Heart failure in children with cardiomyopathy. Which markers can be used to predict outcome?

Published: 26-08-2010
Last updated: 01-05-2024

Primary - to determine factors that predict outcome in children with symptomatic heart failure secondary to cardiomyopathy, in order to choose an optimal management strategy for these children. Secondary - to identify predictive factors that can be...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON39252

Source
ToetsingOnline

Brief title
Cardiomyopathy in children

Condition

- Heart failures
- Cardiac and vascular disorders congenital

Synonym
cardiomyopathy, heart muscle disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Stichting Hartendroom

Intervention

Keyword: cardiomyopathy, child, heart failure, outcome

Outcome measures

Primary outcome

o death, heart transplantation or institution of mechanical support of the

circulation

Secondary outcome

o listing for heart transplantation, hospitalization for worsening heart

failure, hospitalization for all causes

Study description

Background summary

Cardiomyopathy is an important cause of heart failure in children. The incidence of cardiomyopathy in infancy is high (8/100.000) as compared to older age groups (0.7/100.000). Dilated cardiomyopathy is the most common form and carries a high mortality and morbidity. After presentation, transplantation-free survival at 1 and 5 years is only 70% and 50%, respectively. Beyond infancy, cardiomyopathy is the most important indication for heart transplantation. A subset of children, however, will do clinically well for years or recover completely. Prognostic factors that reliably predict outcome at presentation or during follow-up are lacking]. The majority of children (*) with dilated cardiomyopathy have idiopathic disease, in the remainder neuromuscular disorders and myocarditis are most prevalent]. It has been suggested that prior myocarditis [8] and familial disease [9] each may account for * of idiopathic cases.
The pathogenic mechanisms underlying dilated cardiomyopathy share common features. In most genetic forms proteins are affected that somehow link the contractile apparatus to the sarcolemma and extracellular structures. In enteroviral myocarditis proteases disrupt dystrophin, a crucial protein linking the cytoskeleton to the sarcolemma. Similarly, in Duchenne (DMD) and Becker (BMD) muscular dystrophy, two common neuromuscular disorders, dystrophin is disrupted, causing skeletal muscle weakness and dilated cardiomyopathy in a very high percentage of affected individuals. Irrespective of the underlying initial insult causing cardiomyocyte dysfunction, compensatory neurohumoral

mechanisms are activated that, initially, maintain myocardial function, but ultimately are responsible for adverse myocardial remodelling and the development of overt heart failure]. Based on these concepts asymptomatic stages (A & B) of heart failure are recognized in subjects either having risk factors or asymptomatic myocardial dysfunction with a high risk to develop symptomatic heart failure (stages C & D). In the majority of children, the first presentation is with an episode of symptomatic heart failure. However, subjects with neuromuscular disorders generally can be recognized in the asymptomatic stage of heart failure. This may allow studying early markers of myocardial disease and subsequently designing strategies to modify the course of the disease by early intervention. DMD patients generally are diagnosed before the age of 6 years and develop dilated cardiomyopathy between the age of 10-16 yrs in the majority of cases]. Prognostic markers in asymptomatic DMD patients may be applicable to other forms of cardiomyopathy and thus may be relevant to a much broader group of children.

The treatment strategies for children with symptomatic heart failure and cardiomyopathy are, in general, similar to those recommended for adults with heart failure. They include ACE inhibitors (ACEI) and β-blockers, in addition to diuretics and digoxin. However, the efficacy of medical therapy in paediatric heart failure is poorly defined. The beneficial effects in children are based on small non-randomized and often non-controlled studies. These have suggested favourable effects of ACEI and of β-blockers in children with symptomatic heart failure and of ACEI in presymptomatic boys with DMD. However, in a recent randomized placebo-controlled trial the beneficial effect of carvedilol in children with heart failure could not, statistically, be demonstrated. The somewhat disappointing result of this study reflects the difficulties to overcome in such studies in children. These include, amongst others, the ability to attain sufficient statistical power, the heterogeneity of underlying heart disease in children included in such studies, the lack of meaningful endpoints and the uncertainty of adequate drug dosing in children.

A number of studies have analyzed outcome parameters in children with heart failure. Collectively, these studies have demonstrated that signs of congestive heart failure at presentation, poor ventricular function and older age are related to an unfavourable outcome. Furthermore, the outcome in children with idiopathic disease and neuromuscular disorders is uniformly poor. However, these factors lack sufficient predictive power in individual patients.

What might be useful predictors to assess the outcome in children with heart failure, based on what we know from adult and paediatric studies?

In many instances subtle changes in clinical condition herald the onset of deterioration in these children, but these are often difficult to quantify. Furthermore, longitudinal assessment of parameters within children may contain important prognostic information. We are not aware of studies that have systematically and prospectively analyzed a broad range of such parameters. Scoring systems to objectify the clinical condition of children may be useful in the longitudinal follow-up. Functional class scoring systems, the paediatric equivalents of the NYHA classification, have mainly been used in patients with congenital heart disease. Similarly, health related quality of life, may reveal

information about the clinical condition, but has hardly been measured in children with heart failure and cardiomyopathy.
Growth failure in children with chronic illnesses is a common problem and, in general, a marker of poor outcome. In children with heart failure secondary to congenital heart disease growth failure has been well documented, but in heart failure secondary to cardiomyopathy almost no data are available on the incidence, the prognostic significance and the outcome. Recently, a single-centre retrospective review revealed that * of the patients on the waiting list for heart transplantation were wasted. Despite the lack of information, growth failure in children attributable to heart failure (stage C) has been accepted as a class I indication for heart transplantation.
Echocardiography has been one of the cornerstones for the diagnosis and follow-up of children with heart failure. Severely depressed LV function at presentation and during follow-up carries a poor prognosis. Only few studies have evaluated newer echocardiographic techniques in children. One study revealed that a decreased diastolic and systolic function of the RV, measured by pulse wave TDI, was related to an unfavorable outcome. In another study, using 3D echocardiography, dyssynchrony was found to be common but unrelated to outcome. In asymptomatic boys with DMD diastolic dysfunction has been found and its severity correlates with the onset of systolic dysfunction.
MRI has been used to a limited extent in adults with cardiomyopathy. In adults with non-ischemic cardiomyopathy positive late enhancement was found to convey a higher risk of adverse events and to predict a diminished response to β-blocker therapy. In patients with DMD progressive abnormalities in strain and fibrosis have been demonstrated as the disease progresses from the asymptomatic to the symptomatic stage. MRI has hardly been systematically employed in paediatric heart failure, but it conveys potentially important anatomical and functional information.
In adults, the determination of oxygen uptake at peak exercise level (VO2max) has been a very important prognostic marker and a cornerstone in selecting candidates for heart transplantation. Recent studies, however, have suggested that the addition of β-blockers might favour medical therapy over transplantation in subgroups of patients. Notably, for the translation of these results to younger subjects, it has been demonstrated that a cut-off level of VO2max < 50% of predicted would yield similar results in adults. Although formal data in children are lacking a VO2max < 50% of predicted has been accepted as a class I indication for transplantation in children with stage C heart failure. Exercise testing in (young) children may be challenging, especially obtaining VO2max. In younger children, as of 6-7 years of age, performing a 6-minute walk test is generally possible. Reference data in children have recently be obtained. Furthermore, the 6-minute walk test has been used as a follow-up tool in various cardiovascular disease states in both children and adults, including pulmonary hypertension and congenital heart disease. In general, follow-up measurements were found to correlate with clinical condition as well as with VO2max. Thus, the 6-minute walk test may be a useful follow-up tool in children with heart failure and cardiomyopathy.
Neurohumoral axis activation is a prominent feature in heart failure. In recent

years, numerous studies in adults with heart failure have demonstrated the diagnostic and predictive value of natriuretic peptides. BNP and NT-proBNP levels have been found to correlate closely. In adults increased BNP levels predict a higher risk of adverse cardiovascular events and longitudinal alterations in BNP levels have been related to outcome. Interventional strategies aiming at a decrease in BNP have also resulted in improved outcome. In children, BNP is increased immediately after birth and rapidly drops of to levels at or slightly above those in older children and adults]. BNP levels are increased in children with heart disease and are higher in LV systolic dysfunction than in congenital heart disease. In children with LV dysfunction elevated BNP levels were found to predict adverse cardiovascular events. These results suggest that longitudinal assessment of (NT-pro)BNP may be a sensitive predictor of outcome in children.
Central sleep apnoea/hypoventilation has been well documented in adults with systolic heart failure, but not in children. Recently, we found this phenomenon in children with severe heart failure (see pilot results), but the incidence and the prognostic significance is unclear.
In summary, heart failure in children secondary to cardiomyopathy carries a poor prognosis. The paradigms used to treat these children have been obtained from insights obtained in adults, but to a large extent have not been tested in children. We propose to study systematically and prospectively a set of potential prognostic markers that will allow better selection of patients for various treatment strategies and that may serve as surrogate markers in future therapeutical trials.
We hypothesize that longitudinal, in-depth, follow of children after presentation with symptomatic heart failure will reveal markers that predict (adverse) outcome. We speculate that alterations within patients during follow-up may provide sensitive prognostic markers. In this part of the study we will address questions arising in children that have developed signs of heart failure.

Study objective

Primary - to determine factors that predict outcome in children with symptomatic heart failure secondary to cardiomyopathy, in order to choose an optimal management strategy for these children.
Secondary - to identify predictive factors that can be used as surrogate markers in future outcome research.

Study design

multi-center, prospective, longitudinal, observational study in children with symptoms of heart failure secondary to cardiomyopathy

Study burden and risks

The risk of participating in this study is nil, especially in relation to the "natural history" of the disease with an transplantation-free survival of 70 and 50% respectively afer 1 and 5 years after presentation.
The burden of participating is low as all data will be collected at time points that coincide with normal follow-up in the vast majority of participating patients. Furthermore most data that are collected belong to the routine follow-up for these patients. There is no short-term benefit for participating patients, the long-term benefit may include the potential for improvement of clinical care.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Children with dilated cardiomyopathy

Exclusion criteria

inabilty to cooperate with the study protocol (i.e mental retardation)
For specific procedures within the protocol general accepted contra-indications may apply. Specifiically, for MRI the presence of MRI incompatible materials in the body and for the application of contrast because of renal impairment.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-10-2010
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO

Date:	26-08-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	12-04-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	NL30649.078.10
CCMO	NL32651.078.10