ORIGINAL ARTICLE

Identifying Non-invasive Tools to Distinguish Acute Myocarditis from Dilated Cardiomyopathy in Children

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Abstract

There is often a diagnostic dilemma in pediatric patients presenting with depressed ventricular function, as myocarditis and dilated cardiomyopathy (DCM) of other etiologies can appear very similar. Accurate identification is critical to guide treatment and to provide families with the most accurate expectation of long-term outcomes. The objective of this study was to identify patterns of clinical presentation and to assess non-invasive measures to differentiate patients with acute myocarditis from other forms of DCM. We identified all children (< 18 years) from our institution with a diagnosis of idiopathic DCM or myocarditis based on endomyocardial biopsy or explant pathology (1996–2015). Characteristics at the time of presentation were compared between patients with a definite diagnosis of myocarditis and those with idiopathic DCM. Data collected included clinical and laboratory data, radiography, echocardiography, and cardiac catheterization data. A total of 58 patients were included in the study; 46 (79%) with idiopathic DCM and 12 (21%) with acute myocarditis. Findings favoring a diagnosis of myocarditis included a history of fever (58 vs. 15%, $p = 0.002$), arrhythmia (17 vs. 0%, $p = 0.003$), higher degree of cardiac enzyme elevation, absence of left ventricular dilation (42 vs. 7%, $p = 0.002$), segmental wall motion abnormalities (58 vs. 13%, $p = 0.001$), lower left ventricular dimension z-score (3.7 vs. 5.2, $p = 0.031$), and less severe depression of left ventricular systolic function. There are notable differences between patients with myocarditis and other forms of DCM that can be detected non-invasively at the time of presentation without the need for endomyocardial biopsy. These data suggest that it may be possible to develop a predictive model to differentiate myocarditis from other forms of DCM using non-invasive measures.

Keywords Myocarditis · Dilated cardiomyopathy · Brain natriuretic peptide (BNP) · Pediatric · Echocardiography · Left ventricular dysfunction

Introduction

Dilated cardiomyopathy (DCM) in children carries a high risk of mortality and many patients eventually require heart transplantation [1, 2]. The published incidence of cardiomyopathy in the pediatric population varies, with reports from the Pediatric Cardiomyopathy Registry documenting an annual incidence of 1.13 cases per 100,000 for all forms of cardiomyopathy and 0.56 cases per 100,000 for pure DCM [1, 3, 4]. The majority of cases of DCM are idiopathic with a cause identified in only 32–34% of patients [1, 3, 4].

Of patients with DCM, myocarditis and neuromuscular disorders represent the most common identifiable etiologies [1, 4]. Importantly, patient outcomes vary significantly based on the etiology of DCM and therefore identification is of critical importance to provide the most accurate expectation of long-term outcomes [1]. Patients with myocarditis have improved transplant-free survival compared to patients with idiopathic DCM [1, 4–7]. In addition to this, accurate identification of myocarditis may impact clinical management as immunosuppressive therapies continue to be widely utilized in children with myocarditis [8].

Pathologic identification of an inflammatory cellular infiltrate is required for a definite diagnosis of myocarditis [8,

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9]. While endomyocardial biopsy (EMB) is typically well-tolerated, there are potential risks including the development of tricuspid valve regurgitation, arrhythmia, and cardiac perforation [10–13]. These risks are likely magnified in small patients, and this is especially important considering children < 1 year of age have the highest incidence of DCM [1]. Prior studies have suggested a potential role for non-invasive measures to aid in the differentiation of myocarditis from other forms of DCM [5, 14, 15], while other studies have failed to demonstrate a utility for non-invasive measures [16]. The aim of this study was to assess the utility of non-invasive measures in the current era to distinguish myocarditis from other forms of DCM, potentially obviating the need for EMB.

Methods

This retrospective study was approved by the Vanderbilt University Institutional Review Board. All children < 18 years of age (1996–2015) that presented with left ventricular dysfunction and underwent EMB or orthotopic heart transplantation with available pathology were included in the analysis. At our institution, we typically perform EMB within 24–72 h of admission to the intensive care unit in patients > 6 months of age presenting with depressed left ventricular systolic function of unknown etiology. The subjects were divided into two groups based on the presence or absence of a myocardial inflammatory infiltrate according to the Dallas criteria [17]: Group 1: acute myocarditis, Group 2: idiopathic DCM. Patients with associated structural heart disease, mixed phenotype (restrictive or hypertrophic cardiomyopathy), or other identifiable etiologies were excluded.

Baseline data at the time of initial presentation were compared between patients with histologically proven myocarditis and those with idiopathic DCM. Data reviewed included basic demographic information, initial clinical presentation including symptoms and physical exam findings, laboratory data, radiography, echocardiography, and cardiac catheterization hemodynamics. Standard descriptive statistics were used with comparisons made using the Wilcoxon rank sum test for continuous variables and Chi-square test for categorical variables. A 2-tailed $\alpha < 0.05$ was considered statistically significant. All statistical analyses were performed in STATA version 13 (STATA Corp LP, College Station, TX, USA).

Results

A total of 58 patients were included in the analysis with 12 (21%) demonstrating a myocardial inflammatory infiltrate consistent with myocarditis (Group 1: myocarditis) and 46 (79%) with non-specific pathologic findings (Group 2: idiopathic DCM). A total of 23 (40%) patients were diagnosed by EMB. 7 (12%) patients were diagnosed by explant alone, and 28 (48%) patients had pathology from both EMB and explant (Table 1). For patients with both EMB and explant pathology, the findings correlated in all except for one patient with myocarditis demonstrating a lymphocytic infiltrate on EMB that resolved on explant pathology ~6 months later. Patient demographics are shown in Table 2. There was no significant difference in age, sex, or race distribution between groups, although there was a trend towards patients with myocarditis being younger (1.6 vs. 4.4 years, $p = 0.291$).

As shown in Table 2, a diagnosis of myocarditis was associated with a history of fever (58 vs. 15%, $p = 0.002$), arrhythmia (17 vs. 0%, $p = 0.003$), greater elevation of troponin I (18.94 vs. 0.075, $p = 0.01$), creatinine kinase (CK) (544 vs. 107, $p = 0.024$), and CK–MB (52.45 vs. 8.3, $p = 0.036$) at time of initial presentation. Arrhythmias noted at the time of presentation included atrial tachycardia with a 3:1 block and ventricular tachycardia.

There was no difference between groups based on evidence of a viral infection detected on respiratory viral panel, viral culture, serology, or serum PCR.

Echocardiographic features associated with a diagnosis of myocarditis include a lower frequency of and less severe LV dilation (Frequency: 58 vs. 93%, $p = 0.002$; LV z-score: 3.7 vs. 5.16, $p = 0.031$), the presence of regional wall motion abnormalities (58 vs. 13%, $p = 0.001$), less mitral valve regurgitation (33 vs. 65%, $p = 0.046$), and less severe depression of LV systolic function (LV fractional shortening: 14 vs. 10.7%, $p = 0.011$; LV ejection fraction: 26.5 vs. 18.6%, $p = 0.026$). There was no significant difference in hemodynamics at the time of cardiac catheterization

Table 1 Methods of diagnosis

	Myocarditis $N = 12$	Idiopathic DCM $N = 46$	Total $N = 58$	p-value
Biopsy only	9 (75%)	14 (30%)	23 (40%)	0.005
Explant only	1 (8%)	6 (13%)	7 (12%)	0.656
Both biopsy and explant	2 (17%)	26 (57%)	28 (48%)	0.014

p-values from the Chi-square test

Table 2 Comparison of patients with myocarditis and idiopathic DCM

	Myocarditis N = 12	Total	Idiopathic DCM N = 46	Total	p-value
Demographics					
Male sex	6 (50%)	12	28 (61%)	46	0.496
Age (years)	1.6 (0.6–7.5)		4.4 (0.5–14.3)	46	0.291
Race					
Caucasian	6 (50%)	12	25 (56%)	45	
African American	5 (42%)	12	19 (42%)	45	0.588
Other	1 (8%)	12	1 (2%)	45	
Clinical presentation					
Fever	7 (58%)	12	7 (15%)	46	0.002
Constitutional symptoms[a]	11 (92%)	12	33 (72%)	46	0.151
Cardiac symptoms[b]	5 (42%)	12	19 (42%)	45	0.972
Hyperdynamic precordium	2 (17%)	12	9 (20%)	45	0.892
Murmur	3 (25%)	12	17 (37%)	46	0.545
Gallop	7 (58%)	12	30 (65%)	46	0.921
Cardiomegaly on CXR	10 (83%)	12	40 (87%)	46	0.746
Arrhythmia	2 (17%)	12	0 (0%)	46	0.003
Laboratory data					
White blood cell count (× 1000/μL)	10.9 (6.8–14.1)	12	9.6 (8.0–13.2)	44	0.921
Brain natriuretic peptide (pg/mL)	1401.5 (992.3–3170.3)	8	1936 (721–2875)	29	0.941
Troponin I (ng/mL)	18.94 (2.35–31.48)	4	0.075 (0.45–0.53)	26	0.01
Creatinine kinase (units/L)	544 (390–889.5)	6	107 (65–291.3)	20	0.024
Creatinine kinase-MB (ng/mL)	52.45 (17.3–94.8)	6	8.3 (2.07–23.5)	15	0.036
C-reactive protein (mg/L)[c]	3.95 (1.95–10.23)	8	4.8 (1.9–9.8)	22	0.815
Evidence of viral infection[d]	4 (36%)	11	10 (26%)	39	0.484
Echocardiography					
> Mild right atrial enlargement	2 (16%)	12	6 (13%)	46	0.746
> Mild left atrial enlargement	5 (42%)	12	28 (60%)	46	0.232
Left ventricular hypertrophy	0 (0%)	12	1 (2%)	46	0.606
Left ventricular dilation	7 (58%)	12	43 (93%)	46	0.002
> Mild mitral regurgitation	4 (33%)	12	30 (65%)	46	0.046
> Mild tricuspid regurgitation	2 (16%)	12	15 (33%)	45	0.262
Segmental wall motion abnormalities	7 (58%)	12	6 (13%)	46	0.001
LV end diastolic dimension z-score	3.7 (2.5–4.2)	7	5.16 (3.98–7)	32	0.031
Left ventricular fractional shortening (%)	14 (13–28.4)	7	10.7 (7.09–14)	40	0.011
Left ventricular ejection fraction (%)	26.5 (19.95–38.45)	10	18.6 (14.8–26.5)	35	0.026
> Trivial pericardial effusion	2 (16%)	12	5 (11%)	45	0.602
Catheterization					
Fick cardiac index (L/min/m^2)	2.83 (1.83–4.70)	5	3 (2.4–3.85)	28	0.88
Thermodilution cardiac index (L/min/m^2)	2.66 (1.47–3.46)	6	2.85 (2.4–3.7)	35	0.417
Right atrial pressure, mean (mmHg)	11 (7–15)	10	7 (4–12.75)	40	0.174
Pulmonary capillary wedge pressure, mean (mmHg)	17 (14.25–21)	8	17 (11–24)	39	0.843
Left ventricular end diastolic pressure (mmHg)	18 (17–23)	7	17 (11–28)	38	0.521
Systemic vascular resistance (wu m^2)	19.52 (13.56–27.11)	6	18.15 (14–22.63)	34	0.545
Pulmonary vascular resistance (wu m^2)	2.31 (0.89–3.84)	6	2.86 (1.93–4.06)	40	0.353

Data expressed as N (%) for categorical variables and median (IQR) for continuous variables

p-values from the Wilcoxon rank sum test for continuous variables and the Chi-square test for categorical variables

[a]Constitutional symptoms defined as malaise, lethargy, decreased appetite, pallor

[b]Cardiac symptoms defined as chest pain, palpitations, syncope, exercise intolerance, diaphoresis

[c]Routine CRP, not high-sensitivity CRP

[d]Viral infections detected on respiratory viral panel, viral culture, serology, or serum PCR

between groups. Due to the limited number of patients, a multivariable analysis could not be performed.

Discussion

Our analysis demonstrates that there are notable differences between patients with myocarditis and idiopathic DCM that can be detected non-invasively without the need for EMB. No single variable allows precise discrimination between these diagnoses. However, development of a predictive model combining clinical, laboratory, and echocardiographic features may prove clinically useful to distinguish myocarditis from idiopathic DCM, but was not feasible given the limited number of patients included in our analysis.

Similar to studies published by Soongswang et al. [14, 15], our analysis demonstrates the potential utility of cardiac enzyme testing to differentiate myocarditis from other forms of DCM. While cardiac enzyme elevation can be found in patients with idiopathic DCM, more significant elevation is associated with a diagnosis of myocarditis. Soonswang and colleagues suggested a troponin T cutoff of 0.052 ng/mL to diagnose myocarditis with a sensitivity of 71% and a specificity of 86% [14]. Our analysis cannot assess this cutoff given that troponin I is routinely used at our institution and troponin T values were unavailable for the majority of patients. Additionally, the limited number of patients in our analysis precludes our ability to define cutoff points for other cardiac enzymes.

Myocarditis is most often infectious in etiology [8, 18] and therefore we hypothesized that differences would be present in laboratory markers of inflammation including white blood cell count and C-reactive protein (routine CRP, not high-sensitivity CRP). Surprisingly, there was no significant difference in these values between patients with myocarditis and those with idiopathic DCM. Our study may have been underpowered to detect a difference, but it is also not uncommon for patients with idiopathic DCM to present following an infection that precipitates clinical deterioration, possibly impacting these results.

Both the myocarditis and idiopathic DCM groups demonstrated significant elevation of BNP. In fact, only 2 (both DCM) of 37 patients had BNP results in the normal range for the assay used at our institution (< 100 pg/mL). This suggests that BNP is likely not a reliable marker to distinguish myocarditis from idiopathic DCM. Instead, BNP may be more useful as a screening tool in symptomatic pediatric patients to identify DCM, and could be combined with other reported markers for DCM including hepatomegaly, cardiomegaly, and abnormal electrocardiogram findings [19].

In addition to laboratory markers, there are echocardiographic features that may help to differentiate between myocarditis and idiopathic DCM. Segmental wall motion

abnormalities were more common in patients with myocarditis, consistent with a prior report from Angelini et al. suggesting that acute myocarditis can mimic myocardial infarction [20]. In addition to this, patients with idiopathic DCM were more likely to have mitral valve regurgitation and a greater frequency and degree of LV dilation and depressed LV systolic function. These findings are likely secondary to the chronic nature of patients presenting with idiopathic DCM, while patients with myocarditis present more acutely when LV dilation and systolic function have demonstrated less significant changes from baseline.

Limitations

Our analysis has inherent limitations. The sample size was small, limiting our ability to conduct a robust multivariable analysis. There is also the potential for significant results arising from multiple comparisons. Given that only patients with tissue available for pathologic diagnosis were included, there is likely a selection bias, which may impact the generalizability of our results. The decisions regarding which patients to biopsy were clinician dependent, potentially impacting the findings of our analysis. Additionally, all included patients were symptomatic and admitted to the intensive care unit, limiting the generalizability of these data to asymptomatic patients or less severe cases. Given that only patients with pathological specimens were included, it is unknown how many patients with ventricular dysfunction of varying degrees were excluded due to the unavailability of tissue for histologic analysis. Cardiac MRI is becoming increasingly used in the diagnosis of myocarditis due to its ability to localize tissue injury increasing diagnostic accuracy [8]. Unfortunately, these data were not available in our cohort but may be the focus of future study. Lastly, given the retrospective nature of this study, some degree of missing data was unavoidable and data points were not assessed uniformly across all patients.

Conclusion

There are notable differences between patients with acute myocarditis and those with idiopathic DCM that can be detected non-invasively. It may be possible to develop a predictive multivariable model to aid in the differentiation of these diagnoses, potentially obviating the need for EMB in this high-risk patient group.

Compliance with Ethical Standards

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