Acta Biomed 2025; Vol. 96, N. 6: 16675 DOI: 10.23750/abm.v96i6.16675 

Case report

# Encephalitis in multisystem inflammatory syndrome in children (MIS-C) associated with Sars-CoV-2 infection: A case series

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**Abstract.** *Background and aim:* Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV2 infection is a systemic hyper-inflammatory condition affecting children with a recent acute SARS-CoV2 infection. It is usually characterized by persistent fever, mucocutaneous involvement, lymphadenopathy, gastrointestinal symptoms, cardiac dysfunction. Neurological involvement in MIS-C is frequent but not clearly defined: patients may develop acute neurological involvement, characterized by rapid onset of focal neurological signs and electrical abnormalities. *Methods and Results:* Herein we report 3 cases of children with MIS-C developing an acute encephalopathy. *Conclusion:* Additional data are needed in order to evaluate the prevalence of acute encephalitis in patients with MIS-C and characterize its presentation and define long-term outcomes. (www.actabiomedica.it)

**Key words:** multisystem inflammatory disease, neurological involvement, children, SARS-CoV2

## Introduction

Multisystem inflammatory syndrome in children (MIS-C) is an inflammatory condition characterized by a multiorgan involvement affecting children with recent Sars-Cov-2 infection, firstly described in April 2020 by Riphagen et al and Verdoni et al (1, 3). Case definition of MIS-C was proposed by the United States Centres for Disease Control and Prevention (CDC) (4), the United Kingdom Royal College of Paediatrics and Child Health (RCPCH) (5) and the World Health Organization (WHO) (6). Diagnostic criteria are reported in Table 1.

MIS-C symptoms are non-specific and similar to other clinical condition, such as Kawasaki Disease (KD). Actually, children usually presented persistent fever, mucocutaneous involvement (rash, conjunctivitis, cracking lips, hands and feet edema), lymphadenopathy, gastrointestinal symptoms (vomiting, abdominal pain, and/or diarrhea) cardiac dysfunction (electrocardiogram abnormalities, myocarditis, valvular dysfunction, shock) (7, 8). Neurological involvement in MIS-C is frequent but not clearly defined. Pathophysiology of neurological involvement in MIS-C seems to be linked to an hyperactivity of vascular inflammatory responses and dysregulation in neuronal mediators, caused by Sars-Cov-2 infection (9). Frequently, non specific symptoms such as meningism, headache, hypotonia, drowsiness and irritability have been described (10); severe encephalopathy described as changes and focal brain abnormalities in children with MIS-C were reported (11).

Herein we describe 3 cases of patients with MIS-C associated with acute encephalopathy.

**Table 1.** Definition of MIS-C according CDC, WHO and Royal College

| | **CDC** | **WHO** | **ROYAL COLLEGE** |
|---|---|---|---|
| | MIS-C | MIS-C | PIMS-TS |
| **AGE** | < 21 years of age | 0-19 years of age | children |
| **FEVER** | Fever >38°C for ³ 24h | Fever ³ 72h | Persistent Fever >38.5°C |
| **CLINICAL FEATURES** | laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); | 2 of the following:<br>• Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).<br>• Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/ NT-proBNP),<br>• Hypotension or shock.<br>• Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).<br>• Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).<br>AND<br>Elevated markers of inflammation | persistent inflammation and evidence of single or multi-organ dysfunction This may include children fulfilling full or partial criteria for Kawasaki |
| **COVID-19 INFECTION** | Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms. | Evidence of COVID-19 **(**RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19 | SARS-CoV-2 PCR testing may be positive or negative |
| | **No other plausible diagnoses** | **No other plausible diagnoses** | **No other plausible diagnoses** |

## Case presentation

*Case 1*

A seven-year-girl was admitted to our hospital with fever unresponsive to paracetamol (T max 39,7°C) appeared five days before, abdominal pain with vomiting and conjunctivitis lasting from three days. He was treated with an antibiotic for four days without improvement. It was reported a medical history of Covid-19 infection approximately twenty days before. Swab test for SARS-CoV-2 was negative. Admitted to the ward, vital signs were in range. Physical examination revealed conjunctivitis, cracking lips and pharyngitis and foot and hands edema. Routine blood tests were performed and resulted negative except for increased inflammatory markers (C-reactive protein (CRP) 150 mg/L (normal value < 0,5 mg/L), procalcitonin 12 ng/mL (normal value < 0.5 ng/mL), ferritin 500 ng/mL (normal range 11–250 ng/mL), D-dimer 550 ng/mL (normal range < 500 ng/mL) and BNP: 115 pg/ml (normal value <100 pg/ml), troponin 33 ng/LL (normal value < 15), higher values of fibrinogen: 750 mg/dL (normal range 200–400 mg/dL).

A COVID-19 serology test revealed positive for IgG. Echocardiogram, electrocardiogram, and chest X-ray did not show pathological findings. Abdomen ultrasound showed a fluid between ileal loops; but no other findings were reported. A diagnosis of MIS-C was performed. Therefore, she was treated with IV immunoglobulin (IVIG) 2gr/Kg, IV methylprednisolone 30 mg/Kg, supportive therapy and antibioticotherapy. Three days after hospital admission, the child referred onset of headache, and she appeared irritable and drowsy. The electroencephalogram (EEG) showed a slow and unmodulated activity in the bilateral parieto-occipital areas associated with a sharp morphology and desynchronized activities. The cervico-dorsal MRI was normal, so she didn't perform rachicentesis. Therefore, she started dexamethasone (10 mg/$m^2$/die) and anakinra (4 mg/kg/die) with a clinical improvement of neurological symptoms and normalization of blood and radiological tests. The follow-up visit after two months revealed a complete clinically and radiologically resolution of the inflammatory conditions.

*Case 2*

A previously health five-years old boy was admitted to our hospital with a four-day lasting fever poorly responsive to paracetamol, associated with conjunctivitis, watery diarrhoea and rash. SARS-COV-2 infection has been reported fifiteen days before. Vital signs showed temperature of 39°C, respiratory rate 17 breaths/min, blood pressure of 105/60 mmHg, heart rate of 145 beats/min, and an oxygen saturation of 96%. Physical examination showed diffuse macular popular rash on the face, the trunk and the lower limbs with confluent elements, symmetric non purulent conjunctivitis and a discomfort at the abdomen evaluation. Neurological evaluation was unremarkable. Blood tests revealed lymphopenia, increases in C-reactive protein 130 mg/L (normal value < 0,5 mg/L), PCT 7 ng/dL (normal value<0,5 ng/ml), and a slight elevation in troponin 30 mg/L (normal value<15), D-dimer 1250 ng/mL(normal value < 500), fibrinogen 600 mg/dL(normal 200-400 mg/dL), ferritin 485 ng/mL (normal range 11-250 ng/ml), BNP 860 pg/mL (normal value < 100 pg/ml). Serology for IgG SARS-CoV-2 antibody testing was positive, while the IgM was negative. Swab test for Sars-Cov-2 was negative. The abdominal ultrasound scan showed an edematous mesenteric tissue with peritoneal fluid in peri-splenic and perihepatic areas. The echocardiogram showed slight pericardial effusion. Electrocardiogram demonstrated sinus tachycardia, supraventricular. After three days, the patient developed irritability, drowsiness and ideomotor slowness. Brain MRI revealed diffuse hyperintensity area, with perivascular enlarged vessels, particularly in thalamic area. Rachicentesis was negative. Electroencephalogram (EEG) showed a globally slow electroencephalographic activity. Therefore, diagnosis of MIS-C was made and therapy with immunoglobulin (IVIG) 2gr/Kg, dexamethasone (10 mg/$m^2$), ASA (100 mg/day) was started. The clinical conditions and neurological symptoms progressively improve. Inflammatory markers such as C-reactive protein, PCT, ferritin, troponin decreased. Repeated EEG showed only mild diffuse slowing waves. He was discharged after twenty-five days with normal blood and instrumetal tests. At follow-up after one month, the patient was asymptomatic, and instrumental tests demonstrated no abnormalities.

*Case 3*

A 10-year-old boy presented to our hospital with a 7-day history of fever (T max 39°C) and headache associated with 4-day abdominal pain and diarrhoea. He was treated with antibiotic therapy for one day without improvement. No recent Sars-Cov-2 infection was reported. The vital signs showed temperature 38,5° C, oxygen saturation 99%, heart rate 130 bpm, blood pressure 100/61 mmHg, 3-second refill. He appeared in poor clinical conditions with pale, cold skin, cheilitis, bilateral conjunctivitis, painful abdomen, hyperaemic pharynx and macular non-itchy rash on the trunk and upper and lower limbs. Blood tests revealed increases in inflammation markers CRP 250 mg/L (normal value < 0,5 mg/dL), procalcitonin 12 ng/mL (normal value

< 0.5 ng/mL), fibrinogen: 900 mg/dL (normal range 200–400 mg/dL), ferritin 1000 ng/mL (normal range 11–306 ng/mL), D-dimer 1890 ng/mL (normal range < 500 ng/mL)) and an increase of BNP: 2750 pg/ml (normal value <100 pg/ml) and Troponin 300 mg/L (normal value<15).A molecular swab test for SARS-CoV-2 was performed and was negative. Serology for SARS- CoV 2 revealed positive IgG, while IgM was negative. Blood, urine cultures and coproculture were negative. Abdomen ultrasound and chest X ray were normal. The echocardiogram showed a reduction in left ventricular global ejection fraction (FE 40%) and a mild systolic insufficiency; thus, he began therapy with methylprednisolone bolus (30mg/kg/die) for 3 days, ASA (100 mg / day). Dur to the worsening of general conditions and the reduction of FE at 32 % and plasma expanders and inotropes was started associated with intravenous anakinra (8 mg/kg/die) was started. He was admitted to the Intensive Care Unit.After seven days, the patient appeared irritable with slow speech with preserved comprehension. EEG showed a generalized slowing of brain activity, especially in fronto-parietal area; so, he started dexamethasone (20 mg/day). Cerebral MRI showed hyperintensity in the fronto-parietal bi-hemispheric subcortical sites. Rachicentesis was performed but negative SARS-CoV-2 PCR in cerebrospinal fluid (CSF) was found. Based on clinical findings, a diagnosis of encephalitis in MIS-C was performed. During hospitalization he revealed a slow progressive clinical and laboratory improvement, with reduction of cardiac and inflammatory indices and a resolution of neurological symptoms. After 30 days, the patient was discharged on subcutaneous anakinra, and he continued dexamethasone tapering and ASA. At follow-up after three weeks, the patient was asymptomatic.

## Discussion

Neurological involvement in children with MIS-C has been described but is still poorly understood (12, 13). Feldstein et al. reported that about 5% of children with MIS-C may develop severe neurological complications (14). The neurological damage could be secondary to damage of blood brain barrier integrity due to cytokine and immune-mediated toxicity in the absence of direct viral spread or invasion (9). All our patients presented a neurological involvement after the onset of classical MIS-C symptoms (fever, conjunctivitis, and gastrointestinal symptoms and, in 2/3 patients showed cardiological involvement). Olivotto et al. presented 7 cases of encephalitis in patients with MIS-C and divided patients into two groups with severe and mild phenotypes. As in our first case mild phenotype patients presented irritability, drowsiness and headache. On the other hand, in the last two case series, severe phenotype patients presented focal neurological signs such as hypotonia, reduction in spontaneous movements and speech impairment. Moreover, also EEG showed slow brain activity in patients with severe neurological deficit (15). Our second case report reported alteration at MR, in accordance to Abel et al. which reported restricted signal in thalamic nuclei (16). As in our case series, in literature has been described the absence of Sars-cov-2 or other anomalies in the CSF (15). Elevated ferritin and IL-6, markers of hyper-inflammation, have been linked to a worse outcome in COVID-19 natural infection (17). Actually, our patients showed an increase of ferritin, particularly at the onset of neurological symptoms and with a correlation with the severity of clinical course in MIS-C syndrome. This may be linked to the pathogenesis of MIS-C which has been explained by an immune dysregulation causing the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 (17). All our cases were treated in accordance with the guidelines on MIS-C, with intravenous immunoglobulin (IVIG) 2gr/Kg, dexamethasone 10 mg/m$^2$, empiric broad spectrum antibiotics and supportive therapy (18 – 21). In conclusion, patients with MIS-C may develop acute neurological involvement, characterized by rapid onset of focal neurological signs and EEG abnormalities. Additional studies data are needed in order to evaluate the prevalence of acute encephalitis in patients with MIS-C and characterize its presentation and define long-term outcomes.

Parents provide the written informed consent to the cases description and publication.

**Ethic Approval:** None.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

**Authors' Contribution:** B.L. and MA contributed to the conception and design of the study, supervised the project, and drafted the main manuscript; B.M. CF, DMC and S.M. participated in the collection and analysis of clinical data; S.MU. conducted the literature review, synthesized the clinical cases, and interpreted the results in the context of existing scientific knowledge;

**Declaration on the Use of AI:** none.

**Consent for Publication:** Parents provide the written informed consent to the cases description and publication.

**Acknowledgments:** None.

**Funding:** None.

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Received: 9 December 2024
Accepted: 19 March 2025
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