Submitted: 12.11.2023
Accepted: 22.12.2023
Early publication date: 05.03.2024

Endokrynologia Polska
DOI: 10.5603/ep.98192
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 75; Number/Numer 2/2024

Multisystem inflammatory syndrome in children with Kawasaki disease-like manifestations in MMA

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Key words: *organic acidaemias; multisystem inflammation syndrome; coronavirus disease*

Methylmalonic acidaemia (MMA) is a disorder caused by pathogenic variants in the *MUT* gene (OMIM #609058) encoding methylmalonyl-CoA mutase. Although metabolic crises tend to occur during infections, cases presenting with multisystem inflammatory response syndrome and Kawasaki disease-like symptoms are rare.

The patient was born via vaginal delivery at 39 weeks and 3 days of gestation, with a birth weight of 2880 g. The diagnosis of methylmalonic academia (subtype mut0) was confirmed in the neonatal period. At the age of 3 years and 5 months, the patient was admitted to the hospital due to a 4-day fever and 1-day vomiting bout. The patient tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Mycoplasma pneumoniae (MP) infection. The child had a high fever for 12 days, accompanied by cough, vomiting, diarrhea, shortness of breath, and sinus tachycardia. On the 10th day of fever, he exhibited drowsiness, irritability, and a positive Babinski sign. The numbers of white blood cells, neutrophils, lymphocytes, and platelets decreased. Metabolic acidosis, hyperlactatemia, hyperammonemia, impaired liver and kidney function, elevated triglycerides, electrolyte imbalances (low potassium, low calcium, low sodium, low chloride), and elevated D-dimer were observed (Tab. 1). A chest computed tomography scan revealed multiple patchy and indistinct shadows in both lungs. The electrocardiogram indicated a prolonged QT interval, and the left coronary artery was dilated (Fig. 1).Dexamethasone was administered at a dose of 0.1–0.15 mg/kg per day for 3 days.

Multisystem inflammatory syndrome in children (MIS-C) is characterized by common clinical features, including fever, mucocutaneous manifestations (rash, conjunctivitis, hand/foot swelling, red/cracked lips, and strawberry tongue), myocardial dysfunction, cardiac conduction abnormalities, shock, gastrointestinal symptoms, and lymphadenopathy. In this case, the patient presented with a recurrent high fever that lasted for 12 days, in addition to vomiting, diarrhea, mild coronary artery dilation detected on day 6 of fever via cardiac ultrasound,and prolonged QT interval on the electrocardiogram.This presentation aligns with the diagnostic criteria for MIS-C and fulfills the diagnostic criteria for Kawasaki disease.

MIS-C and Kawasaki disease are two distinct conditions that share common clinical features. MIS-C with Coronary Arterial Lesion (CAL) are rare. In contrast, CAL are more common in Kawasaki disease [1]. The patient continued to show coronary artery dilation during the fifth week of illness. Fever is a key feature of MIS-C, and affected children often exhibit higher body temperatures and longer duration of fever compared to children with other common pediatric illnesses [2]. This case also presented neurological manifestations. Headache and acute encephalopathy are primary neurological manifestations of MIS-C, particularly following Omicron infection in children.

Lymphopenia is a typical finding in MIS-C, which is rarely reported in Kawasaki disease. The severity of lymphopenia is directly related to the likelihood of MIS-C diagnosis. In this case, not only was there lymphopenia, but also leukopenia, eutropenia, and thrombocytopenia, possibly related to hematopoietic dysfunction caused by MMA.

SARS-CoV-2 infection can lead to two distinct inflammatory diseases in children: Kawasaki disease

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Table 1. *Demographic and clinical data of the patient*

Age onset of the diagnosis	20 days	COVID-19 RNA	+
PEG	Yes	MP-IGM	+
Current age	3 years	WBC × 109/L	2.24
Genovariation	mut0	Lymphocyte × 109/L	0.23
Genetic locus	c.323G > A(p.R108H) c.914T > C(p.I.305S)	Platelets × 1012/l	41
Highest degree of fever	40.6	CRP [mg/L]	20.9
Days of fever	12	PCT [ng/mL]	0.25
Cough	√	BE [mmol/L]	–9.6
Shortness breath	√	HCO3- [mmol/L]	14.3
Vomiting	√	Lactic acid [mmol/L]	8.1
Diarrhoea	√	Blood ammonia [umol/L]	100
Tachycardia	√	ALT [U/L]	761
Neurological manifestations	√	AST [U/L]	348
Somnolence	√	Creatinine [umol/L]	53
Agitated	√	Urea [umol/L]	547.3
Babbitt sign+	√	Potassium [mmol/L]	2.55
Antibiotics	Linezolid, meropenem, cefuroxime, azithromycin	Serum calcium [mmol/L]	1.6
PICU therapy	√ (2 days)	Sodium [mmol/L]	128.4
Dexamethasone	0.1–0.15 mg/kg. Days for 3 days	Chlorine [mmol/L]	90.3
Inpatient days	12	D-dimer [ng/mL]	728

PEG — percutaneous endoscopic gastrostomy; PICU — paediatric intensive care unit; MP-IGM — mycoplasma pneumoniae-IGM WBC — white blood cells; CRP — C-reactive protein; PCT — procalcitonin; BE — base excess; HCO3– — bicarbonate; ALT — alanine transaminase; AST — aspartate aminotransferase

and MIS-C, with the best response to treatment being glucocorticoids and intravenous immunoglobulin, resulting in good outcomes and rare complications [3]. On this basis, the patient was administered low-dose glucocorticoids and intravenous immunoglobulin on the sixth day of fever; unfortunately, the recurrent fever persisted, indicating a suboptimal response to conventional treatment methods in MMA patients.

Percutaneous endoscopic gastrostomy(PEG) surgery is associated with minimal post-operative complications, is well-tolerated by pediatric patients, and is suitable for long-term tube feeding, simultaneously reducing negative psychological impacts on the patients

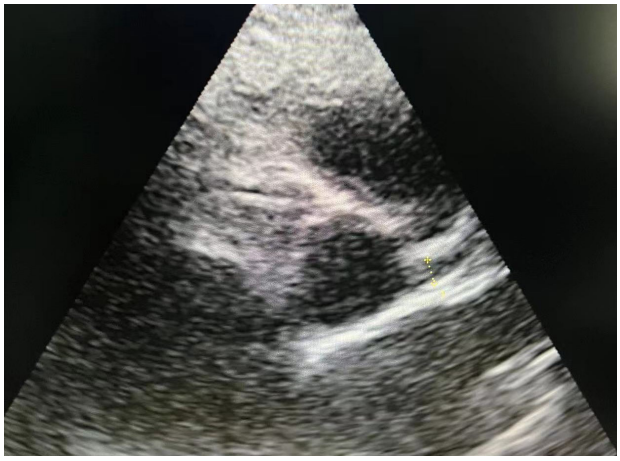

Figure 1. *Echocardiography: The internal diameters of the left and right coronary artery origins are approximately 0.34 cm (z-score 2.6) and 0.27 cm (z-score 1.6), respectively. Indicating: An enlargement of the left coronary artery origin*

[4]. The patient underwent PEG surgery at the age of 2, significantly reducing the frequency of metabolic disturbances. Additionally, during episodes of infection in the patient, the use of PEG can help shorten the hospital stay and facilitate the recovery process.

In summary, when treating patients with MMA who experience prolonged fever during concurrent infections, clinicians should remain watchful for the development of MIS-C and should also consider the possibility of Kawasaki disease.

Ethics statement

The study participant provided informed consent, and was approved by the Medical Ethics Committee of Shenzhen Maternal and Child Health Hospital (No. SFYLS2022075).

Conflict of interest

The authors declare that they have no competing interests.

Funding

This study was supported by Sanming Project of Medicine in Shenzhen (SZSM201812056).

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