



The importance of heart and brain imaging in children and adolescents with Multisystem Inflammatory Syndrome in Children (MIS-C)

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Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) recently reported in a minority of children affected by SARS-CoV-2, mimics Kawasaki disease (KD), a medium vessel vasculitis of unknown cause. In contrast to acute COVID-19 infection, which is usually mild in children, 68% of patients with MIS-C will need intensive care unit. Myocarditis and coronary artery ectasia/aneurysm are included between the main cardiovascular complications in MIS-C. Therefore, close clinical assessment is needed both at diagnosis and during follow-up. Echocardiography is the cornerstone modality for myocardial function and coronary artery evaluation in the acute phase. Cardiovascular magnetic resonance (CMR) detects diffuse myocardial inflammation including oedema/fibrosis, myocardial perfusion and coronary arteries anatomy during the convalescence and in adolescents, where echocardiography may provide inadequate images. Brain involvement in MIS-C is less frequent compared to cardiovascular disease. However, it is not unusual and should be monitored by clinical evaluation and brain magnetic resonance (MRI), as we still do not know its effect in brain development. Brain MRI in MIS-C shows T2-hyperintense lesions associated with restricted diffusion and bilateral thalamic lesions. To conclude, MIS-C is a multisystem disease affecting many vital organs, such as heart and brain. Clinical awareness, application of innovative, high technology imaging modalities and advanced treatment protocols including supportive and anti-inflammatory medication will help physicians to prevent the dreadful complications of MIS-C.

Keywords MIS-C, multisystem inflammatory syndrome in children · Echocardiography · Cardiovascular magnetic resonance · Brain magnetic resonance

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Introduction

Multisystem Inflammatory Syndrome (MIS-C) has been recently reported in a minority of children affected by SARS-CoV-2 [1, 2]. MIS-C mimics Kawasaki disease (KD), a medium vessel vasculitis of unknown cause that affects mainly children < 5 years [3–5]. Several terminologies have been used to describe this disease including Kawasaki-like syndrome (KLS), atypical Kawasaki disease, incomplete Kawasaki disease, SARS-CoV-2-induced Kawasaki-like Hyper-inflammatory Syndrome (SCiKH Syndrome) and Kawa-COVID-19 [1, 2]. The Centers for Disease Control and Prevention (CDC), United States (US) has termed this disease as MIS-C, the World Health Organization has used the term Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19, while the Royal College of Paediatrics and Child Health have used the term PIMS-TS (paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2) [6].

Pediatric COVID-19 patients usually present with mild symptoms including cough, fever, sore throat and diarrhea, but low respiratory tract symptomatology is rather unusual, compared to adults. Fortunately, children account for only 1–5% of COVID-19 cases and more than 80% of them are asymptomatic or mildly symptomatic [7]. Mortality due to COVID-19 is also significantly lower in children, compared to adults (< 0.1% versus 5–15%). In contrast

to acute COVID-19 infection, which is mild in children, 68% of MIS-C patients present an extremely severe condition and need intensive care support, due to cardiovascular complications [8]. MIS-C and KD differ in the following clinical and laboratory features. (1) Gastrointestinal complications, neurological symptoms, shock and coagulopathy are more common in MIS-C, but unusual in classic KD. (2) Classic KD is common in North East Asian, while MIS-C has been reported more commonly in patients of African, Hispanic or Latino origin. (3) KD is common in children < 5 years, while MIS-C involves children > 5 years of age (4) Low platelets, lymphopenia and high C-reactive protein (CRP) levels are common in MIS-C, but rather unusual in KD [9]. Although COVID-19 in children is mild, MIS-C is a serious condition, similar to other hyper-inflammatory syndromes in children, such as KD shock syndrome, toxic shock syndrome and macrophage activation syndrome [10]. The comparison between KD and MIS-C is presented in Table 1.

Fever, mucocutaneous findings (rash, conjunctivitis, hands/feet edema, red/cracked lips, and strawberry tongue), myocardial dysfunction, cardiac conduction abnormalities, shock, gastro-intestinal symptoms, respiratory signs and lymphadenopathy are included between the main symptoms of MIS-C [11]. In parallel, there is increasing incidence of neurologic involvement, presenting as severe headache, altered mental status, cranial nerve palsies, or meningismus [11]. These findings are non-specific and can also occur in other infectious or non-infectious causes, including

Table 1 Comparison between KD and MIS-C

	MIS-C (WHO)	Complete KD (AHA)	Incomplete KD (AHA)
Age	0–19 yrs	Unspecified	Unspecified
Inflammation	Fever, increased inflammatory markers > 3 days Two of the following: (A) rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet); (B) hypotension or shock; (C) myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiogram findings or elevated troponin or N-terminal pro B-type natriuretic peptide); (D) evidence of coagulopathy (elevated prothrombin time, partial thromboplastin time, and elevated D-dimers); and (E) acute gastro-intestinal problems (diarrhea, vomiting, or abdominal pain)	Fever lasting > 5 days Four or more principal clinical features: (A) erythema and cracking of lips, strawberry tongue or oral and pharyngeal mucosa; (B) bilateral bulbar conjunctival injection without exudate; (C) rash; (D) erythema and edema of the hands and feet in acute phase and periungual desquamation in subacute phase; and (E) cervical lymphadenopathy	Fever lasting > 5 days Two or three principal clinical features or a positive echocardiogram
Exclusion	Other microbial cause of inflammation		
SARS-Covid-2 status	Positive RT-PCR, antigen test, or serology; or any contact with patients with COVID-19		

oncologic or autoimmune disorders. Therefore, it is absolutely necessary to exclude other diseases that may present with similar clinical findings, when we perform the differential diagnosis of patients with potential MIS-C.

The aim of this review is to present cardiovascular and brain involvement and the role of imaging in the early detection of these abnormalities.

Research strategy

A MedLine, Embase and Scopus search was performed according to published guidance on narrative reviews [12] using the following terms: systemic autoimmune diseases, autoimmune rheumatic diseases, cardiovascular involvement, myocarditis, cardiac magnetic resonance, immunosuppressive treatment, systemic lupus erythematosus, systemic sclerosis, vasculitis, rheumatoid arthritis, ankylosing spondylitis. Original research papers and review articles focusing on the effect of immunosuppressive treatment on myocardial and cardiac disease evaluated by CMR in patients with ARDs up to December 2020 were selected to be included in this review. Publications not in English and data from ongoing research were excluded.

Cardiovascular disease in MIS-C

Cardiovascular complications and particularly left ventricular dysfunction is the commonest complication in patients with MIS-C. Cardiac biomarkers including N-terminal pro b-type Natriuretic Peptide (NT-pro-BNP) and troponin levels are extremely high, compared to KD and indicate severe myocardial damage that may lead to heart failure. Symptomatic myocarditis was found in 40–80% of patients with MIS-C [13, 14]. In contrast, symptomatic myocarditis is seen in <5% of KD patients [15–17]. Pouletty et al. documented the presence of severe myocarditis in approximately 50% of MIS-C patients with higher risk in older children [13].

Coronary artery abnormalities (CAAs) have been diagnosed in 9–24% of patients with MIS-C, as common as in KD in the intravenous immunoglobulin (IVIG) era [6, 18–21]. CAAs may present as dilatation or small-sized aneurysms in most patients. Pericarditis and valvular regurgitations are not unusual. Both NT-pro-BNP and cardiac troponin levels are extremely high in patients with MIS-C compared to KD [6, 18, 22]. In a recent study, NT-pro-BNP levels were elevated in 83% patients, while troponins in 68% of them [6].

Finally, the evaluation of 286 children from 55 centers in 17 European countries showed that cardiac involvement was common in children with MIS-C. The majority of them have significantly increased levels of NT-pro-BNP, ferritin, D-dimers and cardiac troponin in addition to high CRP and

procalcitonin levels. According to this publication, children with MIS-C should be monitored for shock, cardiac arrhythmias, pericardial effusion, and coronary artery dilatation which were the 4 most common cardiovascular complications in this cohort. Despite high D-dimer levels, only a small number of MIS-C patients develop deep vein thrombosis or pulmonary embolism [23]. Furthermore, a statistically significant correlation between elevation in cardiac/biochemical indices and the need of intensive care support was found. However, compared to adults, the mortality in children with MIS-C was uncommon, despite the high levels of inflammatory indices and the multi-system presentation of the disease [24].

Children with MIS-C need to be treated in a hospital and some of them should be treated in a pediatric intensive care unit. The treatment should include supportive care and medication to reduce inflammation in affected organs and protect them from permanent damage [24].

Cardiovascular Diagnostic Approach

Electrocardiogram (ECG)

There are only few reports about the role of electrocardiogram (ECG) in MIS-C. According to a recent study, ECG abnormalities were found in 56% of MIS-C patients. First-degree atrioventricular block (AVB) was seen in 20% of patients 6 days after the onset of fever with progression to second- or third-degree AVB, but none of them required pacemaker. No patient with AVB had an elevated troponin level. QTc prolongation was seen in 28% and nonspecific ST segment changes were seen in 56% of them. Ectopic atrial tachycardia was observed in 1 patient, and none developed ventricular arrhythmias [16].

Echocardiography

Due to the high incidence of cardiovascular disease (CVD) in MIS-C, echocardiography is of great value at disease diagnosis to assess the severity of cardiovascular involvement. The main findings expected in MIS-C include: (a) depressed LV function [25, 26] (b) Coronary artery abnormalities, including dilation or aneurysm [27, 28], (c) Mitral valve regurgitation, (d) Pericardial effusion [6, 25]. Comparisons between echocardiographic images in MIS-C and KD are presented in Fig. 1a, b.

Echocardiography is also of great value during follow-up. According to our experience from KD [28], in patients with normal function and normal CA dimensions, a follow-up echocardiogram should be performed two weeks post diagnosis to re-evaluate CA dimensions. In patients with CA ectasia/aneurysm at diagnosis, an echocardiogram should be repeated every week until CA dimensions

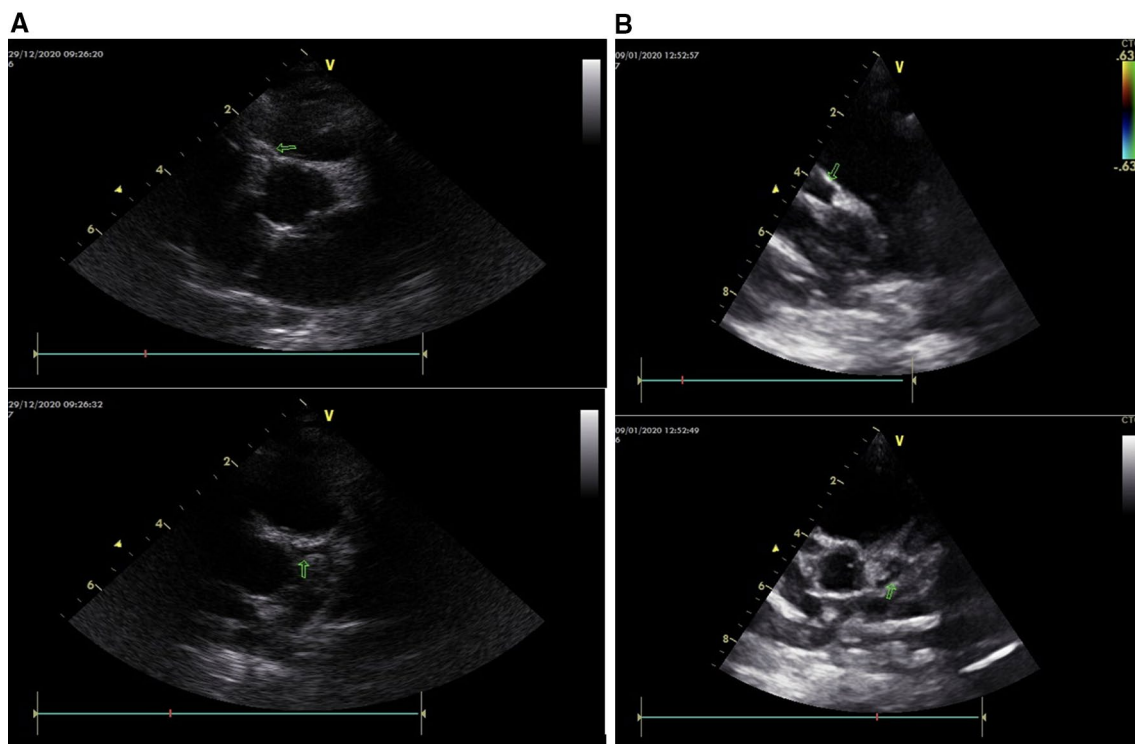


Fig. 1 a Echocardiographic image of the coronary arteries in a patient with MIS-C. Normal Left Main and Left Anterior Descending artery and Right coronary artery. **b** Echocardiographic image of

the coronary arteries in a patient with Patient with Kawasaki disease. Dilatation of Left Main and Left Anterior Descending artery and Dilatation of Right coronary artery

will be normalized. In children with systolic dysfunction and/or myocarditis and normal CAs at diagnosis, the echocardiogram should be repeated every month, including repeat imaging of the CAs in each study. Finally, in patients with CA abnormalities and systolic dysfunction/myocarditis at diagnosis, cardiovascular magnetic resonance imaging (CMR) should be considered in 2–6 months post MIS-C to perform ventricular function evaluation and tissue characterization [27, 28].

According to a recent publication, MIS-C behaves differently from classic KD, presenting greater incidence of myocardial injury and sparing of the coronary arteries. However, longtime evaluation of coronary arteries in MIS-C is still missing. Even in cases with preserved systolic function, there are subtle changes in diastolic function and strain parameters supporting myocardial injury. In short-term follow-up, persistence of diastolic dysfunction was observed, although the systolic function may be normalized [29]. According to other studies, the involvement of coronary arteries is not unusual in MIS-C. In one study by Kelly et al., mild coronary artery dilatation/ectasia was found [30].

Cardiovascular Magnetic Resonance (CMR)

CMR has the unique capability to perform coronary arteries, biventricular function and tissue characterization in the same radiation-free examination with excellent reproducibility [28]. The diagnosis of myocarditis, which represents the main lesion during MIS-C, is based on the Lake Louis (LL) criteria. LL have a diagnostic accuracy of 78% in identifying myocarditis. LL criteria include the evaluation of edema on T2-weighted images, of hyperemia and early capillary leakage on T1-weighted early gadolinium enhancement images (EGE), and of fibrosis using late gadolinium-enhanced images (LGE). LL criteria have a high specificity and positive predictive value, when 2 out of 3 indices are abnormal [31]. Myocarditis-induced alterations may present with several LGE patterns, are typically localized at the sub-epicardial or intramural areas of LV and are frequently located in the basal to mid-inferolateral wall. LGE-positive patients are at increased risk of adverse cardiac events, while LGE-negative patients usually have an excellent prognosis, independently of their symptomatology [32]. The CMR diagnostic accuracy can increase significantly using the

proposed updated LL criteria. These criteria include the addition of parametric mapping techniques (T2 mapping, T1 mapping and extracellular volume fraction = ECV). In more details, T2 mapping images can identify acute myocardial edema with higher signal-to-noise ratio, shorter breath-hold time and fewer motion artifacts, compared to classic T2-W images. Native T1 mapping is sensitive to intracellular and extracellular changes in free water content and is increased during acute inflammation. Finally, ECV detects an expanded extracellular space and can assess diffuse fibrosis, missed by LGE [33]. A recent research by Puntmann et al. including 100 patients recovered from COVID-19 infection, showed that native T1 and T2 mapping provides the best parameters to detect COVID-19-related myocardial injuries [34]. In contrast to adults, myocarditis in MIS-C is characterized by diffuse edema (Fig. 2) without LGE (Fig. 3) and this should be taken under consideration, when we evaluate CMR results in MIS-C patients [35].

Coronary artery evaluation using CMR coronary angiography has been extensively used in the evaluation of coronary artery ectasia/aneurysm in KD alone or in combination with assessment of inflammation/fibrosis [36, 37]. Although echocardiographic assessment is easy and reliable, it is inadequate in adolescents, and CMR or CT coronary angiography (Fig. 4) should be considered as a noninvasive modality without radiation [28].

Diagnosis and treatment

Previously published guidelines and management recommendations by the American College of Rheumatology (ACR) emphasize the role of biomarkers, ECG, and echocardiography both during the acute phase and the follow-up time until complete recovery of cardiac function will be noticed. Furthermore, CMR and CT should be considered in individualized cases [38]. Regarding treatment, IVIG, corticosteroids, anakinra, antiplatelets and cardiac supportive medication has been proposed [38]. All these measurements

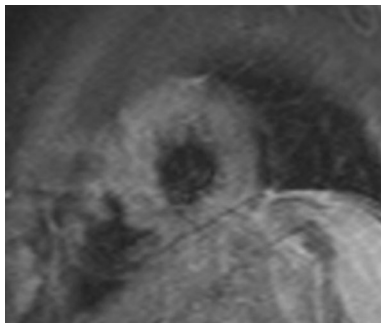


Fig. 2 Short axis CMR image showing diffuse edema

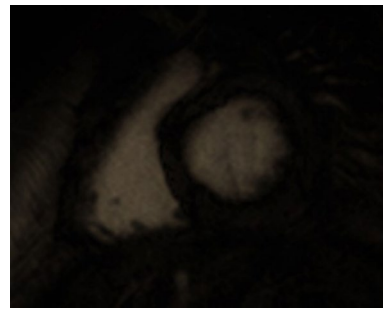


Fig. 3 Short axis CMR image showing absence of LGE

target to the rapid deterioration of the inflammatory syndrome and protection of acute and late cardiac complication that usually accompany MIS-C [38].

Brain involvement during MIS-C

Mental alteration has been described during COVID-19 [39]. However, there are only rare reports of severe encephalopathy in MIS-C patients. A multicenter study in adults with COVID-19 and neurologic symptoms showed ischemic infarcts in 31%, intracranial hemorrhage in 6%, and nonspecific T2/fluid-attenuated inversion recovery hyperintensity [14] with restricted diffusion in a small percentage of them [39]. The revision of 187 children from six recent reports of MIS-C showed that these children had an unexpectedly high incidence (34%) of neurological involvement [13, 14, 18, 40–42]. The pathophysiologic mechanism of neurologic complications in children with MIS-C remains unclear. Potentially, the mechanism in MIS-C is different from that of the thromboembolic cerebrovascular events observed in adults with COVID-19 [43]. The pathophysiologic mechanism of MIS-C meningoencephalitis is still unknown, but it may be related to neuronal cell edema as a result of cytokine storm syndrome, due to overreaction of monocytes, macrophages, T cells and release of interleukins-6 (IL-6) post SARS-CoV-2 infection. Furthermore, it may be



Fig. 4 CT coronary angiography in a patient with MIS-C showing normal coronary arteries

related to acute necrotizing encephalopathy, a para-infection described mainly in the pediatric population [44]. Although direct invasion of central nervous system (CNS), due to COVID-19 or metabolic encephalopathy as a result of severe hypoxia has also been reported in adults [44]. However, the lack of positive SARS-CoV-2 reverse transcription polymerase chain reaction test in cerebrospinal fluid (CSF) and the mild lung involvement in these cases does not support the hypothesis of COVID-19 encephalopathy. Finally, another entity called reversible splenial lesion syndrome (RESLES) should be discussed. This is characterized by a temporary lesion in the splenium of the corpus callosum, related to encephalitis, seizures, withdrawal of antiepileptic drug, or metabolic disturbances. RESLES with mild encephalitis/encephalopathy and reversible splenial lesion has been defined as a distinct syndrome, associated with various viral infections [45].

Brain MRI in MIS-C

A recent study in the UK showed changes in the splenium of the corpus callosum (SCC) in all 4 patients with neurologic signs. T2-hyperintense lesions associated with restricted diffusion were seen in 3 children. The fourth patient presented with a splenial lesion on computed tomography, but on brain MRI, no restricted diffusion was found, although the signal change remained unchanged. The genu was involved in 2 patients and the bilateral centrum semi-ovale in 2 patients. Finally, spinal cord pathologic enhancement was not identified. Patient 2 had a repeated MRI on day 5 that showed resolution of diffusion restriction in the SCC and centrum semi-ovale [46]. Furthermore, a case report presented a previously healthy child with MIS-C, who developed reversible encephalopathy with moderate EEG slowing and bilateral thalamic lesions in brain MRI. The child was improved with continued anti-inflammatory treatment [47]. In another study of 47 children with MIS-C, 4/47 underwent brain MRI. One of these children, with fluctuating mental status and laboratory evidence of thrombotic microangiopathy with hemolytic anemia, had fluid-attenuated inversion recovery (FLAIR) MRI hyperintensity with restricted diffusion involving the bilateral parieto-occipital cortices with mild cortical thickening and T2/FLAIR hyperintensity in the left fronto-parietal centrum semi-ovale. A second brain MRI for evaluation of vision defects and cranial nerve palsy demonstrated MR findings compatible with papilledema. Two additional brain MRIs for evaluation of mental alterations and headache were normal [48].

Impact of CMR and brain MRI in the MIS-C patients' follow-up

The severity of cardiac involvement has important implications in the patient's future. Myocardial function

deterioration may lead to future intractable heart failure, if it is incompletely treated. Furthermore, the persistence of myocardial inflammation may suggest treatment of the immunomodulatory medication. Finally, the presence of CAA demands continuous assessment of coronary arteries anatomy and myocardial perfusion evaluation to assess the need of potential intervention.

Regarding brain MRI, it has an important value in the evaluation of neurologic deficits after MIS-C and can guide further treatment.

Conclusion

Although rare, MIS-C involves many vital organs including heart and brain. Patients with MIS-C should be treated in hospital and may need intensive care unit. Imaging modalities including echocardiography and CMR may guide successfully the effect on cardiovascular disease of both supportive and anti-inflammatory medication. Furthermore, brain MRI can reveal brain involvement, which may have significant clinical implications both in acute and follow-up periods and should be treated adequately.

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Declarations

Conflict of interest Authors declare no relevant conflict of interest.

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