MIS-C may be at particularly high risk of stroke [3]. The use of Fraxiparine (Aspen Notre-Dame-de-Bondeville) as soon as the diagnosis of MIS-C was established did not prevent CVD in our patient. O'Loughlin et al. [4] 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 CVD was diagnosed in 38 cases. 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 the 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, the presence of MIS-C, and very early appearance (on the same day as hemiparesis occurred) of neuroimaging finding of a huge ischemic lesion and cerebral edema, suggested considering that vessels' occlusion is not the only mechanism. Clinical signs of the cytokine storm including cardio-circulatory shock together with increased inflammatory biomarkers (CRP, IL-6, D-dimers) 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. [6] described favorable prognosis in 22 children with MIS-C treated by IVIG and steroids as the first-line treatment, suggesting that this approach could explain the favorable prognosis. Despite the same treatment in our case, neurological complications were in fact taking place. Recovery rates, including occurrence and resolution of coronary artery aneurysms, were similar for primary treatment with IVIG when compared to glucocorticoids or IVIG 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 CSWS. N-terminal pro-brain natriuretic peptide (NT-proBNP) plays vital roles in the regulation of the volume status. There is no data if an 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 by de Faries et al. [10], death occurred in 21.5% of children with COVID-19 and MISC, reporting that the mortality was associated with higher levels of the vasoactive-inotropic score, the presence of acute respiratory distress syndrome, higher levels of erythrocyte sedimentation rate, and thrombocytopenia.

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.

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## Тешке неуролошке компликације мултисистемског инфламаторног синдрома код деце после асимптоматског ковида 19

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**САЖЕТАК**

**Увод** Болест изазвана вирусом корона (ковид 19) најчешће има благи клинички ток код деце, али у овом раду су описане 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 могућим механизмима који до ње доводе.

**Приказ болесника** Код осмогодишње девојчице постављена је дијагноза *MIS-C* на основу: клиничке слике која је обухватала пролонгирану фебрилност, циркулаторни шок, срчану и бубрежну инсуфицијенцију, промене на кожи, конјунктивалну хиперемију и болове у стомаку; резултата лабораторијских анализа (повишени *CRP*, *D*-димери, *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 магнетне резонанце ендоканијума доказана је 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 трајао је 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**: ковид 19; *MIS-C*; цереброваскуларна болест; синдром губитка соли