Pediatric Cardiomyopathies

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Pediatric inherited cardiomyopathies (CMPs) and channelopathies (CNPs) remain important causes of death in this population, therefore, there is a need for prompt diagnosis and tailored treatment. Conventional evaluation fails to establish the diagnosis of pediatric CMPs and CNPs in a significant proportion, prompting further, more complex testing to make a diagnosis that could influence the implementation of lifesaving strategies. Genetic testing in CMPs and CNPs may help unveil the underlying cause, but needs to be carried out with caution given the lack of uniform recommendations in guidelines about the precise time to start the genetic evaluation or the type of targeted testing or whole-genome sequencing. A very diverse etiology and the scarce number of randomized studies of pediatric CMPs and CNPs make genetic testing of these maladies far more particular than their adult counterpart. The genetic diagnosis is even more puzzling if the psychological impact point of view is taken into account. This review aims to put together different perspectives, state-of-the art recommendations—synthetizing the major indications from European and American guidelines—and psychosocial outlooks to construct a comprehensive genetic assessment of pediatric CMPs and CNPs.

Keywords: pediatrics ; cardiomyopathies ; channelopathies ; genetic testing ; psychological impact

1. Introduction

Inherited cardiomyopathies (CMPs) and channelopathies (CNPs) are cardiac disorders with a very heterogenous presentation, following a complex continuum from genetic mutations to clinical manifestations. Genetic testing may allow early detection of CMPs and CNPs with the implementation of lifesaving strategies when genetic testing is performed. Pediatric CMPs and CNPs, although rare, represent a serious condition, remaining a leading cause of death in children. CMPs are rare in the pediatric population with a prevalence of 1–2/100.000 [1]. Although pediatric and adult CMPs share the same morphological characteristics, the cause, evolution and outcome are largely different. What is particular in CMPs developed at pediatric age is the high likelihood of an underlying metabolic or mitochondrial cause. The genetic mutations involved in pediatric CMPs are extremely heterogenous as these can be due to inborn metabolic disorders or neuromuscular or genetic syndromic conditions. Thus, the genetic testing in pediatric subjects is difficult due to the comprehensive panel of genes to be included, as the CMP can be only one manifestation of the disease, not entirely displayed due to early age, as well as due to the scarce data. Moreover, the difficulty also comes from the fact that most of the data and literature concentrated on the pediatric counterpart. The exact timing for genetic testing in pediatric patients with CMPs is not known since there have been no prospective, large-scale studies due the difficulty to assure in this population all ethical principles such as autonomy, beneficence, non-maleficence and justice. In the American Heart Failure Society (HFS)[2] there is the recommendation to have a genetic analysis for all affected family members as soon as the diagnosis is made, with the possibility of re-testing especially in those CMPs, such as DCM where new rapid panels of genes expand constantly, with the remark that evaluation of infants and children with CMPs and CNPs needs referral to highly specialized centers. Pediatric CMPs have been classified, based on morphology, into five categories: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic cardiomyopathy (ACM) and left ventricular non-compaction (LVNC). Each of this CMP has unique particularities influencing the time and importance of genetic testing.

2. Genetic Testing

CNPs' genetic testing recommendations have been published in 2011 by Ackerman et al. in a consensus document on behalf of HRS and EHRA and reaffirmed in 2018 [3]. In this guideline it is clearly stated that the age for genetic testing is disease dependent. For diseases such as long QT syndrome (LQTS) and cathecolaminergic polymorphic ventricular tachycardia (CPVT) were preventive measures exist for genotype positive individuals, the test should be done independent of age, in infancy as available. For other conditions, monitoring the onset of symptoms is recommended rather than discovering a genotype positive-phenotype negative for a disease that may never develop or may develop lately. The exact time for genetic screening must be rigorously discussed with the family. The diagnostic criteria and

management recommendations for patients with hereditary arrhythmic syndromes have initially been proposed by a consensus by HRS/EHRA/APHRS in 2013 and have been revised through the ESC guidelines for prevention of SCD in 2015. In the AHA/ACC/HRS guideline for the management of patients with ventricular arrhythmias and prevention of SCD, patients younger than 40 years of age without structural heart disease, but who experienced unexplained cardiac arrest, recurrent syncope during exertion or unexplained near drowning, genetic testing is seen as important as it may detect an arrhythmia syndrome as aetiology of the aforementioned events. The main CNPs associated with SCD are: LQTS, Brugada syndrome, CPVT and short QT syndrome.

While genetic testing is increasingly incorporated into the management of subjects with CMPs and CNPs, little is known about its psychological impact, aspect highlighting the importance of adequate genetic counselling. Some studies investigated the impact on the patients' quality of life (QoL) undertaking a cardio-genetic test and showed that such an investigation did not influence the health-related QoL on long and short [4], but larger cohorts of patients need to be conducted to have a more comprehensive understanding of the psychological impact of genetic testing.

References

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