Late-Term Cardiac Magnetic Resonance Imaging in Multisystem Inflammatory Syndrome in Children

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Abstract

Multisystem inflammatory syndrome in children (MIS-C) develops as an exaggerated, complex, postinfectious immune response related to severe acute respiratory syndrome coronavirus (SARS-CoV-2 virus), which affects all systems in the body. Cardiac involvement in children can have a spectrum ranging from mild disease to severe heart failure due to fulminant myocarditis. Cardiac involvement usually resolves after clinical recovery. However, the adverse effect of myocarditis on cardiac function after recovery is not fully known. In this study, we aimed to investigate cardiac involvement by performing cardiac magnetic resonance imaging (MRI) after acute and recovery stage. Here, we describe the clinical and laboratory features and the effect of treatment on the development of fibrosis on cardiac MRI in 21 patients with MIS-C and the localization of fibrosis in five patients.

When compared with 16 patients with normal cardiac MRI, five patients with cardiac fibrosis on MRI had a greater age (mean 14.4 ± 4.0 years vs 8.9 ± 3.5 years; $p=0.007$), a similar gender distribution (male/female: 3/2 vs 5/11; $p=0.325$), a greater body mass index (BMI) (mean 22.68 ± 4.48 kg/m² vs 17.73 ± 3.15 kg/m²; $p=0.012$), a lower leucocyte count, [median 5250/ μ l (3880-7790) vs 12065/ μ l (4210-21210); $p=0.011$], a lower neutrophil count [median 4000/ μ l (2150-6560) vs 9875/ μ l (2540-18500); $p=0.019$], a higher blood urea nitrogen level [median 15 mg/dL (11-26.8) vs 8.5 mg/dL (4-18); $p=0.025$], and a higher creatinine level (mean 0.61 ± 0.07 mg/dL vs 0.45 ± 0.14 mg/dL; $p=0.024$). Cardiac fibrosis on MRI was located in the region of posterior right ventricle insertion point and in the midventricular septum.

Conclusions

Adolescence and obesity appear as risk factors for the development of fibrosis as a late-term sequela of myocarditis. We believe that other mechanisms such as a complex immune system response and hemodynamic instability causing acute kidney injury may similarly play a role for the development of cardiac fibrosis. However, this subject should be clarified by more comprehensive studies. Furthermore, future studies reporting the follow-up data of patients with fibrosis are necessary to predict and manage adverse outcomes.

What Is Known

The degree of cardiac involvement in the acute phase of MIS-C determines the clinical severity and course of the disease.

MIS-C associated myocarditis usually fully recovers clinically with the resolution of the disease. Adverse cardiac effects of MIS-C after the acute and recovery phases are over, on the other hand, remain unclear.

What is New:

Adolescence and obesity appear to be risk factors for the development of fibrosis in the late-term among patients with MIS-C.

Some data indicating that other mechanisms such as a complex immune system response and hemodynamic instability causing acute kidney injury may similarly play a role for the development of cardiac fibrosis were obtained.

Cardiac fibrosis on MRI was located in the region of posterior right ventricle insertion point and in the midventricular septum.

Introduction

Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) has caused millions of people around the world to become infected and die since December 2019 when the first case was reported. COVID-19 disease has an asymptomatic or mild course in a majority of children.[1] However, towards the end of April 2020, a life-threatening condition resembling severe Kawasaki disease and hyperinflammatory shock syndrome, and children hospitalized due to it, were identified across Europe for the first time, which was thought to be associated with COVID-19. Most children affected by this condition had a negative real-time reverse transcription-polymerase chain reaction (RT-PCR) but a positive antibody test for the SARS-CoV-2 virus, indicating past infection. The cause of this clinical syndrome was assumed to be an inflammatory reaction following SARS-CoV-2 infection.[2] In May 2020, the Center for Disease Control (CDC) and World Health Organization (WHO) denominated the disease as multisystem inflammatory syndrome in children (MIS-C).[3],[4]

MIS-C, a rare but serious complication of COVID-19, is defined by CDC as follows: (1) a person younger than 21 years of age, fever lasting for more than one day, laboratory evidence of inflammation, and evidence for clinically severe disease with multiorgan involvement requiring hospital admission; (2) absence of alternative diagnoses; and (3) with a temporal association with COVID-19 demonstrated by a positive current or recent SARS-CoV-2 RT-PCR, serology, or antigen test or known COVID-19 exposure within the four weeks prior to symptom onset.[5] WHO criteria include some differences: 0-19 years of age, fever for ≥ 3 days, multisystem (≥ 2) organ involvement (mucocutaneous, hypotension/shock, cardiac, gastrointestinal), and the absence of a microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. SARS-CoV-2 epidemiological link is based on RT-PCR, antigen test, positive serology, or possible contact with SARS-CoV-2 patients.[6]

Although fever is the primary diagnostic criterion, gastrointestinal symptoms including abdominal pain, vomiting, and diarrhea are the most common symptoms. Other signs and symptoms include rash, conjunctivitis, oral mucosal changes, peripheral edema, and headache. Fifty percent of children with MIS-C may present with shock. Approximately 50-80% of patients have critical disease requiring intensive care. Cardiac involvement is seen in 80% of affected patients. Patients may present with a wide spectrum of cardiac abnormalities ranging from mild atrioventricular valve insufficiency to heart failure and shock, which may be considerably severe and sudden.[7] Cardiac signs include ventricular dysfunction, valvular dysfunction, pericardial effusion, coronary artery dilation and aneurysm, conduction system abnormalities and arrhythmias. In case series, left ventricular ejection fraction (LVEF) reduction of 40-60%

has been reported. Reduced left ventricular ejection fraction normalizes by 1-2 weeks in a majority of patients.[3],[8],[9]

Compared to Kawasaki disease, left ventricular dysfunction and distributive shock are more common in MIS-C disease. Although MIS-C exhibits some features overlapping with those of Kawasaki disease, there is evidence that they are two distinct syndromes with differences in the degree of hyperinflammation and irregular immune reaction.[10],[11] The cardiac signs of such a newly identified disease have been described only by short-term follow-up data, echocardiographic findings, limited cardiac magnetic resonance imaging (MRI) findings, and data obtained from biopsies and autopsy series. However, the adverse effects of the disease on cardiac function after its acute and recovery phases remain unclear.

In the present study, we aimed to show whether cardiac involvement occurred after the acute and recovery phases with cardiac MRI and its relationship with clinical and laboratory findings in patients with MIS-C.

Material And Methods

Ethical Approval and Consent to Participate

This study was approved by Kayseri City Hospital Clinical Research Ethics Committee (February/2021; no.320). The study was conducted in accordance with the declaration of Helsinki. Informed consent was obtained from the parents of all patients and also from the adolescent patients themselves.

Subjects

Out of 25 patients diagnosed with MIS-C according to the CDC and WHO MIS-C diagnostic criteria between November 2020 and February 2021, 21 patients with clinical and laboratory signs of myocarditis including left ventricular systolic dysfunction, mitral valve insufficiency, elevated troponin T, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), and/or electrocardiographic (ECG) changes, who gave consent to undergo cardiac MRI, underwent cardiac MRI at outpatient follow-up after the completion of the acute and recovery phases. The demographic, clinical, laboratory, electrocardiographic, echocardiographic data, treatment modalities, and disease course of the patients were recorded. The follow-up examinations of the patients after the acute phase were carried out and recorded by the same pediatric cardiology and infectious disease specialists.

Inclusion and Exclusion Criteria

We included patients with clinical and laboratory findings that complied with the MIS-C diagnostic criteria defined by CDC and WHO.

We excluded patients with a microbial etiology of inflammation, such as sepsis and septic shock, viral exanthematous diseases, alternative diagnoses such as anaphylaxis, chronic comorbid conditions, and antiinflammatory drug use.

Evidence for SARS-Cov2 Infection

The history of close contact with a person positive for SARS-CoV-2 infection until 4-6 weeks prior to symptom onset was questioned. The history of symptomatic or asymptomatic infection was recorded. A nasopharyngeal swab RT-PCR test was performed for SARS-CoV-2 virus in all patients during hospital presentation. Enzyme-Linked ImmunoSorbent Assay (ELISA) was used to determine serum anti-SARS-CoV-2 IgG.

General Laboratory Test

Complete blood count, routine biochemistry, C-reactive protein (CRP), sedimentation rate, and procalcitonin were studied at the time of diagnosis and follow-up.

Cardiac Biomarkers, Electrocardiography and Echocardiography

Troponin T and NT-proBNP were measured in all patients at the time of diagnosis and follow-up. At our clinical biochemistry laboratory, the normal level of troponin T and NT-proBNP are <14 ng/L and <300 ng/L, respectively. All patients underwent a 12-lead standard ECG at the time of diagnosis. Two-dimensional, color Doppler, and M-mode echocardiography were performed by the same pediatric cardiology specialist using Vivid 7 pro (GE Medical Systems) at the time of diagnosis and follow-up visits.

Cardiac MRI

Cardiac MRI was performed at pediatric cardiology outpatient follow-up visits after the completion of the acute and recovery phases in all MIS-C patients. Cardiac MRI was performed with a 1.5-T scanner (Magnetom Aera, Siemens Healthineers, Erlangen, Germany). Intravenous sedation was required for three children under seven age. Before administration of contrast agents, only native T1 maps were obtained (field of view, 340 x 340 mm; matrix, 256 x 256; slice thickness, 8 mm; TR/TE, 358/1.3 ms; flip angle, 35°; no interslice gap). After intravenous administration of contrast medium (gadobutrol [Gadovist, Bayer AG, Berlin] 0.1 mmol/kg of body weight), perfusion, cine, late gadolinium-enhanced (LGE) and myocardial T1 maps were performed, respectively. Except for three sedated children whose images were acquired using free-breathing with motion correction (MOCO), all other scannings (18 patients) were performed with breath-holding. Myocardial T1 maps (native and postcontrast) were acquired using the modified look-locker inversion recovery (MOLLI) sequence.

Four to five standard short-axis slices at the basal and mid-ventricular levels were acquired for myocardial T1 maps (native and postcontrast), perfusion and LGE images. Also, there were single 2-chamber and 4-chamber slices in all sequences except perfusion. LGE sequences were obtained 8 to 10 min after injection of the contrast agent (field of view, 340 x 340 mm; matrix, 256 x 256; slice thickness, 8 mm; TR/TE, 495/3 ms; flip angle, 25°; no interslice gap). Cine images were acquired in the 4-chamber, 2-chamber and short-axis heart views using steady-state free precession (SSFP) sequences.

Image analysis was performed by a radiologist with five years of experience in cardiac MRI. All cardiac MRI image analyses were performed on a Syngo Via (Software Version VA30A, Siemens AG, Germany) Workstation. Perfusion, LGE, and ventricular functions were evaluated qualitatively, T1 maps were evaluated quantitatively, due to 16-segment left ventricle (LV) model of the American Heart Association (AHA).[12] Noticeable high signal intensity in LGE was considered as fibrosis. Apical slices were not analyzed because of motion artefacts

Regions of interest were drawn global and focal on native and postcontrast short-axis T1 maps. From our previous experiences, we saw that the cutoff value of myocardial T1 relaxation time in 1.5 T MRI in normal patients was about 1060 ms, as determined by Burkhardt et al.[13] Focal (due to AHA segmentation) or global, T1 relaxation time greater than 1060 ms was accepted as myocardial fibrosis. Extracellular volume was calculated in patients with fibrosis in LGE and native T1 maps. Slices of the T1 map with motion artefacts were not analysed. Endocardial contours of the left and right ventricle were manually traced on end-diastolic and end-systolic frames of each SSFP *cine image*.

Statistical Analysis

The study data were analyzed with IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, ABD) statistical software package. Descriptive statistics were reported as number of unit (*n*), percentage (%), mean $\pm$ standard deviation, median (*M*), minimum (*min*) and maximum (*max*). Normality of distribution of numerical data was tested with Shapiro Wilk normality test. Homogeneity of variances was tested using Levene test. Comparisons between the groups were carried out using independent samples t test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using Fisher's exact test. A p value of less than 0.05 was considered statistically significant.

Results

Demographics

This study included 21 patients (8 males, 13 females) with a mean age of 122.9 ± 51.3 months (range 44–214 months) who underwent cardiac MRI examination out of 25 patients with MIS-C (9 males, 16 females) with a mean age of 8.8 ± 4.4 years (range 1.8 – 17.8 years).

As compared with patients with a normal cardiac MRI examination, those with cardiac fibrosis on MRI had a significantly higher age (mean 14.4 ± 4.0 years vs 8.9 ± 3.5 years; $p=0.007$), a similar gender distribution (male/female: 3/2 vs 5/11; $p=0.325$), a significantly greater body weight (mean 61.0 ± 22.4 kg vs 29.7 ± 10.1 kg; $p<0.000$), a significantly greater body length (mean 162.6 ± 26.5 cm vs 128.4 ± 16.7 cm; $p=0.003$), a significantly greater body surface area (mean 1.67 ± 0.42 m² vs 1.07 ± 0.25 m²; $p=0.002$), and a significantly greater body mass index (BMI) (mean 22.68 ± 4.48 kg/m² vs 17.73 ± 3.15 kg/m²; $p=0.012$) (two patients with BMI>25 had fibrosis), (Table 1).

Table 1
Demographic data of patients with normal cardiac MRI and cardiac MRI fibrosis

	Kardiyak MRI Normal (n=16)	Kardiyak MRI Fibrosis (n=5)	P Values
*Age, years	8.4±3.5	14.4±4.0	0.007
Gender (male/female)	5 /11	3 /2	0.325
*Body weight, kg	29.7±10.1	61.0±22.4	<0.001
*Height, cm	128.4±16.7	162.6±26.5	0.003
*BSA, m ²	1.07±0.25	1.67±0.42	0.002
*BMI, kg/m ²	17.73±3.15	22.68±4.48	0.012
* = A p value of less than 0.05 was considered statistically significant.			

Clinical characteristics of patients with MIS-C

All patients had fever for at least three days prior to hospital admission. Additionally, restlessness, loss of appetite, redness of eyes, skin rash, vomiting, diarrhea, and abdominal pain were the most common presenting symptoms. On physical examination, the patients most commonly had impaired general condition, restlessness, conjunctivitis, hyperemia of lips, strawberry tongue, maculopapular skin rash, and abdominal tenderness upon palpation. The rates of symptoms and physical examination findings were similar between patients with and without cardiac fibrosis on MRI (Table 2).

Table 2

Presenting symptoms and physical examination findings at the time of diagnosis in patients with normal cardiac MRI and cardiac MRI fibrosis

	Cardiac MRI Normal (n=16)	Cardiac MRI Fibrosis (n=5)	P Values
SYMPTOMS (presence/ absence)			
Fever	16/0	5/0	-
Unrest	15/1	5/0	1
Anorexia	16/0	5/0	-
Myalgia	2/14	1/4	1
Redness in eyes	11/5	4/1	1
Sore throat	1/15	1/4	0.429
Nasal discharge	0/16	0/5	-
Cough	1/15	0/5	1
Strawberry tongue	9/7	1/4	0.311
Cervical Lymphadenopathy	2/14	2/3	0.228
Skin rash	12/4	2/3	0.280
Hand and foot edema	4/12	0/5	0.532
Vomiting	10/6	3/2	1
Diarrhea	6/10	4/1	0.149
Abdominal pain	10/6	4/1	0.624
PHYSICAL EXAMINATION (presence/ absence)			
Clinical Severity (mild/severe)	16/0	4/1	-
Unrest	16/0	5/0	-
Conjunctivitis	11/5	3/2	1
Lip hyperemia	12/4	3/2	0.598
Strawberry tongue	9/7	1/4	0.311

* = A p value of less than 0.05 was considered statistically significant.

	Cardiac MRI Normal (n=16)	Cardiac MRI Fibrosis (n=5)	P Values
Oropharyngeal hyperemia	4/12	1/4	1
Cervical Lymphadenopathy	2/14	2/3	0.228
Skin rash	12/4	2/3	0.280
Hand and foot edema	4/12	1/4	1
Heart rate (beats per minute)	122±17	115±15	0.455
Pathological Murmur	1/15	1/4	0.429
Respiration rate (per minute)	24±5	22±5	0.402
Respiratory system normal	16/0	5/0	-
Abdominal tenderness	9/7	4/1	0.606
Hepatomegaly	0/16	0/16	-
Splenomegaly	0/16	0/5	-
* = A p value of less than 0.05 was considered statistically significant.			

Evidence of SARS-CoV-2 Infection

All patients had a history of being in close contact with a SARS-CoV-2 positive person until 4-6 weeks prior to symptom onset. The patients were either asymptomatic or had very mild symptoms. None of our patients had a history of moderate to severe infection. All but one patient had a negative RT-PCR test in nasopharyngeal swab test for SARS-CoV-2 virus. SARS-CoV-2 IgG was positive in all patients.

Complete blood count, acute phase reactants and biochemical parameters

When compared with patients with normal cardiac MRI, those with cardiac fibrosis on MRI had a significantly lower leucocyte count [median 5250/μl (3880-7790) vs 12065/μl (4210-21210); p=0.011] and a significantly lower neutrophil count [median 4000/μl (2150-6560) vs 9875/μl (2540-18500); p=0.019]. There were 4 (80%) patients with a lymphocyte count of <1000/μl in the cardiac fibrosis group and 7 (43%) patients in the normal cardiac MRI group, and there was no significant difference between the two groups [median 680/μl (420-2480) vs 1185/μl (560-2330); p= 0.240]. Other full blood count parameters, CRP level, sedimentation rate, and procalcitonin level were similar. Patients with fibrosis on

cardiac MRI had a significantly higher blood urea nitrogen [median 15 mg/dL (11-26.8) vs 8.5 mg/dL (4-18); $p=0.025$], creatinine level (mean 0.61 ± 0.07 mg/dL vs 0.45 ± 0.14 mg/dL; $p=0.024$), and sodium level (mean 137.8 ± 2.5 mEq/L vs 133.2 ± 4.4 mEq/L; $p=0.015$) (Table 3).

Table 3

Hemogram, acute phase reactants, biochemical parameters, urine analysis results of patients with normal cardiac MRI and cardiac MRI fibrosis.

	Cardiac MRI Normal (n=16)	Cardiac MRI Fibrosis (n=5)	P Values
HEMOGRAM			
*Leukocyte, 10 ³ /μL	12065 (4210-21210)	5250 (3880-7790)	0.011
*Neutrophil, 10 ³ /μL	9875 (2540-18500)	4000 (2150-6560)	0.019
Monocyte, 10 ³ /μL	325 (130-680)	320 (110-410)	0.494
Lymphocyte,	1185 (560-2330)	680 (420-2480)	0.240
Hemoglobin, (gr/dl)	12.17±1.36	13.20±1.70	0.181
Htc (%)	36.0±3.4	39.1±2.8	0.091
Platelet, 10 ³ /μL	183500 (100000-320000)	163000 (112000-460000)	0.905
ACUTE PHASE REACTANTS			
CRP, mg/L	170±68	172±90	0.952
Sedimentation, mm/hour	34.5 (18-101)	43 (16-65)	0.893
Procalcitonin, μg/L	3.93 (0.96-13.03)	0.58 (0.55-12.67)	0.362
BIOCHEMICAL PARAMETERS			
Albumin, g/L	28.9±5.8	30.5±1.7	0.372
*BUN, mg/dl	8.5 (4-18)	15 (11-26.8)	0.025
*Creatinine, mg/dl	0.45±0.14	0.61±0.07	0.024
Uric acid, mg/dl	3.25 (1.70-6.60)	3.90 (3.38-5.50)	0.385
*Na, U/L	133.2±4.4	137.8±2.5	0.015
K, U/L	3.86±0.51	4.07±0.33	0.409
Ca, mg/dl	8.69±0.47	8.82±0.29	0.612
ALP, U/L	126.5 (52-209)	152 (71-162)	1

* = A p value of less than 0.05 was considered statistically significant.

	Cardiac MRI Normal (n=16)	Cardiac MRI Fibrosis (n=5)	P Values
GGT, U/L	16 (9-94)	29 (27-119)	0.164
AST, U/L	27.5 (15-111)	28 (10-101)	0.603
ALT, U/L	18.5 (10-154)	24 (5-85)	0.905
Total Bilirubin, mg/dl	0.3 (0.2-1.3)	0.6 (0.34-1.40)	0.152
Direct Bilirubin, mg/dl	0.2 (0.1-0.7)	0.25 (0.07-0.80)	0.596
Amylase, U/L	38.5 (13-84)	73 (17-75)	0.509
Lipase, U/L	31 (11-104)	30 (8-98)	0.900
Ferritin, µg/L	452 (141-731)	276 (58-2011)	0.676
URINE EXAMINATION			
TiT dansite	1019.8±11.7	1025.0±8.3	0.373
Piyüri	8/8	0/5	0.111
* = A p value of less than 0.05 was considered statistically significant.			

Cardiac Biomarker, Electrocardiography and Echocardiography

The number of patients with high troponin T level was 13 (61%); the number of patients with high NT-proBNP level was 13 (61%). The patients with cardiac fibrosis had similar troponin T and NT-proBNP levels when compared with patients with normal cardiac MRI.

Six (28%) patients had T flattening and 2 (9.5%) patients had voltage depression in electrocardiogram. None of the patients had tachyarrhythmias such as supraventricular tachycardia and ventricular tachycardia, nor they had bradyarrhythmias such as atrioventricular block and sinus node dysfunction.

There were five patients with a LVEF of less than 55% on echocardiographic examination. One patient had a LVEF of 43% at the time of diagnosis and significantly deteriorated during follow-up. Six patients had mild mitral insufficiency and five patients had moderate mitral insufficiency, making up a total of 11 (54%) patients with mitral insufficiency. Six (30%) patients had slight pericardial effusion at the time of diagnosis, which completely disappeared during follow-up. No patient had coronary artery dilation and/or aneurysm on echocardiogram.

Patients with and without fibrosis on cardiac MRI had similar rates of mitral insufficiency and pericardial effusion, coronary arteries, left ventricular end-diastolic z scores, left ventricular end-systolic z scores, LVEF, and fractional shortening (FS) on echocardiographic examination (Table 4).

Table 4
Biomarker, ECG and echocardiography results of patients with normal cardiac MRI and cardiac MRI fibrosis.

	Cardiac MRI Normal (n=16)	Cardiac MRI Fibrosis (n=5)	P Values
CARDIAC BIOMARKER			
Troponin, ng/L	16.09 (1.80-101)	29.1 (4.35-252.9)	0.240
NT proBNP, ng/L	5257 (57-35000)	1300 (158-6553)	0.320
ECHOCARDIOGRAPHY			
Mitral valve regurgitation	Minimal (4 cases) First degree (3 cases),	Minimal (2 cases), First degree (1 cases), Second degree (1 case)	0.174
Pericardial effusion	5/11	1/4	1
Coronary normal	16	5	-
LVIDd z score	0.42±1.07	0.46±1.15	0.939
LVIDs z score	0.84±1.18	0.91±1.29	0.908
EF (%)	60.8±7.5	59.8±6.3	0.790
FS (%)	31.8±5.7	32.0±4.0	0.965
* = A p value of less than 0.05 was considered statistically significant.			

Treatment and Outcome

According to the MIS-C clinical severity score, developed by Jonat et al. [14], which is based on the vasoactive inotrope score, the degree of respiratory support, and the evidence of organ injury, 20 patients was in the mild group, and a patient was in the severe group. All patients were administered intravenous (IV) immunoglobulin (IVIG) at a dose of 2 gr/kg (maximum 100 gr). Only three patients received a second IVIG dose because of unremitting fever 24 hours after the first IVIG dose. In addition to IVIG treatment, 11 patients were administered 2 mg/kg/day IV steroid and six patients 80-100 mg/kg/day po acetylsalicylic acid. Three patients were administered only IVIG treatment. A patient with serious clinical condition was

administered 2 gram/kg IV immunoglobulin (twice), IV pulse steroid, and anakinra 2 mg/kg/dose single dose via subcutaneous route. That patient also received inotropic support, intravenous furosemide, and mechanical ventilation due to shock secondary to heart failure and severe respiratory distress due to pulmonary congestion. There was no significant difference between 12 patients that received IVIG and steroid and six patients that received IVIG and acetylsalicylic with respect to cardiac fibrosis ($p=>0.999$).

All of 21 patients who underwent cardiac MRI had their cardiac systolic function completely normalized by a 1-year of follow-up. Their mitral valve insufficiency recovered in time, with only three patients having remained to have mild mitral valve insufficiency at the end of 1 year. The echocardiographic evaluation of coronary arteries was normal in all patients at follow-up. No patient had tachyarrhythmia or bradyarrhythmia during follow-up. None of the patients died at the hospital or during follow-up.

Cardiac MRI

Cardiac MRI examination was performed at a mean of 123.2 ± 62.7 days after the diagnosis in five patients with cardiac fibrosis and 117.7 ± 35.8 days after the diagnosis in 16 patients with normal cardiac MRI ($p=0.968$). The cardiac MRI findings of each of the five patients with cardiac fibrosis are described in detail below.

In patient number 1, midmyocardial contrast enhancement (focal fibrosis) was observed at the posterior right ventricle insertion point (PRVIP) at midventricular level. The regional mean native T1 relaxation time prolongation (1185 msec) at this level in T1 mapping and an increase in extracellular volume (ECV) (36%) supported fibrosis. Since global mean myocardial native T1 relaxation time (995 msec) and ECV (28%) were in normal limits, diffuse fibrosis was excluded. Regional wall motion and systolic function are normal in cine sequences.

In patient number 2, midmyocardial contrast enhancement (focal fibrosis) was observed in PRVIP at midventricular level in LGE. The regional mean native T1 relaxation time prolongation (1170 msec) at this level in T1 mapping and an increase in extracellular volume (ECV) (33%) supported focal fibrosis. Since global mean myocardial native T1 relaxation time (995 msec) and ECV (28%) were in normal limits, diffuse fibrosis was excluded. Cine sequences showed normal regional wall motion and systolic function.

In patient number 3, there was midmyocardial contrast enhancement (focal fibrosis) in midventricular anterior septum (AHA segment 8), transmural contrast enhancement in anterolateral wall (AHA segment 11), and midmyocardial contrast enhancement in posterolateral wall (AHA segment 12) on LGE. In T1 mapping, regional mean native T1 relaxation times were prolonged (1080 msec at AHA segment 8, 1083 msec at AHA segment 11, and 1075 msec at AHA segment 12), and ECVs increased approximately 30%. These findings supported LGE findings. Since global mean myocardial native T1 relaxation time (1040 msec) and ECV (28%) were in normal limits, diffuse fibrosis was excluded. Cine sequences showed normal regional wall motion and systolic function.

In patient number 4, midmyocardial contrast enhancement was detected in midventricular septum (AHA segments 8 and 9) and PRVIP, and subepicardial contrast enhancement in inferior wall (AHA segment 10)

(focal fibrosis) on LGE. T1 mapping showed prolonged regional mean native T1 relaxation times and increased ECVs (1090 msec and 29%, respectively, at AHA segment 8; 1100 msec and 30%, respectively, at AHA segment 9; 1150 msec and 32%, respectively, at PRVIP, and 1097 msec and 30% at AHA segment 10). These findings supported LGE findings. Since global mean myocardial native T1 relaxation time (1027 msec) and ECV (26%) were in normal limits, diffuse fibrosis was excluded. In cine sequences, normal regional wall motion and systolic function were observed.

In patient number 5, midventricular contrast enhancement was observed in inferior wall and inferior septum (AHA segments 9 and 10), and transmural contrast enhancement in PRVIP (focal fibrosis) on LGE. T1 mapping showed prolonged regional mean native T1 relaxation times and increased ECVs (1100 msec and 44%, respectively, at AHA segment 9; 1275 msec and 50%, respectively, at PRVIP; and 1093 msec and 44% at AHA segment 10). These findings supported LGE findings. Since global mean myocardial native T1 relaxation time (1027 msec) and ECV (26%) were in normal limits, diffuse fibrosis was excluded. In cine sequences, there was normal regional wall motion and systolic function (Figure).

Discussion

In this study, we found that cardiac fibrosis, a sign of cardiac involvement, was more common in adolescents and obese children after the recovery of MIS-C. We also demonstrated that symptoms and physical examination findings were not effective in the development of fibrosis. Since we lacked a sufficient number of patients, we cannot make any extrapolation as to the effect of clinical severity on fibrosis development. Leucocyte and neutrophil counts were lower, while blood urea nitrogen, creatinine, and sodium level were higher in patients who developed fibrosis. Cardiac fibrosis on MRI was located in the region of posterior right ventricle insertion point and midventricular septum.

A previous meta-analysis reported that 58% (55-61%) of children with MIS-C were male and their median age was 8.9 years [15]. In our patient population, on the other hand, female gender was predominant (61%) while their mean age was similar to the figures reported in the literature [8.8 ± 4.4 years (range 1.8 – 17.8 years)].

Hoste L. et al.[16], in a systematic review article, reported that obesity (having a BMI > 25 kg/m² or being >85th percentile for age/gender) was present in 25.3% of patients. Other comorbidities were quite uncommon, with asthma being present in 4.1% of patients, chronic pulmonary disease in 1.5%, cardiovascular diseases in 1.3%, and immune deficiencies in 1%. They reported that obesity as a comorbidity was present in four out of eight (1.9%) patients who died. In a review article, Panigrahy et al. [17] reported that obesity (16.4%) and asthma (13.4%) were the most common comorbidities. In our study population, 2 (9.5%) patients had a BMI > 25; these patients had cardiac fibrosis on cardiac MRI. None of our patients died.

In a systemic review, Radia et al.[2] reported that inflammatory markers increased in most cases, with CRP increase being detected in 94% of patients, neutrophilia in 83%, and lymphopenia in 50%. In a study

of 286 patients from 55 European centers, Valverde I. et al. [18] reported a median CRP level of 165 mg/L and a median procalcitonin level of 4.2 ng/mL. Hoste L. et al.[16], in a review article, reported that leucocyte count frequently increased [12,800/ μ l (9150–20,075)], and lymphopenia was common [831.5/ μ l (510–1157.5)]. In our study, leucocyte and neutrophil counts were significantly lower in patients with cardiac fibrosis on MRI compared with those with a normal cardiac MRI. The patients had general lymphopenia (<1000/ μ l), which was present in 11 (54%) patients. Lymphocyte counts were similar in the groups with and without fibrosis. In accordance with the literature, our patients had elevated sedimentation rate and procalcitonin level and substantially elevated CRP level.

In MIS-C, cardiac involvement, shock, and a complex inflammatory process affecting all systems is an exaggerated immune reaction involving overlapping mechanisms. This immune reaction and hemodynamic instability can cause tubular injury, podocytopathy, inflammatory process, and acute kidney injury secondary to vascular endothelial dysfunction.[19] Significantly higher BUN and creatinine levels in patients with cardiac fibrosis on MRI compared with those with a normal MRI suggest that the mechanisms causing renal injury may overlap with the mechanisms giving rise to cardiac fibrosis.

In many studies it has been reported that troponin and NT-proBNP levels were especially affected by cardiac function and increased, particularly in MIS-C patients with signs of shock.[20] In 61% of our patients, both troponin T and NT-proBNP were increased. There was no significant difference between patients with and without fibrosis regarding troponin T and NT-proBNP levels.

MIS-C can cause many ECG changes. Sinus tachycardia is usually observed due to cardiac involvement and shock. Large case series have demonstrated PR prolongation, low QRS voltage, ST-segment and T wave changes. Ventricular tachycardia, a malignant tachyarrhythmia form, rarely occurs due to myocarditis and electrolyte disorders.[3][21] In our case series, six patients had T wave flattening and 2 had low voltage as a pathological sign.

Reduced LVEF is defined as EF<55%. Many studies have reported a percentage of 13-69% for patients with reduced LVEF.³ [10][22][23] Similar to literature findings, we had 23% patients with LVEF< 55% on echocardiography.

Varying degrees of atrioventricular valve insufficiency have been reported in patients with MIS-C. Valverde I. et al. reported mild mitral insufficiency in 103 (38%) patients, moderate mitral insufficiency in 11 (4.2%) patients, and severe mitral insufficiency in 1 (0.3%) patient.[18] Similarly, we detected nine cases of mild mitral insufficiency, and one case of moderate mitral insufficiency, making a total of 47% of patients having mitral insufficiency.

Pericardial effusion has been reported as “mild” in about 20% of patients at the time of diagnosis. Pericardial effusion usually improves over time, without causing any clinical problem.[23] Minimal pericardial effusion that was present in 30% of our patients completely disappeared over time.

The reported rate of coronary artery involvement at the time of diagnosis is 14-28% in the literature. In a large-scale study, coronary dilation (Z score <2) in echocardiography was reported in 69 (24.1%) patients at the time of diagnosis.[18] However, it is well-known that coronary artery evaluation by echocardiography may be subjective. None of our patients had coronary artery dilation or aneurysm in echocardiography at the time of diagnosis.

Blondiaux E. et al. ¹⁹ performed cardiac MRI and showed diffuse myocardial edema in 4 patients, three of whom were in the acute phase and one in the recovery phase, when the first MIS-C cases started to be reported in April 2020. There was no evidence of replacement fibrosis or late gadolinium enhancement indicating focal necrosis. These findings were interpreted as suggestive of post-infectious myocarditis among children and adolescents with COVID-19.[24] Theocharis P. et al. [25] performed cardiac MRI in 20 MIS-C patients whom they diagnosed in May 2020 after a median of 20 days. Cardiac MRI showed abnormal strain in 7 patients with global dysfunction (EF<55%), myocardial edema in 10 (50%) patients, and subendocardial infarction in 1 (5%) patient. Capone CA. et al.[26] performed MRI in 11 patients with left ventricular systolic dysfunction, troponin elevation and/or ECG changes 1-4 weeks after hospital discharge. None of the patients showed persistent edema or an evidence of fibrosis. No coronary artery dilation or aneurysm was shown.

Aeschlimann FA. et al.[27] published an article including 111 children with MIS-C (38% girls, median age ten years) from 17 centers, who had clinical cardiac involvement and undergone cardiac MRI. Sixty-five percent of patients had a depressed LVEF at the time of diagnosis. Cardiac MRI was performed a median of 28 (19-47) days after the symptom onset. Cardiac MRI diagnostic criteria for acute myocarditis were present in 20 patients; 18 of them also had evidence of myocardial necrosis indicated by subepicardial LGE. A comparison of patients with and without myocarditis on cardiac MRI regarding clinical signs, laboratory data, and the applied treatment modalities revealed that the myocarditis positive group had a significantly greater rate of NYHA class IV disease, a significantly greater need for mechanical support, and a significantly higher lymphocyte count. In that study, LGE was identified in multiple different LV sites, most commonly in basal and mid inferolateral regions. In our research, on the other hand, late-term cardiac fibrosis on MRI was located in the region of posterior right ventricular insertion point and midventricular septum.

It has been reported that LGE is correlated to a worse composite end-point of all-cause mortality, cardiac mortality, and/or major adverse cardiovascular events in adults with acute myocarditis.[28] It would be appropriate to follow MIS-C patients for such adverse outcomes in the long term.

Limitations

The limitation of the study is its small sample size, which hampered any comparison regarding disease severity.

Conclusions

Clinically, MIS-C patients usually recover completely, irrespective of having cardiac fibrosis on MRI. Adolescence and obesity appear to be risk factors for cardiac fibrosis of MRI as a late sequela of myocarditis. We believe that the way the immune system reacts and other mechanisms causing acute kidney injury may be effective in the occurrence of cardiac fibrosis through complex overlapping mechanisms. Cardiac fibrosis on MRI was located in the region of posterior right ventricle insertion point and midventricular septum. However, this subject should be further clarified by more comprehensive studies. Future studies reporting the follow-up data of patients with fibrosis are necessary to predict and manage adverse outcomes.

List Of Abbreviations

AHA: American Heart Association

BMI: Body mass index

CDC: Center for Disease Control

COVID-19: Coronavirus disease 2019

CRP: C-reactive protein

ECG: Electrocardiography

ECV: Extracellular volume

EF: Ejection fraction

ELISA: Enzyme-Linked Immunosorbent Assay

FS: Fractional shortening

IV: Intravenous

IVIG: Intravenous immunoglobulin

LGE: Late gadolinium-enhanced

LVEF: Left ventricular ejection fraction

MIS-C: Multisystem Inflammatory Syndrome in Children

MOCO: Motion correction

MOLLI: Modified look-locker inversion recovery

MRI: Magnetic resonance imaging

NT-proBNP: N-terminal pro–B-type natriuretic peptide

PRVIP: posterior right ventricle insertion point

RT-PCR: reverse transcription-polymerase chain reaction

SARS-CoV-2 virus: severe acute respiratory syndrome coronavirus

SSFP: Steady-state free precession

WHO: World Health Organization

Declarations

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Authors' contributions: MA designed the study, collected the data, interpreted it, and wrote the article. TS interpreted cardiac MRI and contributed to the discussion. SYD contributed to the follow-up of patients and the collection of data. IH, OT, SS, SÖ contributed to data interpretation. FE analyzed the data All authors critically revised the manuscript and read and approved the final manuscript for submission.

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Figures

Figure 1

Midventricular short axis cardiac MRI images in five children after mean of 123.2 ± 62.7 days of clinical diagnosis of MIS-C. First row shows no significant finding on cine images. Second row shows late gadolinium enhancement (LGE) confined to PRVIP (posterior right ventricular insertion points) in patients 1, 2, 4, 5 (black arrows) and anteroseptal wall adjacent to the septal papillary muscle attachment in patients 3, 4 (white arrows). Third row demonstrates abnormal native T1 mapping which was greater than 1060 msec, on same localisations as LGE (second row) in all patients.