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Cardiac manifestations of multisystem inflammatory syndrome

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Key words:

MIS-C; multisystem inflammatory syndrome; SARS-CoV-2; COVID-19; coronary abnormalities.

ABSTRACT

Introduction and purpose:

Multisystem inflammatory syndrome (MIS) in children and adolescents is an excessive inflammatory response syndrome after storage of COVID-19, which can lead to serious complications. The course of the disease may vary from mild to requiring intensive therapy. In our review, we try to draw attention to the importance of cardiological complications and present the currently used treatment. In medical professionals vigilant should be increased in order to early recognize this disease, and to be alert to the need for early cardiological evaluation and follow-up.

Description of the state of knowledge:

MIS can cause myocardial dysfunction, shock, coronary artery lesions, pericardial effusion, valvulitis, and electrophysiological abnormalities. Patients may require intensive medical care, careful fluid therapy, the use of pressor amines and, in rare cases, extra corporeal membrane oxygenation (ECMO). Coronary aneurysms are the most important long-term complication of MIS. They occur in up to 25% of patients. Most abnormalities are retreated within 2-3 months. MIS has a good prognosis with a mortality rate of 2%.

Summary:

Cardiac complications, although serious, rarely require urgent intervention. Patients with diagnosed dilatation of the coronary arteries or aneurysm require intensive medical review in the initial period of recovery. The control must include a medical examination, ECG, ECHO and evaluation of markers of myocardial damage. Patients who have undergone MIS should be released from physical education for at least 6 weeks or until the changes in the coronary arteries disappear. The lesions resolve spontaneously in 2-3 months in most patients and do not recur, suggesting the possibility of waiving long-term patient follow-up.

Introduction

Multisystem inflammatory syndrome (in children) - (MIS (-C)) otherwise paediatric inflammatory multisystem syndrome (PIMS) is a condition associated with COVID-19. The first description is from May 2020. Initial reports described it as a disease similar to Kawasaki disease (KD) and toxic shock syndrome leading to multiorgan failure and shock [1, 2]. The most accurate definition for MIS has been provided by WHO (Table 1). However, this is a new disease entity, the definition is subject to change [3].

Pediatric hyperinflammatory condition begins between 3-6 weeks after infection with SARS-CoV-2 virus [4, 5]. It most often affects school-age children, the median is 9 years. American data published so far suggest, that MIS-C develops in 1/1000 of children infected with SARS-CoV-2 virus, most often with little or no symptoms. The relationship of MIS with COVID-19 has been established on the base of positive serological test results in the majority of patients [6].

MIS is a significant clinical challenge, patients may present a wide spectrum of symptoms and disease severity. It is characterized by a fever lasting more than 3 days, an increase in inflammatory parameters, gastrointestinal symptoms, symptoms of the heart muscle damage, muco-cutaneous and neurological symptoms. About half of the patients also present respiratory symptoms [7]. For diagnosis, it is necessary to fulfil the clinical and laboratory criteria and to exclude other causes. The biggest challenge is to quickly identify the disease and manage emergencies. The general condition of the patient usually deteriorates dramatically 5-6 days after the onset of symptoms. In the treatment parenteral immunoglobulins, steroids and aminosalicyclic acid (ASA) are used. Some patients require intensive care unit (ICU) hospitalization, intensive fluid therapy, treatment with pressor amines, and even mechanical circulatory assistance. Proper management enables quick recovery, mortality is 2% [6]. Among the most common permanent complications are cardiac complications. Coronary artery aneurysms may occur in up to 25% of patients [3]. Apart from obesity, there has been no evidence of association between MIS and other chronic diseases [7].

WHO Preliminary case definition
Children and adolescents 0–19 years of age with fever ≥ 3 days
AND <u>two</u> of the following:
1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP).
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).
AND Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.
AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.'

Table 1. World Health Organization's definition of Multisystem inflammatory syndrome in children and adolescents [3]. Abbreviations: N-terminal prohormone of brain natriuretic peptide (NT-proBNP), prothrombin time (PT), partial thromboplastin time (PTT), erythrocyte sedimentation rate (ESR), Real Time PCR (RT-PCR). Created with Biorender.com

Symptoms and course of the disease

The disease affects children and young adults, the median age of onset is approximately 9 years. The necessary criterion for the diagnosis is a fever lasting at least 3 days or longer. Gastrointestinal symptoms such as vomiting, diarrhea and abdominal pain of varying severity are often the first symptoms. Then, the differential diagnosis of MIS-C is necessary with acute appendicitis and other acute conditions affecting the abdominal organs, that may require urgent surgical intervention. The most characteristic of MIS-C is involvement of the cardiovascular system, symptoms of shock, myocarditis, coronary aneurysms, cardiac arrhythmias, fluid in the pericardium, furthermore chest pain may appear. Additionally, patients may suffer from cough, dyspnea, apathy, headache, drowsiness, irritability, paresis, features of aseptic meningitis, anuria, acute kidney damage [4]. A number of characteristic muco-cutaneous symptoms that require differentiation from Kawasaki Disease are swelling of the hands and feet, polymorphic rash, conjunctivitis, strawberry tongue, erythema on the face, hands and feet [2, 4, 8]. Laboratory tests show increased parameters of inflammatory markers: C-reactive protein (CRP), procalcitonin, elevated erythrocyte sedimentation rate (ESR), D-dimers, ferritin, lactate dehydrogenase (LDH), interleukin-6 (IL-6). Other common findings include positive test for antibodies to SARS-CoV-2 in the majority of patients, or active SARS-CoV-2 infection. We also observe an increase in troponin, B-type natriuretic peptide (BNP), NT-proBNP levels, which are markers of myocardial damage. Patients with MIS may also be characterized by hyponatremia, lymphopenia, neutrophilia, thrombocytopenia, or hypoalbuminemia [4, 5, 9]. These patients should be hospitalized and monitored, because more than half of them may develop heart failure or shock in the course of the disease. Ideally, hospitalization should take place in a hospital with access to cardiological consultation and ICU. However, transfer to a higher-reference hospital should not delay the start of treatment.

In children with suspected MIS-C, the necessary laboratory tests should be performed - biochemical tests, inflammatory parameters and microbiological tests, depending on the clinical presentation of the patient. Patients diagnosed with MIS-C should have an ECG and an ECHO [10]. Chest X-ray or computed tomography (CT) scan are frequently performed tests in this group of patients. In the case of abdominal symptoms, an ultrasound of the abdomen is recommended.

Cardiac manifestation

The most characteristic feature of MIS patients is cardiovascular involvement, which may be directly related to the life-threatening course of the disease. Clinical manifestations include hypotension (49.5%), shock (35.4%), left ventricular dysfunction (40.6%), mitral regurgitation (25.5%), pericardial effusion (23.9%), myocarditis (22.8%), coronary ectasia and aneurysms (18.6%), arrhythmias and conduction system disease [5, 11, 12]. Most common cardiovascular manifestations are presented on figure 1.

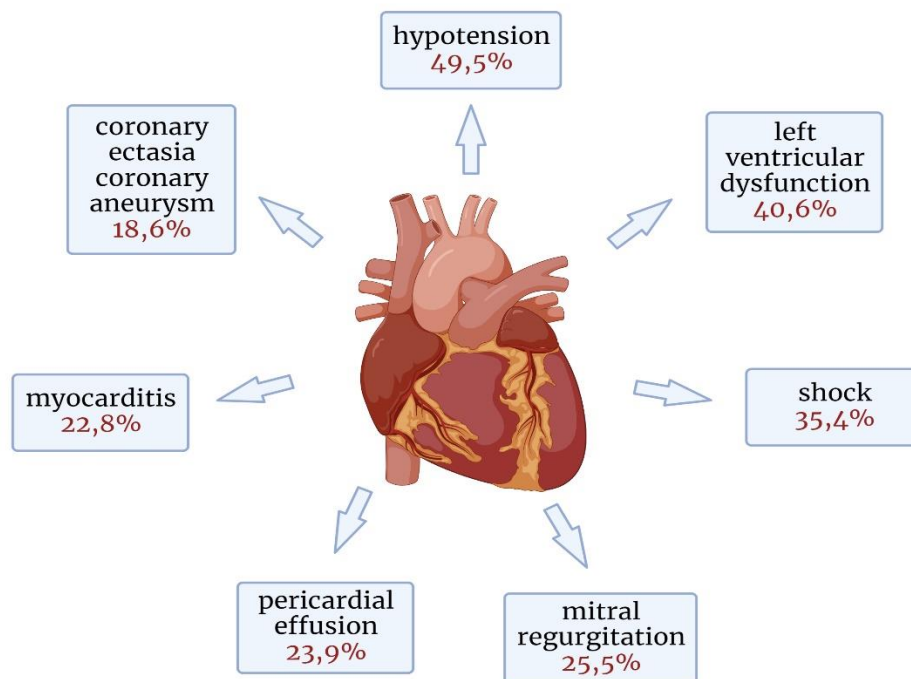


Fig.1 The most common cardiovascular manifestations of MIS-C. Created with Biorender.com

The involvement of the cardiovascular system is more severe in MIS than in KD. Patients more often require a hospitalization in the ICU and require multiple vasoactive agents therapy. Patients with shock or symptoms of left ventricular failure most often presented elevated troponin or NT-proBNP values. Cardiac consultation should not be delayed by a negative SARS-CoV-2 RT PCR result or a negative IgG test result, but should be based on the results of troponin or NT-proBNP [13].

ECG abnormalities may have various manifestations and different dynamics. Diffuse ST-segment elevation, increased QT interval, atrioventricular block (AV), transient AV block and ventricular tachycardia have been observed. The majority of patients with arrhythmia had decreased left ventricular function. Electrophysiological abnormalities were rare, however, they may have a significant clinical impact and require monitoring [5, 13]. ECG should be performed immediately when MIS is suspected and for control purposes, especially when there is a significant damage to the heart muscle.

Echocardiography should be performed as early as possible, due to the possibility of detecting coronary aneurysms, ventricular dysfunction, valvulitis or pericardial effusion in the early stages of the disease. In previous studies it was shown that patients may develop pericardial effusion, tricuspid regurgitation, mitral regurgitation, left ventricular dilation and aortic insufficiency during follow-up period [13]. Compared to KD, aneurysms in MIS appear quickly, even within 1 week of the disease. Patients with coronary artery lesions should be subjected to control echocardiographic examinations. Follow-up examinations should be performed after 7-14 days, after 6 weeks, and after 6-12 months in uncomplicated cases. If the course of the disease is worse, the intensity of echocardiographic assessment should be

increased depending on the clinical situation [4]. Normalization of coronary aneurysms is observed within 2-3 months after onset in the majority of patients [9]. We should be the vigilant in caring for a patient with MIS, because the changes in the coronary arteries may appear during the hospitalization or after discharge, even if the first ECHO examination was normal [9]. The aim of the treatment is to stabilize the general condition in the short term, and in the long term to prevent chronic sequelae in the form of coronary aneurysms, scars and fibrosis of the heart muscle, and to prevent arrhythmias. This explains the use of aspirin in treatment and its continuation for another 6 weeks. It should be added that we have insufficient data on the impact of the treatment used on the prevention of cardiovascular complications. Spontaneous disappearance of changes is often observed. Even the most serious of them do not require immediate intervention, including large pericardial effusions or significant coronary dilatation. Despite the high risk of life-threatening complications, heart involvement in MIS appears to have a favorable prognosis, suggesting a need for reduction of medical follow-up after complete recovery.

Treatment

In treatment, fluid therapy should be used carefully, because of the risk of heart failure and pulmonary edema. Empirical antibiotic therapy is indicated in the case of suspected sepsis and other manifestations of bacterial infection until negative microbiological results are obtained. Antiviral therapy (remdesivir) is indicated only in cases of confirmed infection with SARS-CoV-2 virus, with reduced saturation (<94%) [4, 10]. It seems that the first-line treatment in the form of intravascular immunoglobulines (IVIg) infusion, using the IBW (ideal body weight) dosage, plays the most important role in the therapy. In the second line, glucocorticosteroids are used, most often pulses of methylprednisolone for the next 3 days. The third line, similar to Kawasaki disease, is the biological treatment of anakinra, infliximab, tocilizumab [10]. ASA is used as an additional treatment, especially in patients with the Kawasaki Disease phenotype. Patients with coronary aneurysms should receive anticoagulation and antiplatelet therapy in line with the Kawasaki disease guidelines. It is important to remember about the possibility of developing macrophage activation syndrome (MAS) in some patients with MIS-C, such diagnosis requires multi-specialist treatment. [4, 14]

Prognosis

With early recognition and treatment, the prognosis is good, the mortality rate is approximately 2%. The onset of the disease requires hospitalization. It lasts average 7-10 days. The first sign of recovery is most often reduction of levels of markers of myocardial damage. Coronary arteries changes usually normalize within 3 months of follow-up, and ECG changes may persist for longer [9].

What about sport?

Patients who have undergone MIS should be exempt from physical education (PE) at school and from additional sports activities for a period of at least 6 weeks. Patients with documented damage to the coronary arteries should be excused from participating in PE classes until the arterial diameter is normalized. A patient with a history of MIS should still be subjected to medical evaluation, the frequency of visits depends on the severity of the disease and its complications [4].

Limitations

We are aware of the limitations of our review. So far results of only a few small cohorts studies and single case reports on the cardiac manifestations of MIS have been published. In a large studies cardiac manifestations are treated briefly, paying attention only to the most important

facts. There is a need for a bigger studies focused on cardiac manifestations occurrence and management.

Summary

MIS is a severe, life-threatening multi-system inflammatory syndrome that requires immediate treatment and has a good prognosis. The most common manifestations are fever, gastrointestinal symptoms, symptoms from the cardiovascular system, muco-cutaneous manifestations and many others. It requires detailed differential diagnosis and a quick start of treatment. A patient with suspected MIS should be hospitalized in a medical facility with an intensive care unit and the possibility of cardiological consultation. Transport to another center should not delay the start of treatment. Some patients may require cardiovascular stabilization or mechanical ventilation. The most effective in preventing complications are the stabilization of the general condition and treatment with an infusion of IVIG (first line) and glucocorticosteroids therapy (second line). Long-term complications mainly concern the cardiovascular system, and the most dangerous of them are coronary aneurysms. According to the literature, aneurysms retreat spontaneously within 2-3 months. Patients with a history of MIS require increased frequency of medical checks, especially in the initial period after discharge from the hospital. Patients should resign from PE classes at school and additional sports for 6 weeks or until the changes in the coronary arteries have resolved.

References

1. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020. Epub 2020/05/11.
2. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Bradley Segal J, et al. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. *Hosp Pediatr*. 2020. Epub 2020/04/09
3. Multisystem inflammatory syndrome in children and adolescents with COVID19: Scientific brief". www.who.int. World Health Organization. Archived from the original on 15 May 2020
Okarska-Napierała M, Ludwikowska M, Książyk J, Kuchar E, Mazur A, Szenborn L, Werner B, Wysocki J, Jackowska T. Approach to a child with paediatric inflammatory multisystem syndrome with COVID-19 recommendations by the Polish Paediatric Society Expert Group and the National Consultant in the Field of Paediatrics. *Przegląd Pediatryczny* 2020/Vol. 49/No. 4/1-9
4. Okarska-Napierała M, Ludwikowska M, Książyk J, Kuchar E, Mazur A, Szenborn L, Werner B, Wysocki J, Jackowska T. Approach to a child with paediatric inflammatory multisystem syndrome with COVID-19 recommendations by the Polish Paediatric Society Expert Group and the National Consultant in the Field of Paediatrics. *Przegląd Pediatryczny* 2020/Vol. 49/No. 4/1-9
5. Schvartz A, Belot A, Kone-Paut I. Pediatric inflammatory multisystem syndrome and rheumatic diseases during SARS-CoV-2 pandemic. *Front. Pediatr*. 2020, 8
6. Godfred-Cato S, Bryant B, Leung J i wsp.: COVID-19-associated multisystem inflammatory syndrome in children – United States, March-July 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1074-1080.
7. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. *Eur J Pediatr*. 2021 Jul;180(7):2019-2034. doi: 10.1007/s00431-021-03993-5. Epub 2021 Feb 18.

8. Osiejewska A, Wojtachnio D, Bartoszewicz J, Grądzik A, Nowakowska I, Kudan M, Gorajek A. Kawasaki disease: a comprehensive review. *Journal of Education, Health and Sport* [online]. 3 August 2022, T. 12, nr 8, s. 317–327.
9. Felsenstein S, Duong P, Lane S, Jones C, Pain CE, Hedrich CM. Cardiac pathology and outcomes vary between Kawasaki disease and PIMS-TS. *Clin Immunol*. 2021 Aug;229:108780. doi: 10.1016/j.clim.2021.108780. Epub 2021 Jun 9. Erratum in: *Clin Immunol*. 2021 Oct;231:108855.
10. Harwood R, Allin B, Jones CE i wsp.: PIMS-TS National Consensus Management Study Group. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Health* 2020; S2352-S4642 (20)30304-7
11. Opoka-Winiarska V, Grywalska E, Roliński J. PIMS-TS, the New Paediatric Systemic Inflammatory Disease Related to Previous Exposure to SARS-CoV-2 Infection- "Rheumatic Fever" of the 21st Century? *Int J Mol Sci*. 2021 Apr 26;22(9):4488.
12. Yasuhara J, et al., COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis, *Pediatr. Pulmonol*. 56 (5) (2021) 837–848.
13. Clark BC, Sanchez-de-Toledo J, Bautista-Rodriguez C i wsp.: Cardiac abnormalities seen in pediatric patients during the SARS-CoV2 pandemic: an international experience. *J Am Heart Assoc* 2020; 9 (21): e018007.
14. McCrindle BW, Rowley AH, Newburger JW i wsp.: Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals from the American Heart Association. *Circulation* 2017; 135 (17): e927-e999