Archives of Pediatrics
Kake M, et al. Arch Pediatr 8: 235.
www.doi.org/10.29011/2575-825X.100235
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Case Report

Multisystem Inflammatory Syndrome Cardiovascular Complications in Patient associated with SARS-CoV-2 Infection

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Citation: Kaķe M, Šmitiņš E, Apine I, Lubaua I (2023) Multisystem Inflammatory Syndrome Cardiovascular Complications in Patient associated with SARS-CoV-2 Infection. Arch Pediatr 8: 235. DOI: 10.29011/2575-825X.100235

Received Date: 09 January 2023; **Accepted Date:** 17 January 2023; **Published Date:** 20 January 2023.

Abstract

Cases of long-term outcomes of a novel disease MIS-C have rarely been reported. The most common cardiac manifestations of MIS-C are myocarditis, coronary artery aneurysms, conduction abnormalities, and arrhythmias. We report a case of an 8-year-old boy, who has Asperger syndrome, with a complicated course of disease called MIS-C during Covid-19 outbreak, when this was the first diagnosis of MIS-C in Latvia. The patient was tested positive for the SARS-CoV-2 (RNA) and Hemophilus influenza (DNA). In 9th day of hospitalization, the diagnosis of MIS-C was performed. He had involvement of gastrointestinal, cardiovascular, respiratory and coagulation systems. The patient received therapy with IVIG, Anakinra as well antibiotics and cardiovascular medicine. During hospitalisation patient had complications such as anemia of a combined nature, post-infectious bone marrow suppression, hepatosplenomegaly and candidiasis due to CVC. The cardiac magnetic resonance imaging (cMRI) after being diagnosed with MIS-C revealed edema and focal changes in LV inferior wall, although volume of both ventricles and LV systolic function were normal. A year after the follow-up cMRI, showed resolution of the myocardial edema. In existing literature there are several cohort studies about long-term outcome of MIS-C myocarditis in 6 month follow-up visit, showing no evidence of scar tissues in cMRI, but in some patients- diastolic dysfunction was detected. This report emphasizes a complicated form of disease in patient who has Asperger syndrome with excellent outcome.

Keywords: COVID-19 Associated Multisystem Inflammatory Syndrome; Cardiovascular complications; Myocarditis; Long-term outcome cMRI.

Introduction

This clinical case describes the clinical course, treatment, and long-term outcome of Covid-19-induced myocarditis with reversible myocardial damage in a patient who has Asperger syndrome. Most often in the pediatric population myocarditis is caused by a viral infection. Usually, symptoms of the disease are non-specific, fever lasting 7-14 days, myopia, vomiting, diarrhea, and respiratory symptoms [1]. The most frequent causative agents are Coxsackieviruses B, Adenovirus, and Parvovirus B19. Clinical manifestation can vary from unspecific symptoms and successful recovery to arrhythmias, acute heart failure, and sudden cardiac death [1].

On September 6, 2020, the Center for Disease Control and Prevention first defined a new, rare and serious clinical case called Multisystem Inflammatory Syndrome associated with Covid-19 infection [2]. It is known so far that the average patient is 9 years old, the main complications occur 4 weeks after Covid-19 infection. MIS-C patients present with elevated inflammatory markers and cytokine storms with a multi-organs involvement including cardiac manifestations, ranging from pericarditis, myocardial dysfunction,

systemic hyper-inflammation/vasodilation, Kawasaki-like disease to arrhythmias [3].

The pathogenetic mechanisms are still unclear. Recent research suggest that MIS-C is caused by a post-infectious inflammatory syndrome associated with elevation in all cytokines and markers of recent T-cell activation occurring despite a strong and specific humoral response to SARS-COV-2 [4]. Mild, transient coronary artery dilatation may be associated with cytokine storms (IL-6), and direct cardiomyocyte damage may occur upon entry of the virus via the ACE-3 receptor, while activated CD8 + T Ly migrates to the myocardium resulting in cell-mediated cytotoxicity [5].

Latest researh reveals that skin rash and gastrointestinal symptoms are more common in MIS-C, whereas respiratory symptoms are more common in COVID-19. According to a systematic review and meta-analysis in 2021, Brazil, the main complications of MIS-C are fever, gastrointestinal symptoms (82%), and cardiological symptoms (66%), in contrast to adults, respiratory symptoms are less common (39%) less often develop renal and neurological symptoms but in contrast to adults, respiratory symptoms are less common [4,5].

The purpose of this clinical case report is to reflect the course of cardiac complications, the main symptoms, treatment tactics, and results of visual diagnostics, with a particular focus on long-term changes, to enrich the range of clinical case reports for further descriptive studies in Covid-19-associated Multisistemic inflammatory syndrome in children (MIS-C).

Case report

This is an 8-year-old boy with a medical history of combined COVID-19 and Haemophilus influenza infection followed by multisystemic inflammatory syndrome in Children (MIS-C). The patient has Asperger syndrome.

The patient was admitted to the Children Clinical University hospital in Riga, transferred from a regional hospital on December 20, 2020, with a history of persisting fever without other symptoms for more than 2 weeks, without response to antibiotic therapy.

The patient was admitted in the hospital with severe condition. Physical examination showed maculopapular rash on the elbows, "strawberry" tongue, and dry lips. He had SIRS with respiratory distress, fever of 39.7°C, tachycardia of 140 x/min., tachypnoea (55 x/min.), SpO_2 85% without oxygen support, 94-97% with oxygen support (4 l/min). Analysis showed lymphopenia, neutrophilia, thrombocytopenia, anemia, increased CRP and Il-6. See Table 1. In nasopharyngeal swab the patient was tested positive for the SARS-CoV-2 (RNA) and Hemophilus influenza (DNA). The chest radiography showed bilateral pneumonia with a right-side pleural effusion. Patient received therapy with antibiotics - Cefotaxime and Clarithromycin.

In two days, the respiratory distress symptoms and the necessity for oxygen support increased. The fever remained without response to antipyretic therapy. Due to severe clinical condition without improvement the antibiotic therapy was changed to Cefotaxime, Clindamycin and Azithromycin. Also therapy with Dexamethasone and Enoxaparin was initiated.

The patient was diagnosed with MIS-C after 9 days of hospitalization. The patient had a persisting fever (>38 °C), his laboratory findings showed neutrophilia, lymphopenia, hypoalbuminemia, anemia, and constantly increased inflammation biomarkers. Immunogram showed activation of inflammatory cells and humoral immunity with increased IgA levels. There was also natural killer cell insufficiency on the background of Covid 19 infection. Patient also had involvement of gastrointestinal, cardiovascular, respiratory and coagulation systems. See Table 1.

The abdominal x-ray showed partial ileus, and abdominal US revealed mesadenitis with intestinal loop meteorism. The thoracic x-ray showed bilateral pneumonia, and pleural effusion up to 17 mm up to 1,7 cm on right sight. An ECG showed nonspecific ST-T changes in leads V1-V6, AVF, and AVL, and prolongation of QTc interval (484 ms). Echocardiography showed LVEF 68%, mild dilatation of the right ventricle (RV) and right atrium (RA), mild to moderate tricuspid valve regurgitation, mild mitral valve regurgitation, and secondary increased pulmonary pressure (Table 1).

As the patient met the criteria for MIS-C the therapy with IVIG was initiated and the therapy with Dexamethasone, Enoxaparin, diuretics, and Metoprolol was continued.

After initiation of IVIG, patient's condition rapidly improved. Respiratory distress and the necessity for oxygen support resolved. The fever disappeared for 48 hours a day after IVIG was initiated. In 14 days after hospitalization thoracic x-ray findings and the abdominal US improved except for the spleen enlargement (being 14,4 x 4,3 cm).

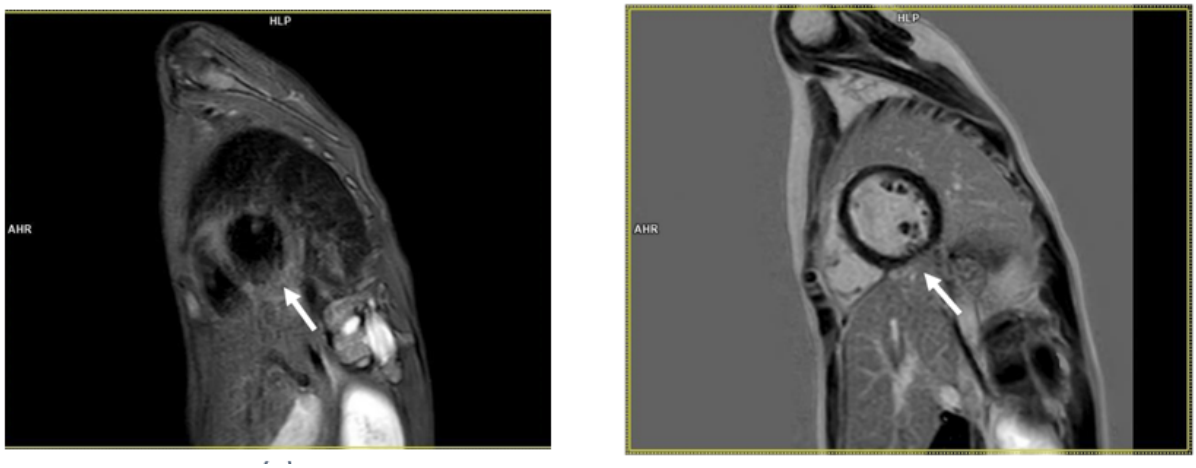
The pleural effusion resolved. ECG showed ST elevations without changes in dynamics. In 15th day of hospitalization echocardiography showed normal left ventricle ejection fraction (LVEF 66%), the disappearance of valvular insufficiency, and no signs of the ventricle or coronary dilatation. The pro-BNP levels normalized to 115 pg/mL. In day 20 of hospitalisation patients isolation was discontinued.

Laboratory test	Admission	MIS-C diagnosis	Discharge	Reference interval
WBC x10^3 /uL	5.86	6.92	12.29	4.31 - 11
NEUT %	81.8	75,7	67.2	28,6-74,5
LYMPH %	12.6	20.4	28.1	15.5 - 56.6
RBC x10^6/uL	2.53	3.33	3.83	3.96 - 5.03
HGB, g/dL	6.9	9.1	11.8	10.7 - 13.4
HCT, %	19.9	26.8	34.7	32.2 - 39.8
PLT, x10^3 /uL	196	203	214	206 - 369
ALAT, U/L	17.6	41.54	22.5	0 - 39
Creatinine, umol/L	26.66	25.53	21	35 - 53
CRP, mg/L	168.26	49.35	1.39	0 - 2.8
Il-6, pg/mL	86.3	40.4	58.7	0 - 5.9
Albumin g/L	24.7	27.3	-	38 – 54
Ferritin, ng/mL	365.4	589.2	-	20 - 200
Transferrin, mg/dL	133	193	-	200 - 360
Fibrinogen g/L	6.32	4,81	1.89	1.7 - 4.2
D-Dimer, mg/L FEU	1.74	1.36	0.19	0 - 0.55
ESR, (mm/h)	-	120	-	0 - 15
NT - proBNP, pg/mL	8138	1162	52	0 – 125
Echocardiography	**Admission**	**MIS-C diagnosis**	**Discharge**	
LVEF %	68	66	66	
LVDId mm	45	42	40	
LVIDs mm	28	27	26	
RVDd mm	38	-	29	
TAPSE mm	25	18	18	
LAVI ml/m2	26 (1.5z)	21	21	
RAVI	35	10	10	
Tricuspid regurgitation	moderate		Dissapeared	
Mitral regurgitation	mild		Trivial	

Table 1: Laboratory and Echocardiography findings during hospitalization.

The patient's hospital course was complicated by anemia of a combined nature, post-infectious bone marrow suppression, hepatosplenomegaly and candidosis due to CVC. Therapy included high-dose Anakinra according to MIS-C therapy guidelines, Metilprednisolone, Fluconazole, antibiotics, and Er mass transfusion. The differential diagnosis included hidden immunodeficiency or underlying inflammatory/ autoinflammatory process.

The cardiac magnetic resonance imaging (cMRI) performed on 27th day after being diagnosed with MIS-C revealed oedema (Figure 1a) and subepicardial contrast enhancement (Figure 1b) in LV inferior wall, despite normal volume of both ventricles and LV systolic function. A year after the patient was discharged, he underwent a follow-up cMRI, showing resolution of the myocardial oedema. Also, subpericardial contrast enhancement was no longer detected.



(1a) (1b)

Figure 1: cMRI showing reversible changes of subacute myocarditis in a patient with complicated MIS-C ; (a) Short-tau inversion recovery (STIR) sequence taken on the 27th day after being diagnosed with MIS-C. In the short-axis mid-ventricular view of the LV inferior wall, there is increased signal intensity indicating oedema (arrow); (b) Phase-sensitive inversion recovery (PSIR) sequence shows subepicardial contrast enhancement (arrow) indicating morphological damage of the myocardium.

Discussion

This is a case report about first diagnosed MIS-C patient in Latvia after 4 months when criteria of this disease were firstly published on CDC. This case report reveals long-term outcome for patient with cardiological complications of complicated MIS-C disease emphasizing the reversible changes in myocardium seen in cMRI one year after MIS-C was diagnosed.

Several research demonstrate that cardiac involvement occurs in up to 67–80% of children with MIS-C. The cardiac clinical presentation of MIS-C can range from minor involvement to cardiovascular collapse and shock. Cardiac pathology includes coronary artery dilation, ventricular dysfunction, conduction abnormalities, and arrhythmias. Interestingly, the severity of clinical manifestations is not related to the gravity of the previous viral disease [7,8].

According to a data of systematic review in 2020, the duration of hospitalisation is aproximately 4–13 days and intensive care was required in 68% of patients. Despite the common necessity of intensive care, mortality rates were low (1,7%) and favorable outcomes were reported in the majority of cases [9]. As stated in a multicenter retrospective study in Italy, that focused on cardiological complications in patients with SARS-CoV-2 infection, MIS-C occurred in 46 out of 294 patients and cardiac manifestations were documented in almost all MIS-C patients (97,8%), from which 59% were admitted in pediatric intensive care unit. Recovery of all patients was satisfactory and during follow-up no additional events were reported [3].

Sensitive and specific tools, to asses cardiac involvement of MIS-C patients early after disease onset, are speckle tracking echocardiography and cMRI [8]. The most common echocardiographic findings include depressed LV function, coronary artery abnormalities, mitral regurgitation and pericardial effusion. The findings in cMRI may vary depending on the time

when it was performed. A study where cMRI was done in acute phase of MIS-C, less than 11 days from symptom onset, showed signs of diffuse myocardial oedema, and hyperemia without evidence of focal myocardial necrosis or replacement fibrosis [10]. In contrast, a cohort study, where cMRI was performed within 19 days of symptom onset revealed pericardial effusion, delayed enhancement for some patients with nodular, subepicardial or mesocardial patterns, and late gadolinium enhancement in quarter of patients [8].

Among the studies that reported outcomes at discharge or during follow-up, almost all patients with cardiac involvement experienced nearly full recovery of left ventricular function and normalization of cardiac inflammatory markers except for mild cardiac dysfunction observed in 9 patients at discharge in one study [11].

Several research have recently demonstrated reversible myocardial changes in cMRI in 6 month follow-up visit in patient's with MIS-C diagnosis, giving information of an uncomplicated course of myocarditis in MIS-C with a favorable outlook on long-term prognosis. In a longitudinal 6 month cohort study cMRI in select high-risk patients revealed no persistent inflammation or scarring suggesting an uncomplicated course of myocarditis in MIS-C with favorable outlook on long-term prognosis. However, there was persistence of echocardiographic diastolic dysfunction in a few patients of uncertain significance [12].

This case report is remarkable for good long-term outcome despite the difficult course of the disease in patient with Asperger syndrome. First of all the patient tested positive for both Covid-19 and Haemophilus Influenza infections, in 9 days the patient met all criteria of MIS-C with cardiological complications, like ST elevations, prolongation of QTc interval, mild dilatation of the right ventricle (RV) and right atrium (RA), mild to moderate tricuspid valve regurgitation, mild mitral valve regurgitation. During hospitalisation the patient developed candidosis, that made it difficult to understand the true diagnosis, but treatment with IVIG and Anakinra according to MIS-C treatment guidelines showed positive results.

The cMRI was done before discharge of the hospital, on 27th day after being diagnosed with MIS-C and a year after in follow-up visit. First cMRI showed myocardial oedema, but in a year, follow-up cMRI showed no pathological changes in myocardium.

Conclusions

MIS-C is new diagnosis that needs to be further studied. There are a lot of studies, that describes short-term outcome of MIS-C cardiological complications, but not as many research papers that reports long-term outcome. This case report is notable for demonstrating a good long-term outcome for a complex form of MIS-C.

All authors have completed the Unified Competing Interest form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Ethics Committee of Riga Stradins University (Nr. 6-1/10/83, 24.09.2020).

This research received no external funding.

Written informed consent has been obtained from the patient to publish this paper.

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