REVIEW ARTICLE

Viral Myocarditis in Children: A Review

Jayranganath Mahimarangaiah[1], Varun Marimuthu[2]

Abstract

In viral myocarditis, viral invasion of the heart can lead to direct and indirect inflammatory destruction of the myocardium. Various etiological agents, ranging from enterovirus to adenovirus can cause myocarditis. The clinical presentation is heterogeneous and can end up in a dilated cardiomyopathy phenotype, leading to major mortality, morbidity, and years lost in children. Early recognition and diagnosis with echocardiogram, endomyocardial biopsy, and cardiac MRI is important. Treatment options include with immunosuppression and immunomodulation in the early phases and may require cardiac transplantation in end-stage heart failure.

Keywords: Children, COVID-19, India, Intravenous immunoglobulin, Laboratory diagnosis, Myocarditis, Pediatric, Review, Severe acute respiratory syndrome coronavirus 2, Viral.

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Introduction

Myocarditis is an inflammation of the myocardial muscle mass. Coined in the 19th century, the term "myocarditis" used to denote an amalgam of conditions ranging from hypertensive heart disease to ischemic heart disease. The World Health Organization in the 1990s differentiated between various cardiomyopathies and defined myocarditis as an inflammatory pathology of the muscle cells with evidence of mononuclear cell infiltrate in the myocardium with or without necrosis.[1] Although various etiologies exist, viral myocarditis is the most common cause.[2,3] Incidence is 1–2 per 100,000 children,[4,5] and is probably underestimated as autopsy studies in children with sudden cardiac death has shown features suggestive of myocarditis in 10–20% of autopsies.[6,7] Children present with a wide variety of presentations ranging from subclinical mild disease, rhythm abnormalities, dilated cardiomyopathy (DCM),[8] left ventricular (LV) dysfunction with cardiogenic shock, to fulminant myocarditis leading to rapid progression and sudden death.[3]

Although the cardiological societies recommend the use of endomyocardial biopsy (EMB) and immunohistochemistry (IHC) to diagnose myocarditis,[9,10] the use is limited in real world clinical practice, including in India. Clinicians, then rely on a galaxy of clinical features, laboratory parameters, echocardiography to diagnose myocarditis. The widespread availability of cardiac MRI (CMRI) is changing the diagnostic paradigm in myocarditis.[11]

Treatment options include conservative management and follow-up, intravenous immunoglobulin (IVIG), and steroids. Mechanical circulatory support (MCS) and heart transplant are also options in refractory disease.[10]

In the current pandemic era with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19), cardiovascular involvement with myocarditis has been reported to be 7–17%.[12,13]

Etiopathogenesis

Myocarditis in children could be a result of a wide variety of insults. Infectious myocarditis is the commonest, with the other causes being toxin mediated, hypersensitivity reactions, radiation induced, and secondary to other systemic disease (Table 1). Among the viruses, enterovirus is the classical agent, but polymerase chain reaction (PCR) of the myocardium has revealed the presence in both children and adults, of other viruses, such as adenovirus, parvovirus B19, human herpesvirus 6 (HHV6), hepatitis C, Epstein–Barr virus, and cytomegalovirus (CMV).[3,10,14] Epidemiology is, however, evolving with enterovirus making way to parvovirus and HHV6 being more common. This could be a result of genomic changes in the viral evolution or geographical shifts in the prevalence.

Dengue and dengue hemorrhagic fever has also been implicated in childhood myocarditis.[15] This atypical manifestation of dengue is difficult to treat and often fatal.[16]

Both human immunodeficiency virus 1 and 2 (HIV 1 and HIV 2) can cause multifactorial LV dysfunction in children. Direct viral-mediated damage and myocarditis has been postulated

Table 1: Etiological agents

Infectious	*Noninfectious*
Viral—Enterovirus, adenovirus, human herpesvirus 6 (HHV6), Epstein–Barr virus (EBV), hepatitis C virus, human immunodeficiency virus (HIV), influenza virus, coronavirus	Toxins
Protozoa—Chagas disease	Autoimmune conditions
Bacterial—Syphilis, *Borrelia*, Streptococci, *Mycobacterium*	Drug-related toxicity, immune checkpoint inhibitors
Others—Fungal, parasites	

[1]Department of Pediatric Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, Karnataka, India

[2]Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, Karnataka, India

Corresponding Author: Varun Marimuthu, Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, Karnataka, India, Phone: +91 9880015014, e-mail: varun.marimuthu@gmail.com

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as a mechanism. Although limited to case reports with no clear incidence numbers, COVID-19 causes features of myocarditis.

The link between viral infection and myocarditis has been conclusively proven by EMB- and PCR-based identification of viral DNA and RNA in affected patients. The utility of serum neutralizing antiviral antibodies has been questioned for diagnosis,[17] but their presence in blood supports causation.[18] In a PCR-based registry, the viral distribution was parvovirus (36.6%), enterovirus (32.6%), HHV6 (10.5%), and adenovirus (8.1%).[19]

We can consider the pathogenesis of viral myocarditis in three phases[20] as elucidated by the European consensus statement from 2013.

Phase 1 starts with the viral entry into the host and the myocardium. This leads to activation of the innate immunity and antibodies are produced. Myocardial damage leading to severe systolic dysfunction and arrhythmias can either be direct viral mediated or antibody mediated. This phase lasts for up to 7 days. Phase 2 can last up to 4 weeks. Here, the persistent presence of virus and antibodies lead to a state of autoreactive myocarditis. Myocardial damage may heal and the disease resolve, or maladaptive mechanisms, cytokine and chemokine release, development of auto-cardiac antibodies may worsen the disease and it can lead to a state of chronic myocarditis. Studies have shown that the cytokine storm which is a consequence of viral infection leads to myocarditis.[21]

In the phase 3 of this disease, chronic myocarditis may resolve over months to years with viral clearance and recovery of systolic function. If the viral clearance is ineffective and myocardial degeneration and fibrosis set in, a phenotype of DCM and reduced LV function develops.

The mechanisms responsible for viral elimination, viral reactivation and chronic myocarditis, persistence of latent infection are unknown.[20]

As children get older, the presence of antiviral antibodies, especially to Coxsackie B virus start appearing in the blood, because of prior subclinical disease. These confer protection against developing viral myocarditis beyond 30 years of age.[22]

Clinical Presentation

Myocarditis is a very heterogeneous disease. Presentation ranges from nonspecific symptoms to fulminant disease, shock, and sudden death.

- Nonspecific symptoms of the viral prodrome, fever ≥38.0°C, tachycardia, palpitations.
- Mimicking acute coronary syndrome (ACS).
  - Chest pain following a recent viral infection.
  - ST elevations and T inversions on the electrocardiogram (ECG).
  - Nonspecific elevation of troponins (troponin I and T) and creatine phosphokinase (CPK) is suggestive of myocarditis. In the myocarditis treatment trial study,[23] sensitivity was 34% and specificity was 89% for diagnosing myocarditis with troponin I in a cohort of EMB proven myocarditis.
  - Regional wall motion abnormalities on echocardiogram (ECHO) or CMRI.
- Heart failure
  - Ranges from mild LV systolic dysfunction to DCM.
  - Rapidly progressive (over 2–4 weeks), new onset left-sided heart failure with significant dyspnea, orthopnea, exercise intolerance, and fatigue.
  - Right heart failure with peripheral edema, hepatomegaly, and congestion.
- Fulminant myocarditis
  - Cardiogenic shock and ventricular arrhythmias.
  - Aborted sudden cardiac death.
  - Complete heart block, bundle branch blocks.

Clinical manifestations stratified by age group are tabulated in Table 2.

Physical examination findings are tabulated in Table 3.

Natural History

The natural history, progression, and disposition depend on the age at presentation, etiological agent, and the severity at presentation. Broadly, in patients who have mild LV dysfunction at presentation, most are expected to recover in a few months. In patients with moderate to severe LV dysfunction, 50% recover, 25% develop chronic LV dysfunction, and 25% develop progressive cardiac dysfunction leading to death, or in rare cases survival with transplantation.[24] In the myocarditis treatment trial,[23] mortality in viral myocarditis was 20% at 1 year and 56% at 4 years. In children, studies have shown that DCM is preceded by myocarditis in 27–40% of cases.[4,25]

With patients going in for early transplantation or with durable MCS, the natural history can change, with survival improving.

Predictors of Mortality

The following parameters portend a worse outcome.

- Syncope, prolonged QRS, left bundle branch block (LBBB), severe pulmonary arterial hypertension (PAH), >New York Heart Association (NYHA) 3 at presentation.[10]
- In patients with EMB and IHC proven viral myocarditis but not on optimal medications, 5-year survival is 39%.[10]
- A recent study from China showed that troponin I >45 ng/mL and left ventricular ejection fraction (LVEF) <42% predicted mortality in a cohort of pediatric myocarditis.[26]

Table 2: Clinical manifestations among various ages

Infants	*Older children*
Refusal of feeds, hurried rapid breathing	Fever
Vomiting	Viral prodrome, followed by fatigue and dyspnea
Pallor	Exercise intolerance
	Chest pain (with concomitant pleuritis and pericarditis)

Table 3: Physical examination in myocarditis

Tachypnea, tachycardia
Bilateral rales
S3, S4, gallop rhythm, murmur of functional mitral regurgitation, pericardial rub
Effusions, peripheral edema, hepatomegaly
Signs of shock and poor perfusion—Altered mentation, cool peripheries, reduced capillary refill time, mottled skin

Diagnosis

Diagnosis can be performed with imaging- and non-imaging-based methods.

ECG

- ECG in a patient with clinical suspicion of myocarditis will be abnormal. ECG can show sinus tachycardia, nonspecific ST T changes, T inversion, premature beats, ventricular tachyarrhythmias are also seen. Heart blocks and bundle branch blocks are also seen. But, however, ECG is of extremely low sensitivity and specificity for the diagnosis.

Biomarkers

- Myocardiocytolytic markers like troponin and CPK may be elevated. Troponin elevation is seen in most patients and is just a sign of myocardial damage.[27] Higher levels do not directly correlate with severity of the disease, with patients with mild LV systolic dysfunction having significant troponin elevation compared to patients with severe LV dysfunction.[28] So, troponin elevation is nonspecific for the diagnosis. Children with heart failure of other etiologies can also have troponin elevation.
- Biomarkers, such as erythrocyte sedimentation rate (ESR), CRP may be elevated. N terminal-pro brain natriuretic peptide (NT-proBNP) can be high when there is significant LV dysfunction.
- Viral serology is another commonly performed test. Positive viral serology only implies an activation of the immune system and production of antibodies, and not a direct infection of the myocardium.[20] No correlation has been found between viral antibodies and EMB-based diagnosis of viral myocarditis.[17] As per the European Society of Cardiology (ESC) consensus, routine viral serology is not recommended for diagnosis.

ECHO

Echocardiogram is a first-line tool and can be used in the initial diagnosis and to follow-up patients over time to document recovery. Classical findings include LV and right ventricular (RV) systolic dysfunction, valvular regurgitation, pericardial effusion, and if the child has myopericarditis, regional wall motion abnormalities of the inferior, lateral wall is often seen. Diastolic dysfunction is also seen. Myocarditis can mimic any of the cardiomyopathy phenotypes—DCM, restricted cardiomyopathy (RCM), or hypertrophic cardiomyopathy (HCM).[20]

Global longitudinal strain (GLS) can also be useful. In several studies, GLS has been found to be helpful in diagnosing subclinical LV dysfunction in patients with preserved LV function, in serial follow-up of patients, and in predicting worsening LV dysfunction.[29,30]

The common differential diagnosis in a case of clinical myocarditis and how to differentiate by ECHO is given in Table 4.

Table 4: Common differentials of viral myocarditis by ECHO

Differential diagnosis	*ECHO*
Acute rheumatic fever	Typical valve thickening, valvular regurgitation
Anomalous left coronary origin from the pulmonary artery	ALCAPA will have a DCM phenotype with glistening endocardium and papillary muscles, mitral regurgitation. The abnormal left coronary origin can be traced back to the pulmonary artery
Idiopathic dilated cardiomyopathy	Often difficult to differentiate. LV dilatation in myocarditis is less than that seen in chronic DCM
Inflammatory myocardial dysfunction	Kawasaki disease will have dilated coronary arteries, severe LV dysfunction is rare. Lupus myocarditis is often indistinguishable from viral myocarditis
Tachycardiomyopathy	Difficult to identify which came first—Arrhythmia or the myocardial dysfunction. Response to treatment can be tracked by ECHO

Table 5: Lake louise criteria MRI criteria (modified 2018)

Main criteria	*Supportive criteria*
Myocardial edema (T2 sequence)	Pericarditis (T1, T2, LGE), Presence of fluid around the heart
Non-ischemic myocardial injury (T1, increased extracellular volume ECV, presence of LGE)	Systolic LV dysfunction
Both T1 and T2 criteria positive—Strongly suggests myocarditis	
Any one of the T1 or T2 criteria positive—May suggest myocarditis	

CMRI

Cardiac MRI should be performed in all suspected myocarditis patients who are hemodynamically stable. In unstable patients suspected to have myocarditis, EMB may be better for diagnosis.[20] Cardiac MRI can detect myocardial inflammation by characterizing edema and hyperemia (T2 sequence). Gadolinium contrast MRI can detect capillary leakage (T1-weighted early gadolinium enhancement, EGE) and myocardial scar (late gadolinium enhancement, LGE). By comparing the presence of edema and necrosis (scar) tissue, characterization and diagnosis of myocarditis is performed. The updated Lake Louise criteria, 2018 (Table 5) refer to performing and reporting a CMRI for diagnosis of myocarditis.[31]

Classically, LGE in myocarditis is either intramural or epicardial and can involve the basal septum and the lateral wall. In an adult population, MRI correlates very well with EMB in patients with viral myocarditis who are troponin positive.[32] In children, a combination of LGE, EGE, and T2 imaging had a 82% sensitivity for identifying myocarditis.[33]

EMB

Endomyocardial biopsy confirms the diagnosis and identifies the etiological agent and is the gold standard. The Dallas histopathological criteria[34] were proposed to identify myocarditis, active myocarditis is defined as an inflammatory infiltrate of the myocardium with necrosis of adjacent myocytes, not typical of that seen in coronary artery disease (CAD).[34] The Dallas criteria yield diagnostic information in only 10–20% of EMBs due to wide interobserver variation, errors in sampling, etc.,[10] and should be combined with IHC and viral genome identification to increase its sensitivity.

- Endomyocardial biopsy should be performed early in the disease.
- Three samples, 1–2 mm size should be taken from the RV and LV and fixed in 10% formalin for light microscopy and frozen and stored for viral PCR analysis.
- Complication rate <1% in most centers.
- Cardiac MRI can identify the locus for EMB, and target biopsy sites in stable patients.
- Endomyocardial biopsy can be repeated to see the progression and relief of the disease.

It must be emphasized that EMB especially in infants is fraught with risks, such as RV perforation, tricuspid valve damage, induction of arrhythmias, vascular injury, and shock. A pathologist experienced in cardiac diseases and myocarditis must be available to interpret, report, and guide further treatment.

Treatment

Medical Management

The initial management is to stabilize the patient, address hemodynamic compromises, and control arrhythmias.

In patients who are hemodynamically stable, treatment should be concurrent with evaluation of the antecedent cause and includes goal-directed use of renin angiotensin aldosterone system (RAAS) inhibitors, beta-blockers, diuretics, and aldosterone inhibitors. Cardiac MRI should be performed in all stable patients at presentation. If with supportive therapy there is no recovery by 3 months, the EMB and viral PCR should be a part of the management plan. If virus negative, then immunosuppression is indicated. If persistently virus positive in EMB, antiviral agents should be started (discussed later). Strict rest and avoidance of exercise is recommended.

Patients who are hemodynamically unstable are at extremely high risk for progressive deterioration and thus management should be aggressive. They should be promptly admitted to intensive care units (ICUs) and need mechanical ventilation. Early institution of MCS like ECMO is indicated as either a bridge to recovery or transplantation. Endomyocardial biopsy is mandatory if local expertise is available to expedite the diagnosis. Cardiac transplantation, if planned should be deferred till the acute phase is over to give chance to the myocardium to recover.

In older children, where the chest cavity is of sufficient size, use of MCS in the form of left and right ventricular assist devices (LVAD and RVAD) should be considered. Continuous flow LVADs used in adults, such as Heartware HVAD or Heartmate 3, could function as a bridge to recovery or to transplant in these patients.[35,36]

In infants <5 kg, it is often difficult to use a LVAD although studies with small devices, such as the berlin EXCOR pump, have been conducted. Although tried in a DCM setting, temporary alternative measures, such a pulmonary artery banding, could be considered to change the LV and RV geometries and improve hemodynamics.[37]

In a child with incessant arrhythmias, guidelines-directed treatment is recommended. Implantable cardioverter defibrillator (ICD) should be temporary, if at all and wearable defibrillator has been shown to impact mortality in a recent trial.[38] Implantable cardioverter defibrillator implantation should be deferred till the acute phase is over to give a chance for the myocardium to recover.

Anticoagulation is essential to avoid LV thrombus formation in children with severe LV dysfunction. In the acute phase, unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) can be considered. Once the acute phase is over, prophylaxis with aspirin is started and continued until LVEF improves to >40%.[39] If LV thrombus is detected, then anticoagulation with warfarin should be started until thrombus resolves.

Immunotherapy

As the myocardial damage depends on the maladaptive immunity in a patient with myocarditis, immunosuppression with steroids, steroid-sparing agents, and IVIG have been tried in children with heterogeneous results.

Immunosuppression

There is no benefit in using steroids or steroid-sparing agents with the Cochrane review showing no or minimal improvement in LVEF and no change in long-term mortality.[40] Some experts do use steroids for the LVEF improvement. So, the initiation of immunosuppression if at all should be done only after ruling out active viral infection by EMB and viral PCR.

The TIMIC study performed in adults showed that in virus negative, inflammatory DCM, prednisolone, and azathioprine given over 6 months resulted in improvements in LVEF and LV dimensions compared to placebo.[41] Such studies are lacking in children.

Immunomodulation

A randomized controlled trial shown that high-dose IVIG use is associated with LVEF improvement and increased survival in pediatric myocarditis patients.[42] Data from observational and retrospective studies are very heterogeneous in their conclusions with most studies showing improvement of LVEF and better survival with IVIG use.[28,43,44]

In mice models of viral myocarditis, TNF-alpha antagonists have shown great benefit. But this was not replicated in human studies in the ATTACH[45] and RENEWAL[46] trials and thus are not recommended. IL6 inhibitors like tocilizumab have been tried in viral myocarditis including in myocarditis associated with COVID-19. But this is limited to case reports.[47,48]

Antiviral Agents

Efficacy of antiviral therapy in children is uncertain and no recommendations exist but targeted treatment based on the pathogen isolated from EMB and viral PCR can be tried. In HHV6 myocarditis, acyclovir, ganciclovir, or valaciclovir can be tried. For enterovirus or adenovirus myocarditis, interferon-beta therapy can be tried.

Follow-up and Tapering of Therapy

Children can make a full or a partial recovery. Some develop persistence disease and develop a DVM phenotype. These patients need to be on goal-directed medical therapy and should be followed up with ECG, ECHO, and clinical examination for long-term.

In patients who recover diuretics should be stopped first and over time, RAAS antagonists and beta-blockers should be tapered and stopped. This tapering should be performed under close medical follow-up and any incidence of relapse or worsening cardiac function should be actively investigated with CMRI and if needed EMB with viral PCR.

Future Perspectives

There is a pressing need for more studies from developing countries looking changing patterns in epidemiology and treatment. Randomized control trials (RCTs) in children comparing

immunosuppression and immunomodulation with routine are needed.

Conclusion

Viral myocarditis as a debilitation disease of children caused by viral invasion and inflammatory destruction of the myocardium. Enteroviridae are the commonly implicated pathogen, but the epidemiology is changing now. The COVID-19 pandemic has further highlighted the need for investigation into understanding and treating viral myocarditis effectively. Clinical presentation is varied, ranging from mild prodromal symptoms to heart failure and cardiogenic shock. Although EMB and viral PCR are the gold standard, CMRI has rapidly emerged as the diagnostic modality of choice. In a resource limited setting like India, need for low cost diagnostic tools is important. Treatment depends on the severity of presentation and can range from supportive care and heart failure therapy including MCS and heart transplantation. Disease-modifying therapy like immunosuppression and immunomodulation are described, with low-quality evidence.

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