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Epidemiological and Outcomes Research in Children with Pediatric Cardiomyopathy: Discussions from the International Workshop on Primary and Idiopathic Cardiomyopathies in Children

Steven E. Lipshultz, MD and James D. Wilkinson, MD, MPH

Department of Pediatrics, Miller School of Medicine, University of Miami, Miami, FL

Abstract

This report summarizes the roundtable discussion held at the first International Workshop on Primary and Idiopathic Cardiomyopathies in Children which focused on future directions for research on the epidemiology, etiology and outcomes for children with cardiomyopathy. Areas identified as important for future research included: 1) developing a standardized approach to the assessment and follow-up of children with myocarditis; 2) investigating the epidemiology of sudden death in children with dilated cardiomyopathy; 3) identification of biomarkers to serve as surrogate endpoints for important clinical outcomes; 4) the continuation of observational studies like the National Heart, Lung, and Blood Institute-sponsored Pediatric Cardiomyopathy Registry; and 5) conducting randomized clinical trials of pharmacological and behavioral interventions. It was concluded that optimal research strategies should employ a multidisciplinary research team including pediatric cardiologists, epidemiologists, biostatisticians, geneticists, patient care staff and advocacy groups. Further, adequately powered clinical trials may be facilitated by the establishment of a pediatric cardiomyopathy clinical trials network.

Introduction

The first International Workshop on Primary and Idiopathic Cardiomyopathies in Children brought together cardiologists, geneticists, epidemiologists, and biostatisticians involved in pediatric cardiomyopathy research. As part of the conference, three roundtable discussions were held on potential directions for cardiomyopathy research in children. The goal of the roundtables was to review the state of the field, in this case epidemiological studies of children with cardiomyopathy, and then to propose important research areas for the next five years. This report summarizes the discussion focusing on future directions for research on the epidemiology, causes, and outcomes for children with cardiomyopathy.

Address for Correspondence: Steven E. Lipshultz, MD, Department of Pediatrics (D820), University of Miami School of Medicine, P.O. Box 016820, Miami, FL 33101, Telephone: 305 243-3993, Fax: 305 243-3990, E-mail: slipshultz@med.miami.edu. Express mail address: Department of Pediatrics, Miller School of Medicine at the University of Miami, Medical Campus-MCCD-D820, 1601 NW 12th Avenue, 9th Floor, Miami, FL 33136.

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Issues in Defining and Treating Myocarditis

Participants discussed several issues regarding myocarditis. First, standardizing approaches to assessing chronic viral infection of the myocardium was thought to be helpful. Some investigators questioned the use of the term *myocarditis* in patients with evidence of viral infection where there is no evidence of inflammation. Another important area for future research in children with myocarditis is investigating interactions of cardiotropic viruses with environmental factors, such as trace elements, which have been previously studied in adults.¹ Finally, more research is needed regarding the appropriate follow-up for children with “resolved” myocarditis whose cardiac function has returned to normal.

Participants discussed an analogous situation in children who developed cardiomyopathy after receiving doxorubicin as part of cancer treatment.² Good cardiac function 5 years after therapy was thought to indicate complete reversibility of cardiotoxicity. However, longer follow up has revealed marked decreases in left ventricular contractility and mass beginning 8 to 10 years after the original chemotherapy. As already recommended for childhood cancer survivors exposed to cardio-toxic therapies, longer follow-up of children with viral myocardial disease would help identify the optimal follow-up schedule, as well as the implications of long-term treatment with medications, such as angiotensin converting enzyme inhibitors.³

The Risk and Treatment of Sudden Death in Dilated Cardiomyopathy

Another area identified as a priority for research was sudden death in patients with dilated cardiomyopathy. Participants believed the data were inadequate to stratify these children by risk for therapies such as automatic implantable cardiac defibrillators.

A recent report found that the combination of peak V02 and microvolt T-wave alternans was a significant predictor of major cardiac events in adults with nonischemic cardiomyopathy.⁴ Such testing is probably underused in children, and valid data regarding the timing and frequency of testing is lacking. Finally, the group agreed that the indications for implanting automatic defibrillators in children with dilated cardiomyopathy are not standardized or particularly evidence-based. One discussant noted that recommendations for the use of automatic defibrillators in adults with idiopathic dilated cardiomyopathy were imminent and that it was important to have studies in children because many recommendations for therapies in adults may or may not be appropriate for children. Finally, many decisions regarding prognosis and treatment are based on echocardiographic data. The variability in interpretation of these studies across centers was identified as a concern. A central echocardiogram reading facility for multi-center studies was considered to be ideal but resource intensive. The validity and appropriateness of using individual center-based echocardiographic studies as surrogate endpoints or outcome predictors for children with cardiomyopathy was considered an important issue requiring further investigation.

The Need for Validated Surrogate Endpoints

Validation of biomarkers against clinically important endpoints was identified by the discussants as another priority. Increasingly, the Food and Drug Administration has emphasized the use of biomarkers in clinical trials. Because many children do not reach endpoints such as death or transplant during most drug trials, surrogate endpoints likely to occur during the duration of a clinical trial would be invaluable. Any such endpoints must be validated against the more typical clinical endpoints of death or transplant.

The Success of the Pediatric Cardiomyopathy Registry

The Pediatric Cardiomyopathy Registry is the largest database of children with primary or idiopathic cardiomyopathy. Funded by the National Heart, Lung, and Blood Institute for the past 13 years, it has detailed data on more than 3000 children with cardiomyopathy and the longest follow-up data of any pediatric cardiomyopathy database.^{5,6} Much of the epidemiological and outcomes knowledge about children with cardiomyopathy has come from studies of Registry data.

Continuing the Registry was considered a research priority because so many of the unanswered causal and clinical questions regarding cardiomyopathy require detailed, long-term follow-up that can best be provided by the Registry. Also, the recent merger of Registry data with data from the Pediatric Heart Transplant Study Group has, for the first time, given a more complete picture of the natural history of cardiomyopathy from diagnosis through both the pre- and post-transplant periods. Continuation of the Registry would allow for additional such data mergers giving a better picture of the long-term clinical course of these patients.

The Need for Longitudinal Observational Studies

Longitudinal observational studies are uniquely situated to answer certain epidemiological questions. Such studies are more robust than case-control or cross-sectional studies in establishing temporal associations between exposures and outcomes. The Pediatric Cardiomyopathy Registry is an excellent example of a large, longitudinal study. Such studies address pertinent issues such as disease incidence and the effect of both baseline and time-dependent covariates and environmental exposures on clinically important outcomes.

Unless specifically funded to do otherwise, most prospective studies use a short, finite enrollment period. Short enrollment periods create temporally homogeneous cohorts that decrease potential confounding when interpreting the association between patient characteristics and outcomes. However, a short enrollment period can be a limitation when addressing new research questions. For example, children with cardiomyopathy live in a dynamic, rapidly changing world. Specifically, psychotropic medications, particularly stimulants for Attention Deficit Hyperactivity Disorder, may have important effects on these children. Similarly, the explosion of childhood obesity in developed countries, accompanied by decreased physical activity and poorer dietary patterns, may adversely affect the natural history of heart disease in children.

To address the potential effect of these exposures on children with cardiomyopathy, we must either add new cohorts to existing observational studies or conduct new observational studies with ongoing enrollment periods, as does the Pediatric Cardiomyopathy Registry, to gather data on these environmental exposures. Likewise, to investigate the associations of proposed biomarkers with clinical endpoints, the biomarker must be measured at baseline (e.g. at diagnosis) and over the course of the illness. Once again, meeting this requirement involves either adding new cohorts to existing observational studies or conducting new longitudinal studies designed to study these associations.

The Difficulties of Conducting Randomized Trials in Rare Diseases

Randomized clinical trials continue to be the preferred study design for assessing the effect of interventions on diseases, including pediatric cardiomyopathy. However, few randomized trials have been conducted on children with cardiomyopathy. A recent example illustrates the challenge of conducting randomized trials on this condition. Shaddy et al., examined the effect of carvedilol on children with heart failure.⁷ Enrolling the required 161 patients involved 26 U.S medical centers and took 5 years (between 2000 and 2004). Patients were randomly

assigned to placebo or one of two carvedilol dosages. Neither dosage group had significant advantages over placebo. However, in a subgroup analysis, the investigators noted an apparent beneficial effect in children with a morphological systemic left ventricle compared to those with a systemic ventricle that was not a morphological left ventricle. Further, the lower-than-expected incidence of event rates reduced the expected statistical power of the study.

The uncertainty of these results exemplifies the challenges in conducting clinical trials on rare diseases. A larger sample may have addressed some of these issues but would have resulted in an even more prolonged and resource-intensive enrollment process. Also, more rigorous enrollment criteria (e.g. patients with systemic left ventricles only) may have resulted in significant findings but, once again, would have required a longer, and perhaps unreasonably so, patient accrual period.

In an editorial in the *New England Journal of Medicine*, Dr. Stephen Lagakos addressed the issues of conducting clinical trials in rare diseases.⁸ One approach is a crossover design in which patients are repeatedly assigned to intervention and control conditions over time. However, validity requires that the number of patients being treated be equal to the number who are receiving placebo during each treatment interval after randomization. He also observed that the endpoints in such trials should have a relatively short latency period to ensure that they are not attributed to the wrong treatment. Alternating exposures also limits the ability to identify long-term effects of study interventions. Finally, Lagakos questioned whether a clinical trial involving patients with a rare disease should be required to meet the usual standards of certainty before justifying changes in clinical practice. He concluded that when an adequately powered study cannot be completed in a reasonable time, it may be advisable to adopt (or not) a new treatment on the basis of results that are suggestive rather than definitive. This may include setting a less rigorous level of statistical significance (eg. $P < 0.10$). The argument for such an approach might be strengthened by offering the new treatment to all patients after the trial finishes and continuing to accrue safety and efficacy data. The author also discusses other strategies for conducting clinical trials for patients with rare diseases.

Successful Approaches to Studying Rare Diseases

An example of a successful approach to epidemiological studies of rare diseases is the NIH-sponsored Rare Diseases Clinical Research Network. The Network facilitates collaborations among clinical researchers for observational and interventional studies of rare diseases, such as urea cycle disorders or bone marrow failure diseases. The Network also facilitates research through funding opportunities, the development of standard protocols, institutional review board applications, patient tracking systems, and a centralized data coordinating center. The network also assists researchers in collaborating with patient advocacy groups to enhance awareness of clinical trials as well as to recruit and retain study patients.

Conclusion

The above highlights the need to be creative in approaching epidemiological studies for patients with rare diseases, such as pediatric cardiomyopathy. The optimal research strategy should employ a multidisciplinary research team of pediatric cardiologists, epidemiologists, biostatisticians, geneticists, patient care staff, and advocacy groups. As has previously been suggested for research in children with ventricular dysfunction from any cause,⁹ the successful conduct of adequately powered clinical trials may be facilitated by establishing a pediatric cardiomyopathy study network analogous to the successful Children's Oncology Group and Pediatric Heart Network.

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