Analysis of Clinical Parameters and Cardiac Magnetic Resonance Imaging as Predictors of Outcome in Pediatric Myocarditis

Shagun Sachdeva, MBBS[a], Xiaoyan Song, PhD, MBBS[b,c], Niti Dham, MD[c,d], Deneen M. Heath, MD[d], and Roberta L. DeBiasi, MD, MS[b,c,e,*]

Myocarditis causes significant morbidity and mortality in pediatric patients, with potential adverse outcomes including heart failure, transplantation requirement, and/or death. The objective of this study was to determine predictors of early and late poor outcomes, defined as requirement for extracorporeal membrane oxygenation, ventricular assist device, transplantation, or death in pediatric myocarditis patients. A retrospective cohort study was conducted to evaluate pediatric myocarditis presenting over a 5-year period at a pediatric institution. Patients were identified using an institutional heart failure database and International Classification of Diseases, Ninth Revision, discharge diagnosis codes for myocarditis and confirmed by review of medical records. Data extraction included epidemiologic factors, the presenting ejection fraction (EF), initial and peak troponin levels, brain natriuretic peptide (BNP) level, pathogen identification, cardiac magnetic resonance imaging (MRI), and outcomes. Univariate and multivariate regression was performed to identify variables predictive of outcomes. Because published pediatric cardiac MRI data are sparse, whether late enhancement was associated with specific clinical variables or predictive of outcomes was also evaluated. Fifty-eight patients were identified. The mean age was 10.5 years, 64% were male, 62% were Caucasian, 15% were African-American, and 23% were Hispanic or Asian. Eighty-one percent presented at the institution <1 week after symptom onset. Presenting EFs were normal (>50%) or mildly decreased (40% to 50%) in 48%, moderately decreased (30% to 40%) in 9%, and severely decreased (<30%) in 42%. Thirty patients (52%) underwent viral studies; 17 of these (56%) had acute viral origins of myocarditis identified, including 8 with parvovirus (2 with influenza coinfection), 7 with enterovirus, 1 with Epstein-Barr virus, and 1 with cytomegalovirus. Twenty-eight percent had poor outcomes. Univariate analysis identified Hispanic or Asian race (odds ratio [OR] 4.5, $p = 0.05$), a severely decreased EF (OR 13, $p = 0.002$), initial BNP >10,000 pg/ml (OR 5.6, $p = 0.01$), and peak BNP >10,000 pg/ml (OR 13.65, $p = 0.001$) as risk factors for poor outcomes; initial and peak troponin >1 ng/ml were correlated significantly with good outcomes (OR 0.22, $p = 0.04$, and OR 0.26, $p = 0.05$, respectively). Multivariate analysis adjusting for severe EF, troponin, BNP, and cardiac MRI revealed peak BNP >10,000 ng/L (OR 27.71, $p = 0.04$), a severely decreased EF (OR 12.8, $p = 0.03$), and late enhancement on cardiac MRI (OR 24.51, $p = 0.04$) as risk factors for poor outcomes. Thirty-four patients underwent cardiac MRI (50% with abnormal and 50% with normal results). No significant differences were found between these groups with respect to gender, race, symptom duration, the EF, BNP, troponin, inflammation on cardiac biopsy, or pathogen identification. In conclusion, this study provides data from a large cohort of pediatric myocarditis patients. A presenting EF <30%, peak BNP >10,000 ng/L, and cardiac MRI late enhancement were identified as predictors of poor outcomes. **(Am J Cardiol 2015;115:499−504)**

In adults, several studies have identified predictors of outcomes in myocarditis patients. One study reported a correlation between pattern of damage on cardiac magnetic resonance imaging (MRI), virus isolated (parvovirus B19 and HHV6), and increased risk for dilated cardiomyopathy and poor outcomes.[1] A retrospective study of approximately 180 adult patients identified advanced New York Heart Association functional class, immunohistologic signs of inflammation, and lack of β-blocker therapy, but not histology (positive Dallas criteria) or viral genome detection, as indicators of poor outcomes.[2] Other studies have

[a]Graduate Medical Education, Department of Pediatrics, Divisions of [b]Infectious Diseases and [d]Cardiology, Children's National Health System, Washington, District of Columbia and Departments of [c]Pediatrics and [e]Microbiology, Immunology and Tropical Medicine, George Washington University School of Medicine, Washington, District of Columbia. Manuscript received August 13, 2014; revised manuscript received and accepted November 12, 2014.

See page 503 for disclosure information.

*Corresponding author: Tel: (202) 476-5051; fax: (202) 476-3850.
E-mail address: rdebiasi@childrensnationalmedicalcenter.org (R.L. DeBiasi).

0002-9149/14/$ - see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2014.11.029

Table 1
Patient characteristics

Characteristic	Number of Patients (%)
Age (years)	0.25-19 (mean 10.5)
Male	37 (64%)
Race	
Caucasian	36 (62%)
Black	9 (16%)
Asian and Hispanic	11 (19%)
Duration of symptoms (weeks)	
<1	47 (81%)
1-3	4 (7%)
>3	4 (7%)
Ejection Fraction (%)	
>50	19 (33%)
40-50	9 (16%)
30-40	5 (9%)
<30	24 (41%)
Cardiac MRI performed	34 (59%)
Endomyocardial biopsy performed	28 (48%)
Acute viral studies performed	30 (52%)
Virus identified	17 (29%)
Parvovirus	6
Parvovirus+Influenza	2
Enterovirus	7
EBV	1
CMV	1
Adenovirus	0
Good Outcome	42 (72%)
Any Poor Outcome	16 (28%)
Early Poor Outcome	
ECMO	10
VAD	2
Late Poor Outcome	
Heart Transplant	7
Death	4

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

demonstrated elevation of serum Fas and Fas ligand levels at initial presentation, biventricular dysfunction at diagnosis, presence of a viral genome, initial presentation with heart failure, prolonged QRS duration, and elevated brain natriuretic peptide (BNP) as predictors of poor outcomes or incomplete recovery.[3–7]

In children, older age, a low initial ejection fraction (EF), mechanical ventilation or extracorporeal membrane oxygenation (ECMO), nonfatal cardiac arrest, and ventricular arrhythmia have been identified as significant risk factors for fatal outcomes.[8] Factors associated with adverse outcome or unremitting heart failure have included left ventricular dilation, an EF <30%, shortening fraction <15%, and moderate to severe mitral regurgitation.[9,10] A more recent study correlated the presence of an arrhythmia on presentation with a poor outcome.[11] A major paradigm change in the diagnostic evaluation of myocarditis is the increased use of cardiac MRI for noninvasive diagnosis and prognostication of acute myocarditis.[12–15] Cardiac MRI may be particularly useful in pediatric patients, considering the risks associated with endomyocardial biopsy in children.[16] To date, no studies have been published in the pediatric population that correlate cardiac MRI findings with clinical and laboratory parameters or with prognosis in myocarditis. No studies in the pediatric population to date have included viral markers or cardiac MRI as predictors of outcome in acute myocarditis.

Methods

This was a retrospective cohort study including pediatric patients with myocarditis presenting at our tertiary care pediatric institution from 2007 to 2012. Patients were identified and included in the study using 2 strategies. First, patients included in the Children's National Medical Center institutional heart failure database, consisting of all patients evaluated and treated by the heart failure team at our institution from 2009 to 2012, with diagnoses of dilated cardiomyopathy secondary to myocarditis were identified. Patients with hypertrophic cardiomyopathy and genetic origins of myocarditis were excluded. This yielded 32 subjects. Second, this group of subjects was supplemented by identifying patients who received International Classification of Diseases, Ninth Revision, primary diagnosis codes indicating myocarditis for the period from 2007 to 2012. The following codes were used to identify patients: 074.23 (Coxsackie myocarditis), 422.0 (acute myocarditis in diseases classified elsewhere), 422.90 (myocarditis, acute), 422.91 (idiopathic myocarditis), 425.4 (cardiomyopathy), and 429.0 (myocarditis, unspecified). This strategy identified 26 additional subjects, leading to a total cohort of 58 patients. Medical records were reviewed to ensure that identified subjects met clinical criteria consistent with myocarditis in conjunction with evidence of recent or ongoing myocardial injury. Clinical signs and symptoms consistent with myocarditis included respiratory distress, dyspnea, orthopnea, chest pain, palpitations, exercise intolerance, and malaise. Evidence of recent or ongoing myocardial injury included ventricular dysfunction, new or persisting electrocardiographic changes, elevated troponins, and elevated BNP.

Medical record data were systematically extracted for epidemiologic factors (age, gender, race, and duration of symptoms before presentation), the presenting EF by echocardiography, initial and peak troponin, initial and peak BNP, pathogen identification (blood and endomyocardial biopsy viral polymerase chain reaction, blood viral serologic studies), presence and pattern of late enhancement on cardiac MRI, treatment given (steroids, intravenous immunoglobulin, azathioprine), and presence of any early poor outcomes, defined as requirement for ECMO or ventricular assist device (VAD), or late poor outcomes, defined as requirement for heart transplantation or death. ECMO and VAD were considered unfavorable early poor outcomes, because they require an extreme level of support, differentiating these patients from others who require only minimal supportive therapy. This is clinically relevant, because patients presenting to centers that may not have access to these modalities and a high level of support are at risk for death.

Patients were followed through the course of the study period from 2007 to 2012 for late outcomes. Analysis was performed to determine associations between cardiac MRI late enhancement and any of the other independent variables. Further analysis using logistic regression was performed to