Published in final edited form as:

Prog Pediatr Cardiol. 2011 August 1; 32(1): 15–18. doi:10.1016/j.ppedcard.2011.06.004.

Recent clinical and translational research on pediatric myocarditis

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Abstract

Myocarditis is one of the most common causes of a pediatric dilated cardiomyopathy phenotype. While pediatric myocarditis is generally associated with resolution of myocardial dysfunction, approximately 30% of pediatric myocarditis patients will die or undergo heart transplantation. Cardiac magnetic resonance imaging is increasingly being utilized as the primary diagnostic modality in adult myocarditis. Animal studies and adult experience suggest that autoimmunity may contribute to cardiac dysfunction in myocarditis. These adult findings have yet to be evaluated fully in children, but may have an impact on the diagnosis and treatment of pediatric myocarditis in the future. The recent availability of pediatric specific ventricular assist devices may offer the potential for long-term support to allow for a greater chance for myocardial recovery.

Keywords

Myocarditis; Cardiomyopathy; Autoimmunity; Dilated cardiomyopathy

Inflammatory cardiomyopathy, or myocarditis, has a wide range of presentations in the pediatric population varying from chest pain associated with EKG changes and elevations of cardiac enzymes imitating myocardial infarction; tachy- and brady-arrhythmias; congestive heart failure with a dilated cardiomyopathy phenotype; and sudden death even in asymptomatic athletes [1]. While myocarditis and dilated cardiomyopathies are considered distinct entities [2], myocarditis is felt to account for 30–35% of patients with dilated cardiomyopathy phenotypes in Australian [3] and North American [4] pediatric cardiomyopathy registries. Myocarditis accounts for 22% of new-onset left ventricular dysfunction in the United Kingdom [5]. Thus myocarditis is one of the most important causes of left ventricular dysfunction in infants, children, and adolescents.

1. Etiology

Viral infections are the most common cause of myocarditis in Western Europe and North America. Many of the viruses associated with common childhood viral infections have been

associated with myocarditis. Over the past two decades the viral genomes detected in myocardium have changed from enterovirus and adenovirus to parvovirus B-19 and human herpes virus-6 in a similar fashion in children and adults. Cytomegalovirus, Epstein–Barr virus, and other herpes viral infections may lead to myocarditis and co-infection with multiple viruses may occur. Inflammatory heart disease in adults has been documented to occur with bacterial, spirochetal, rickettsial, fungal, protozoal, and helminthic infections; toxic effects from drugs, hypersensitivity reactions, and in autoimmune and other systemic diseases [6,7].

2. Presentation, diagnosis, and outcome of myocarditis with a dilated cardiomyopathy phenotype

The classic presentation of myocarditis is the development of a nonischemic dilated cardiomyopathy a few weeks after a history compatible with a viral illness including fever, myalgias, respiratory, and/or gastrointestinal symptoms. Clinical scenarios [7], however, can vary from a rapid onset of symptoms with severe heart failure, termed fulminant myocarditis [8] to a time lapse of many months where endomyocardial biopsies show lymphocytic infiltration and/or presence viral genome in the myocardium. Myocarditis in children is generally felt to present more acutely and with more severe symptomatology compared to a slower, more indolent presentation often seen in adults. A recent [9] review of pediatric myocarditis admissions in 35 American academic children's hospitals found use of inotropic medications in over 40%, use of mechanical ventilation in 37.5%, and use of extracorporeal membrane oxygenators (ECMO) in 7.4%. Acute heart failure accompanied by serious arrhythmias in adults may indicate a patient has giant cell myocarditis, a relatively rare form of myocarditis characterized by giant cells on biopsy, and a progressive course which can be ameliorated with immunosuppressant medication. Giant cell myocarditis may occur in the pediatric population [10].

Echocardiography, especially in children, remains the primary modality for assessment of left ventricular structure and function. Fulminant myocarditis in adults has a characteristic echocardiographic picture of reduced systolic function, normal left ventricular dimensions, and increased septal thickness [11]. In 1986 a pathologic definition of myocarditis requiring inflammatory cellular infiltrate with and without associated myocyte necrosis (the "Dallas" criteria) was proposed [12] and subsequently utilized with evaluation of endomyocardial biopsies. Numerous recent reviews [6,13,14] in adult myocarditis concluded that the diagnosis of myocarditis should not be based on histologic findings alone due to inconsistencies with clinical and histologic features of myocarditis, variability in biopsy interpretation, and low sensitivity from sampling error. Biopsy diagnosis can be enhanced with inclusion of immunostains for cell specific markers for lymphocytes, macrophages, and human leukocyte antigen. Current recommendations from the American College of Cardiology Foundation/American Heart Association/ European Society of Cardiology [15] support a limited role for endomyocardial biopsy in the evaluation of myocarditis that include the clinical scenario of fulminant myocarditis and a clinical picture of heart failure and left ventricular dysfunction associated with ventricular arrhythmias and high-degree atrioventricular block suspicious of giant cell myocarditis. An eosinophilic infiltrate on biopsy can be associated with myocarditis from hypersensitivity.

Cardiac magnetic resonance imaging (MRI) is being used with increasing frequency in adults for noninvasive assessment for myocarditis [16]. Cardiac MRI can evaluate intracellular and interstitial edema, hyperemia, capillary leakage, necrosis, and fibrosis. A recent white paper written by the International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis identified three imaging criteria for cardiac MRI confirmation of myocarditis. When at least 2 of the criteria are positive, myocardial

inflammation can be predicted with a diagnostic accuracy of 78%; if only delayed, postgadolinium enhancement imaging is performed, the diagnostic accuracy decreases to 68% [17]. The published experience of cardiac magnetic resonance imaging for the diagnosis of myocarditis in children is limited.

It is well known that pediatric myocarditis patients with a dilated cardiomyopathy phenotype may experience a recovery of ventricular function. A recent [18] analysis of the Pediatric Cardiomyopathy Registry (PCMR) of 369 patients found that 3 years after presentation, approximately 10% of patients had died; 20% had undergone heart transplantation; and 60% had normal left ventricular structure and systolic function. Similar outcomes occurred whether the diagnosis was made clinically or by histologic evidence fulfilling the Dallas criteria. These outcomes were significantly better than outcomes for children with idiopathic dilated cardiomyopathy in the database. Fulminant myocarditis has been associated with a high likelihood of recovery in adults [8,11]. Pediatric myocarditis patients in the PCMR who exhibited the echocardiographic pattern associated with fulminant myocarditis (reduced left ventricular systolic function with normal chamber size) in adults also had a higher rate of recovery – nearly 80% at 3 years after presentation [18].

3. Myocarditis and autoimmunity

Most of the understanding of the pathophysiology of viral and/or inflammatory myocarditis is derived from animal models [19–29]. Direct myocardial injury from viral proteins may occur acutely. Viral infection stimulates an innate immune response where inflammatory mediators including cytokines, nitric oxide, toll-like receptors and complement are upregulated. An acquired immune response develops which involves T-cell mediated cellular immunity with cytokine production but also the development of autoantibodies to multiple myocardial proteins including cardiac myosin and the β -1 adrenergic receptor [30–32].

The implication from these studies is that myocardial injury and dysfunction initially occur from direct viral injury and a robust innate immune response that leads to an acquired immune response involving antigen-specific T cells and antibodies. In a majority of patients with myocarditis the pathogen is cleared with down-regulation of the immune system with resolution of myocardial injury and dysfunction. However in a minority (one-third) of patients, possibly from molecular mimicry of host myocardial protein antigens that resemble viral or microbial proteins, a chronic immune reaction may occur with and/or without viral persistence in the myocardium leading to chronic dilated cardiomyopathy [33].

Work from the laboratory of Cunningham and colleagues was presented at this conference that begins to link animal studies to human disease. Anti-cardiac myosin autoantibodies from human myocarditis and cardiomyopathy targeted sites in the S2 hinge region of human cardiac myosin. These data are supported by previous animal studies in the Lewis rat [19,20] in which a myocarditic cryptic T cell epitope of cardiac myosin was localized to S2-16 peptide, which contained a sequence identical for human and rat cardiac myosin. In addition, immunization with S2-16 induced myocarditis and high titered antibody against cardiac myosin and coxsackievirus B3 [34]. These data suggest a role for molecular mimicry in recognition of the virus and cardiac myosin as shown previously [35]. In the Lewis rat, human cardiac myosin peptide S2-16 activated lymphocytes reacted to S2-28 peptide, a dominant T cell epitope for cardiac myosin. Myocarditis was associated with upregulation of proinflammatory cytokines suggesting a Th1 mechanism for myocarditis in the rat. Both S2-16 and S2-28 peptides are located in the S2 hinge region of human cardiac myosin where a dominant antibody response is observed in human myocarditis and cardiomyopathy.

Human studies [36] have identified a new class of cross reactive autoantibodies against human cardiac myosin and the β -adrenergic receptor that induced PKA signaling that was abrogated by absorption with anti-human IgG. Antibody mediated cell signaling of PKA was blocked by antigen specific inhibition of the β -adrenergic receptor or cardiac myosin. In the rat model, cardiac myosin-reactive autoantibodies were able to bind to the surface of rat heart cells, induce cAMP-dependent protein kinase A (PKA) cell signaling through the β -adrenergic receptor. Based on passive antibody transfer studies, β -adrenergic receptor cell signaling might eventually lead to apoptosis in the myocardium [20]. Cross-reaction of anti-cardiac myosin antibody with the β -adrenergic receptor was demonstrated with monoclonal antibodies from rats with myocarditis [20].

Furthermore, human cardiac myosin (HCM) has been shown to act as a novel endogenous ligand to activate human toll-like receptors (TLR) 2 and 8 and to stimulate human monocytes to release proinflammatory cytokines IL-6 and IL-8 in particular [37]. Pathogenic epitopes of cardiac myosin, peptides S2-16 and S2-28, stimulated TLRs directly and activated human monocytes confirming the role for cardiac myosin in stimulation of the innate immune system. Our data suggest that cardiac myosin and its pathogenic T cell epitopes may link innate and adaptive immunity in a novel mechanism which could promote chronic inflammation in the myocardium.

In summary, these studies suggest cardiac myosin to be a major autoantigen in human autoimmune myocarditis stimulating both adaptive and innate immune mechanisms which may lead to chronic myocardial disease. Ongoing human studies in adults are investigating their role in early versus progressive disease or recovery.

4. Treatment

Early results in adult randomized trials in adult patients of immunosuppressant or immunomodulating therapy with myocarditis and idiopathic dilated cardiomyopathy were disappointing [6,7]. However recent studies have suggested that a subset of adults with inflammatory cardiomyopathy and evidence of immune activation may respond to such therapy with improvement in left ventricular function [38–40]. Small case series in children with myocarditis [41,42] have suggested similar beneficial effects, especially with the use of intravenous gamma globulin (IVIG) [43]. However in both the recent PCMR [18] and pediatric hospital [9] study of pediatric myocarditis, a beneficial effect of IVIG on outcomes could not be discerned.

Standard supportive therapy of left ventricular dysfunction is the most common therapy used in adult and pediatric myocarditis [6,7,9,18]. Such support can include standard heart failure drugs, mechanical ventilation, and short-term mechanical circulatory support with ECMO. In the past few years, the availability of long-term mechanical circulatory support for children with myocarditis and severe heart failure with pediatric ventricular assist devices, such as the Berlin Heart, offer the promise that more patients could be successfully bridged to heart transplantation or to eventual recovery of left ventricular function [44]. Worldwide experience with the Berlin Heart [45] has demonstrated that 24% of myocarditis patients placed on the device may be weaned from support compared to 8% weaned with a diagnosis of idiopathic cardiomyopathy.

5. Future directions

The studies presented at this NIH conference on pediatric cardiomyopathy underscored the substantial progress that has been made refining the etiology, diagnosis, and role of autoimmunity in adult inflammatory cardiomyopathy. While pediatric myocarditis most often causes a transient period of left ventricular dysfunction which resolves in time, current

outcome studies demonstrate this disease is associated with a 30% rate of death or heart transplantation within 3 years of diagnosis. It remains uncertain, however, what the similarities and differences are between myocarditis/inflammatory dilated cardiomyopathy observed in animals and adults compared to infants, children, and adolescents. Specific questions might include:

1. To what degree can evidence of autoimmunity be detected in pediatric myocarditis patients? When can it be detected within the course of the disease? Does immune activation or specific immune profiles exist in patients with continued disease and disappear with recovery? Can immunosuppression and/or immunomodulation therapy be applied in pediatric patients with evidence of autoimmunity and left ventricular dysfunction to improve their heart disease?
2. Can cardiac MRI findings correlate to the clinical presence of myocarditis in pediatric patients to offer a non-invasive means of diagnosis? How do cardiac MRI findings change over the course of pediatric disease? Can cardiac MRI assist in prognosis of outcome?
3. How can the potential of long-term mechanical ventricular assist affect the outcomes of pediatric myocarditis? Does it have the potential to allow for better chances of recovery and decrease the use heart transplantation or will it primarily allow more myocarditis patients to be bridged to transplant? What will be the therapeutic index for long-term mechanical support?

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