Children with acute myocarditis often have persistent subclinical changes as revealed by cardiac magnetic resonance

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Running title: MRI in the follow-up of myocarditis is children

ABSTRACT

Background. Many children presenting with myocarditis may not fully recover and have long-term complications, including dilated cardiomyopathy. Magnetic resonance imaging (MRI) has a potential for early detection of persistent changes with long-term implications, but is not performed routinely in the monitoring of myocarditis.

Purpose. To monitor adolescents who present with acute myocarditis using MRI and routine diagnostic tests over the short to mid-term.

Study type. Prospective.

Population. 18 consecutive adolescents (median age 15.5, interquartile range 14.8–16.9 years, 78% male) with acute myocarditis.

Field strength.3T scanner including cine steady-state free precession (SSFP), dark-blood T2W images and late gadolinium enhancement (LGE).

Assessment. The diagnosis of acute myocarditis was based on clinical symptoms and signs, and MRI criteria (cine, T2-weighted images, late gadolinium enhancement). Follow-up MRI was performed after median 7 months (range 6–9 months). Other routine diagnostic tests included ECG, high-sensitivity troponin levels, transthoracic echocardiography and Holter monitoring.

Statistical tests. Fisher's exact test, Wilcoxon test for paired samples, Mann-Whitney test for independent samples, Kruskal-Wallis test.

Results. At baseline 17 patients (94%) had elevated troponin levels and/or ST-T changes on resting electrocardiogram, echocardiogram showed depressed left ventricular ejection fraction (LVEF<50%) in 4 patients (22%). At follow-up there was a complete recovery in 16 patients (89%) observed with routinely performed tests, with 2 cases of persistent ventricular arrhythmia. Despite normal left ventricular volume and LVEF, MRI disclosed ongoing active inflammation in 5 patients (28%), healed myocarditis with persistent scars in 8 patients (44%) and complete resolution of initially observed changes in 5 patients (28%).

Data conclusion. In children with acute myocarditis, despite normalization of other routinely assessed parameters (including LVEF), there is a high prevalence of persistent MRI changes showing ongoing disease or remnant scars at follow-up. MRI may allow early detection and prevention of long-term complications of myocarditis in the follow-up care of children with acute myocarditis.

Keywords: myocarditis, children, follow-up study, magnetic resonance

INTRODUCTION

Acute myocarditis is rare in the pediatric population, accounting for 0.05% of pediatric discharges from the hospital (1–3), with a bimodal distribution in infants/toddlers and adolescents (3,4). It is most often an acute, viral infection of the heart following upper respiratory tract infection, manifesting with fever, chest pain, elevated cardiac necrosis markers and, sometimes, ventricular arrhythmias (1,2). Occasionally, myocarditis may cause acute heart failure leading to heart transplantation or death, with an overall rate of 7–15%, more often observed in infants in the pediatric group with acute myocarditis (1–4). On the other hand, in adolescents, symptoms typically resolve after a few days to a few weeks of watchful waiting without noticeable complications. Usually patients may return to normal physical activity after 3-6 months if resolution of symptoms, normalization of cardiac marker levels, normal echocardiography and exercise test are confirmed, and there are no significant arrhythmias on ambulatory Holter monitoring (5,6). During this time, the initial pathogen is usually cleared, the immune reaction settled, but the autoimmune process may continue in a very subtle form that is not obvious in routine testing, leading to ongoing, undetected myocyte damage (1). In fact, up to 30% of patients with biopsy-proven myocarditis may progress to dilated cardiomyopathy (DCM), which is associated with poor prognosis (7).

MRI has an important role in the evaluation of suspected myocarditis in the European Society of Cardiology (ESC) and American Heart Association (AHA) statements, with a Class I indication for assessment of myocarditis in the ESC guidelines on acute and chronic heart failure (7–9). Compared to routine tests, the strength of MRI is myocardial tissue characterization, allowing non-invasive visualization of the pathophysiologic processes seen in myocarditis with high spatial resolution (10,11). These include myocardial edema on T2-weighted imaging (T2W), hyperaemia and capillary leak on early gadolinium enhancement (EGE), and cardiomyocyte necrosis, typically in a non-ischemic pattern on late gadolinium enhancement (LGE) imaging (10,11). These features comprise the Lake Louise MRI diagnostic criteria for myocardial inflammation (12,13). MRI is a well-established, non-invasive method to diagnose acute myocarditis, with accuracy similar to endo-myocardial biopsy (14).

In adolescents presenting with myocarditis, little is known about the course of resolution, even in patients with typical, mostly benign clinical manifestations (11,15–18). In particular, the prevalence of subclinical and incomplete resolution of the myocarditic process missed using routine tests is not well-characterized in this group of children. We therefore

sought to closely examine the cardiac phenotype in adolescents presenting with acute myocarditis using both routine clinical assessment and diagnostic tests, together with advanced MRI myocardial tissue characterization, at baseline and at short- to mid-term follow-up.

MATERIALS AND METHODS

Study Group

We prospectively included 18 consecutive adolescents (median age 15.5 years, interquartile range – IQR 14.8–16.9 years, 78% male) who reported to the Emergency Department or were referred to our tertiary pediatric cardiology centre from other centres between April 2017 and October 2018 and fulfilled clinical and MRI diagnostic criteria for acute myocarditis. Baseline demographic parameters, symptoms, ECG changes, routine transthoracic echocardiography (TTE), continuous ECG monitoring for arrhythmias during hospitalization and high-sensitivity troponin I (hs-TnI) levels closest to the time of MR scan were recorded. Baseline MRI was performed within the 1st week of hospitalization. All patients underwent a second MRI scan (after a median of 7 months, IQR 6–9 months). Patients showing persistent signs of acute myocarditis at the first follow-up received continued pharmacological treatment prescribed at discharge from hospital, and underwent a third MRI scan at a median 8 months from the second MRI scan (IQR 7–8 months) and after a median of 15 months (IQR 12–19 months) from the first MRI scan. The study was performed in accordance with local ethical standards and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Patients from 16 years of age and above and parents of all children participating in the study signed a written informed consent for the research including a consent for the MRI studies and contrast administration.

Cardiac Magnetic Resonance

Imaging was performed with a Siemens Magnetom Skyra 3 Tesla scanner (Siemens, Erlangen, Germany). The protocol included cine steady-state free precession (SSFP) breath-hold sequences in 2-, 3-, 4-chamber long-axis views, and short-axis views covering the ventricles from the mitral and tricuspid annular plane to the apex. This was followed by acquisition of dark-blood T2W images with fat suppression in 2-, 3- and 4-chamber views and

3 short-axis slices (basal, mid-ventricular and apical) for evaluation of myocardial edema. Finally, 0.1 mmol/kg of a gadolinium-based contrast agent (gadobutrol – Gadovist ®, Bayer AG, Leverkusen, Germany), flushed with 30 ml of isotonic saline was administered intravenously. LGE images in 3 long-axis planes and a short-axis stack were obtained with a breath-hold phase-sensitive inversion recovery sequence (PSIR) 10–15 minutes after contrast injection. The inversion time was set with means of the initial TI scout to completely null normal myocardium (typically between 250 and 350 ms).

All MRI studies were of good quality without significant artefacts influencing their assessment. Images were analysed using validated software - MRHeart plugin for Horos [19]. On cine images, epi- and endocardial contours in end-diastole and endocardial contours in end-systole were manually traced on the short-axis views. Delineated contours were used for the quantification of left ventricular (LV) volumes, ejection fraction (LVEF) and mass. Myocardial edema was assessed by comparison of signal intensity of the myocardium regionally and with skeletal muscle on T2-weighted images (12,13). The presence of LGE was assessed visually. Additionally, the presence of pericardial effusion was analysed. All assessments were performed by three readers and or consecutive readouts were blinded to the previous MRI studies (ŁAM – 12 years of experience, Level 3 European Society of Cardiology expert, MBF – 4 years of experience, HK – 4 years of experience).

Acute myocarditis was diagnosed according to the updated Lake Louise criteria using a T2-based criterion with a T1-based criterion (13). In this study, all 18 patients had both: 1) signs of myocardial edema [global or regional increase of myocardial T2 signal intensity (T2 SI) in T2-weighted images; global increase of myocardial T2 SI was defined as a signal intensity ratio of the LV myocardium to skeletal muscle T2 SI ratio ≥2.0], and; 2) a predominantly non-ischemic LGE pattern (mid-wall or sub-epicardial, typically co-localized with LV segments with signs of myocardial edema) (12,13). At all MRI follow-up time-points (2^{nd} MR, 3^{rd} MR), patients were divided into three subgroups based on MRI imaging characteristics on the 2^{nd} MRI: (1) those fulfilling criteria for acute myocarditis (signs of edema on T2W images, typical LGE pattern); (2) those without signs of active myocardial inflammation on T2W images, but with persistent post-myocarditic scars on LGE; (3) those with complete resolution of MRI changes (lack of signs of edema on T2W images and no LGE).

Statistical Analysis

Categorical variables were presented as numbers and percentages; continuous variables were presented as median and interquartile range (IQR). Fisher's exact test was used to compare categorical variables. Wilcoxon test for paired samples or Mann-Whitney test for independent samples were applied to compare continuous variables between two groups. Kruskal-Wallis test was applied to compare one continuous variable between three categorical groups. All tests were two-sided with the significance level set at $p<0.05$. Statistical analyses were performed with MedCalc statistical software 10.0.2.0 (MedCalc, Mariakerke, Belgium).

RESULTS

Initial Evaluation

Baseline characteristics and clinical parameters of the studied group are presented in Tables 1 and 2. The most common signs and symptoms on report to the hospital were chest pain (89%), recent upper respiratory tract infection (39%) and/or fever (33%). ECG on admission demonstrated ST changes in 17 out of 18 patients (94%) consisting of ST segment elevation (10 patients, 56%) and/or T wave inversion (9 patients, 50%) in the infero-lateral leads. There were 2 cases (11%) of ventricular arrhythmias - one of infrequent single premature ventricular complexes (PVCs) and one of 50% of PVCs in 24h monitoring with polymorphic non-sustained ventricular tachycardia runs of 110-200 beats per min. High-sensitivity TnI was markedly elevated in 17 cases (94%), except of the youngest patient with polymorphic ventricular arrhythmia, but without documented troponin increase. TTE showed depressed LVEF (<50%) in 4 patients (22%). Three of those patients had also LVEF <50% in MRI, with one discrepant case of LVEF 58% in MR and 45% in TTE.

MR was performed within one week of admission and all patients had their diagnosis of acute mycarditis confirmed by the exam showing typical features of the disease – all patients had regions of myocardial edema and mid-wall or sub-epicardial LGE. Pericardial effusion accompanying acute myocarditis was found in 4 patients (22%) (Table 2).

All patients were hospitalized (median 17 days; IQR 15–18) with mandatory bed rest and under continuous monitoring. Most of them received medical treatment with angiotensin converting enzyme inhibitors (ACE-I), and those with depressed LV systolic function and arrhythmias also received beta-blockers and/or amiodarone (Table 1). This led to rapid and uneventful recovery and discharge from hospital in all cases.

Follow-up

At the time of the 2nd MRI scan, all patients were free from symptoms, with complete resolution of ECG changes, normalization of hs-TnI levels and LV systolic function (if impaired at baseline). Two patients had persistent asymptomatic benign ventricular arrhythmia (single PVCs with a frequency of 1%/24 hours and without non-sustained ventricular tachycardia). These two patients belonged to the subgroup of healed myocarditis with persistent myocardial scars as reported below (1 segment in one patient and 3 segments in the second patient).

The 2nd MR revealed evidence of persistent inflammation in 5 patients (28%), healed myocarditis with persistent myocardial scars in 8 patients (44%) and complete normalization of initially observed changes in remaining 5 patients (28%) (Figure 1). There was no difference between the 3 subgroups in time of hospitalization (median 16 days, 18 days and 15 days, p=0.61), and from the initial presentation to the 2nd MRI (median 7 months, 6.5 months and 8 months, respectively, p=0.59).

Between the initial and 2nd MRI, the number of segments with visible LGE decreased in 13 patients (72%), remained unchanged in 2 patients (11%, both with healed myocarditis) and increased in 3 patients (16%) – 2 with ongoing disease and in 1 with healed myocarditis.

Patients with signs of persistent inflammation on 2nd MRI had higher T2 SI ratio on the initial MR in comparison to the rest of the studied group (median 3.1 vs. median 2.4, p=0.03) (Table 3). There was also a trend towards a higher median number of segments with LGE on the initial MRI compared to the two other subgroups considered together (median 5 segments vs. median 3 segments, p=0.06). They also had, although only numerically, higher end-diastolic LV volume and mass suggesting more severe global myocardial injury/inflammation.

At 3rd MRI scan persistent active myocarditis was still present in 1 patient, who was also diagnosed with colitis ulcerosa and sclerosing cholangitis, suggesting an auto-immunologic or drug-related cause of the ongoing myocarditis (Figure 2). 3 patients had healed myocarditis with remnant scars and 1 patient had complete resolution of MRI changes (Table 4).

Relation Between MR And Other Tests

The presence of infero-lateral ST segment elevation on baseline ECG did not discriminate those with ongoing inflammation at 2nd MRI from the rest of the studied group (80% vs. 46%, p=0.31). Interestingly however, patients with ST segment elevation at

presentation had higher T2 SI (p=0.006) and larger extent of LGE (p=0.001) on the initial MRI.

There was no difference in hs-TnI levels at baseline between the three subgroups of patients distinguished by findings at the 2nd MRI (median TnI 2800 ng/L in the ongoing myocarditis group, 4877 ng/L in the healed with myocardial scars group and 3884 ng/L in the complete resolution group, p=0.99).

Out of the four patients who had decreased LVEF on TTE on initial presentation, one (with the lowest value) belonged to the ongoing active myocarditis until the 3rd MRI scan, 2 belonged to group with healed myocarditis scars and 1 to the group with completely healed myocarditis group already at 2nd MRI.

DISCUSSION

We report that, in children with acute myocarditis, MRI can detect persistent signs of active disease in a significant number of patients in the short- to medium-term follow-up, despite resolution of clinical symptoms and normal findings in other routinely performed diagnostic tests. Patients with ongoing myocarditis after a median of 7 months from the initial assessment seemed to have more pronounced myocardial edema (higher T2 SI ratio) and myocyte injury (higher number of segments with LGE) on the initial MRI. On the other hand monitoring of LVEF with TTE or even MRI without detailed tissue characterisation could not discriminate between those with healed myocarditis and ongoing inflammation at follow-up. This is an important finding, as ongoing, unresolved myocardial inflammation can lead to dilated cardiomyopathy, heart failure and significant ventricular arrhythmias (1–4,7), but MRI is not part of normal clinical routine in the follow-up of patients with myocarditis. MRI evidence of persistent active myocarditis may prompt more active treatment to either treat the underlying disease, delay in resuming vigorous physical activities, or to initiate/continue potentially cardio-protective treatment with close follow-up. In one of the studied patients, it led to discovery that mesalamine – a medication used to treat colitis ulcerosa - might have been responsible for the persistent myocarditis, as described in another case report (20), although active inflammatory bowel disease could also be contributory (21).

Our study also showed that more than half of patients have permanent myocardial scarring, which may serve as substrates for persistent ventricular arrhythmias, as observed in 2 of the studied patients, whether benign or more malignant forms. Other patients with persistent scars, particularly if they are extensive, may be at risk of ventricular arrhythmias or

sudden cardiac death in the future, as demonstrated in other studies (22–25), and it is unclear at the present whether they may benefit from ongoing cardio-protective treatment as seen in the post-myocardial infarction population.

These insights were made possible by follow-up MRI studies post myocarditis. In the other study including follow-up of children with acute myocarditis, repeated MRI was done in less than half of the patients, it was performed only once (after median 6 months with large interquartile range) and did not necessarily include T2W imaging (11). Despite larger sample size and signs of ongoing inflammation in fraction of patients on follow-up, the study could not elucidate the true prevalence of persistent MRI changes especially in the longer follow-up period. In a study by Berg et al. of 24 patients (mainly adults) with acute myocarditis, MRI performed 3 months after found that LGE resolved in only 17% of patients, decreased in 50%, increased in 21% and did not change in 12.5% (15). Unlike in our study, the authors did not assess edema at follow-up and therefore could not discriminate between ongoing or healed myocarditis. In our study, complete resolution of changes was observed more frequently, but the majority had either a persistent scar or ongoing inflammation. Whether it was higher prescription of ACE-I at discharge or longer time to 2nd MRI in our study that contributed the numerically higher frequency of complete resolution at follow-up remains unknown.

After 3-6 months of uneventful recovery, patients typically would be allowed to return to physical activity, usually without further monitoring (5–6). However, exercising through active/ongoing myocarditis is detrimental and can potentially lead to DCM, heart failure or sudden cardiac death (26-27). MRI may have a role in guiding the optimal timing of reinstating physical activities or participation in vigorous sports in the pediatric population, although this aspect remains ill-defined. Larger studies with long-term, serial prospective follow-up would have to compare the impact of MRI-guided clinical decision-making on outcomes and prognosis.

The study by Berg et al. and others did not find any predictive value of the extent of high-sensitivity troponin rise at baseline, as confirmed in our study (15,28). In contrast, other studies demonstrate that the presence and extent of LGE at baseline MRI is the strongest independent predictor of future outcomes (22–24). Our study was too small to reliably predict hard clinical end-points, but it would be interesting to see the relation between LGE at baseline and LGE on follow-up in terms of clinical outcomes. For instance, is it the extent of the initial LGE or the persistent LGE, which influences prognosis? Are signs of ongoing inflammation on MRI at medium-term follow-up a poor prognostic sign of difficult-to-treat

disease? Larger, prospective longitudinal studies with MRI monitoring after acute myocarditis are needed.

Limitations

Our study has some limitations. First of all, this study followed the clinical schedules of the patients. We were not able to fully standardize the time between baseline and follow-up MRI scans, but our findings nevertheless revealed persistent signs of ongoing myocarditis on MRI in the short- to medium-term (median 7 months after the acute presentation). This study was performed at a time when the newest parametric T1/T2 mapping techniques were unavailable in our centre, which may have been able to detect more subtle myocardial injury or ongoing myocardial inflammation compared to traditional MRI T2W and LGE techniques (29). Theoretically, persistently high T2 SI ratio observed in some patients might have been influenced by lower T2 SI of the skeletal muscles on repeated MRI scans, which however was not observed in our cohort (data not shown). We did not perform myocardial biopsies in our patients as it is an invasive method related to low-yield in most cases and does not usually change clinical management. Clinical presentation was considered as the second best method to suggest diagnosis of myocarditis. However, these limitations do not diminish the importance of our findings, which is that a significant proportion of pediatric patients with acute myocarditis show signs of subclinical ongoing inflammation that could only be detected on MRI.

Ensuring good image quality is essential to provide an accurate diagnosis of myocardial inflammation using MRI, including expertise in distinguishing artefacts from real findings, which requires specialized centres with experienced MRI radiographers and readers; however, MRI is now increasingly available, and there are many training programs to promote the wider availability of this advanced imaging modality. This study has a relatively small number of patients, but all patients with signs of ongoing inflammation had at least 1 follow-up MRI scan, which provided a valuable dataset in the longitudinal follow-up of children with acute myocarditis; larger studies may more accurately estimate the prevalence of persistent changes post-myocarditis in children, and clinical trials using MRI-guided clinical decision-making in pediatric populations are needed to evaluate the role of MRI in optimizing care of children with myocarditis.

In conclusion, children with acute myocarditis, despite normalization of other routinely assessed parameters (including LVEF), have a high prevalence of persistent

myocardial inflammation or remnant scars detectable using MRI at short- to medium-term follow-up. MRI may allow early detection and guide treatment to prevent long-term complications of myocarditis, such as the development of heart failure and DCM, in the follow-up of children with acute myocarditis.

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Table 1. Baseline characteristics of the studied population

Baseline characteristics	Studied group n=18
Age, yrs (IQR)	15.5 (14.8–16.9)
Male sex, n (%)	14 (78)
Height, m (IQR)	1.71 (1.66–1.75)
Weight, kg (IQR)	70 (55–82)
BMI, kg/m^2 (IQR)	23.4 (20.7–26.3)
Time of hospitalization, days (IQR)	17 (15–18)
Medications during hospitalization and on discharge ACE-I, n (%) Beta blocker, n (%) Amiodarone, n (%)	 16 (89) 6 (33) 1 (5.5)
Time from hospital presentation to baseline MRI, days (IQR)	4 (2–6)
Time from baseline MRI until 2nd MRI, months (IQR)	7 (6–9)
Time from baseline MRI until 3rd MRI in those with persistent acute myocarditis on 2nd MRI, months (IQR)	15 (12–19)

ACE-I – angiotensin converting enzyme inhibitors, BMI – body mass index, BSA –body surface area, MRI – magnetic resonance imaging, IQR – interquartile range

Table 2. Clinical and MRI parameters at baseline and 2nd MRI (median 7 months)

	Baseline n=18	**First follow-up n=18**	p
Clinical parameters			
Signs and symptoms, n(%)			
Fever	6 (33)	0 (0)	<0.02
Recent viral infection	7 (39)	0 (0)	<0.01
Chest pain	16 (89)	0 (0)	<0.0001
General malaise	2 (11)	0 (0)	0.49
Arrhythmia	2 (11)	0 (0)	0.49
Heart failure	1 (5.5)	0 (0)	1.00
ECG changes, n (%)			
All	17 (94)	0 (0)	<0.0001
Infero-lateral ST elevation	10 (56)	0 (0)	
Infero-lateral TWI	9 (50)	0 (0)	
Ventricular arrhythmia	2 (11)	2 (11)	1.0
hs-TnI – ng/L, (IQR)*	3884 (2006–11987)	0 (0)	<0.0001
Elevated TnI, n (%)	17 (94)	0 (0)	<0.0001
LVEF on TTE <50%, n (%)	4 (22)	0 (0)	0.10
MRI parameters			
LVEDVI, ml/m² (IQR)	80.5 (72–88)	82.5 (73–89)	0.58
LVESVI, ml/m² (IQR)	30 (26–34)	29.5 (25–33)	0.73
LVEF, % (IQR)	64 (58–66)	63 (60–66)	0.50
LVEF <50%, n (%)	3 (17)	0 (0)	0.23
LVMI, g/m² (IQR)	60 (51–73)	56.5 (51.5–66)	0.04
Pericardial effusion , n (%)	4 (22)	0 (0)	0.10
Signs of edema (T2W), n (%)	18 (100)	5 (28)	<0.0001
Number of segments with edema (IQR)	3 (3–4.5)	0 (0–1)	<0.0001
T2 SI ratio (IQR)	2.5 (2.1–2.8)	1.5 (1.3–2.1)	<0.0001
Presence of LGE, n (%)	18 (100)	13 (72)	0.05
Number of segments with LGE (IQR)	3.5 (3–5)	2 (0–4)	<0.002

Pattern of LGE , n (%)			0.80
Sub-epicardial	17 (94)	11 (61)	0.04
Mid-wall	12 (67)	9 (50)	0.50
Location of LGE, n (%)			
Inferolateral	18 (100)	13 (72)	0.05
Septal	0 (0)	0 (0)	
Anterior	0 (0)	0 (0)	

*normal range of high-sensitivity troponin I assay <19 ng/L

ECG – electrocardiogram, LGE – late gadolinium enhancement, LVEDVI – left ventricular end-diastolic volume index, LVEF – left ventricular ejection fraction, LVESVI – left-ventricular end-systolic volume index, LVMI – left ventricular mass index, T2 SI ratio – ratio of signal intensity between myocardium and skeletal muscle on T2W images, hs-TnI – high-sensitivity troponin I, TTE – transthoracic echocardiography, TWI – T wave inversion

Table 3. MRI parameters between baseline and 2nd MRI (median 7 months) in the three subgroups of patients with myocarditis

	Ongoing myocarditis at follow-up (edema+, LGE+) (n=5)		Healed myocarditis with scars at follow-up (edema-, LGE+) (n=8)		Normalized MRI at follow-up (edema-, LGE-) (n=5)	
	Baseline	2nd MRI	Baseline	2nd MRI	Baseline	2nd MRI
LVEDVI, ml/m^2 (IQR)	87 (69–91)	83 (74–87)	82 (77–87)	82 (74–90)	77 (67–86)	73 (70–88)
LVESVI, ml/m^2 (IQR)	29 (26–38)	29 (23–31)	32 (26–45)	31 (29–35)	30 (24–32)	24 (24–35)
LVEF, % (IQR)	65 (54–66)	67 (64–69)	62 (52–66)	61 (60–63)	64 (60–68)	65 (63–66)
LVMI, g/m^2 (IQR)	73 (60–79)	66 (51–70)	63 (59–76)	63 (53–69)	52 (49–55)	56 (49–58)
Segments with edema, n (IQR)	3 (2.5–5)	2 (1–2.5)	3 (3–4)	0 (0)	3 (2.5–5.0)	0 (0)
T2 SI ratio (IQR)	3.1 (2.6–3.3)*	2.2 (2.1–2.4)	2.5 (2.1–2.7)	1.45 (1.3–1.6)	2.3 (2.2–2.6)	1.3 (1.2–1.6)
Segments with LGE, n (IQR)	5 (4–6.5)**	4 (3–5)	3 (2.5–4.5)	2.5 (1.5–4.0)	3 (2.5–4.0)	0 (0)
Pattern of LGE, n (%)						
Sub-epicardial	4 (80)	4 (80)	8 (100)	7 (87.5)	5 (100)	0 (0)
Mid-wall	4 (80)	4 (80)	5 (62.5)	5 (62.5)	3 (60)	0 (0)

Abbreviations same as for Table 2.

Both *p=0.03 and **p=0.06 are for group 1 vs. group 2&3 taken together

Table 4. MRI parameters of patients with signs of persistent inflammation on MRI at 2nd MRI

	LVEF (%)			LVEDVI (ml/m^2)			T2 SI ratio			LGE (# segments)		
Patient	Baseline	2nd MRI	3rd MRI	Baseline	2nd MRI	3rd MRI	Baseline	2nd MRI	3rd MRI	Baseline	2nd MRI	3rd MRI
1	65	69	67	59	50	52	3.2	2.1	1.4	4	2	1
2	40	65	55	99	83	81	3.6	2.5	2.2	6	3	1
3	59	61	62	72	86	85	3.5	2.4	1.5	5	6	1
4	65	70	68	87	82	72	2.8	2.1	1.4	8	5	2
5	69	67	66	88	90	84	2.1	2.2	1.3	3	4	0

Abbreviations same as for Table 2.

Figure legends

Figure 1. Examples of changes observed between initial and 2nd MRI in the studied group of children (areas with edema and LGE are marked with arrows).

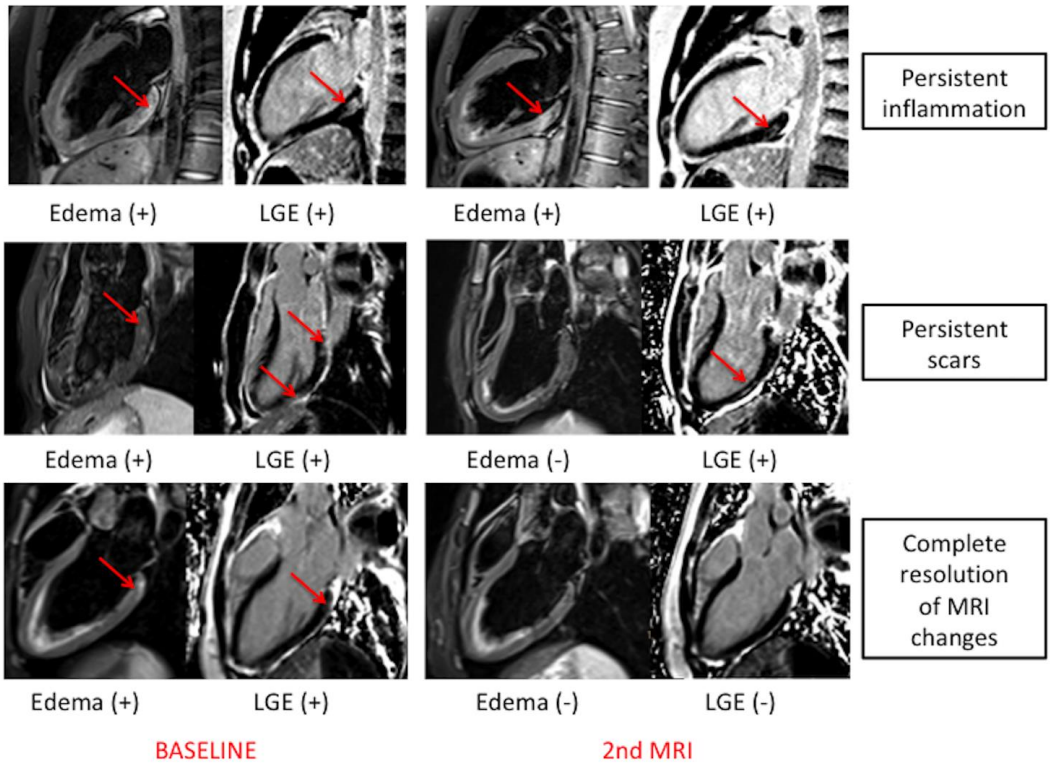

Figure 2. Flow chart showing disease status during follow-up. Only patients with the presence of ongoing myocarditis on the 2nd MRI underwent 3rd MRI. IQR – interquartile range