Viewpoint

Genetic Counseling and Pedigree in Cardiomyopathies – the Role of the Clinical Geneticist

Diane Xavier de Ávila,[1,2] *Frank Nunes,*[3] *Raquel Germer,*[2] *Ana Flávia Malheiros Torbey*[2]

Complexo Hospitalar de Niterói,[1] *Niterói, RJ – Brazil*
Universidade Federal Fluminense,[2] *Niterói, RJ – Brazil*
Hospital César Leite,[3] *Manhuaçu, MG – Brazil*

Introduction

Twenty years ago, the Human Genome Project made history by announcing the sequencing of 92% of the human genome through the development of modern genetic sequencing techniques. In 2022, the complete sequencing of human DNA was announced. This knowledge made it possible to better understand how genetics influences the functioning of the human body and, at the same time, facilitated the identification of genetic variants that can cause diseases.

In the field of cardiology, genetic study assists the assessment of aortopathy, familial hypercholesterolemia, channelopathies, and especially cardiomyopathies.[1]

Genetic cardiomyopathies

The main phenotypic presentations of a genetic cardiomyopathy are hypertrophic, dilated, restrictive, arrhythmogenic, and noncompaction.[2] The majority have a Mendelian autosomal dominant inheritance pattern with variable expressivity and penetrance, which are often influenced by environmental factors. However, autosomal recessive, mitochondrial, and X-linked diseases may also occur.

When evaluating a patient with suspected genetic cardiomyopathy, the first step is to exclude other etiologies, such as ischemic, hypertensive, valvular, congenital malformation, infectious, or related to medications such as anthracyclines.[3] Factors such as early age at presentation, severe cardiomyopathy with no apparent etiological explanation, low voltage on the electrocardiogram, positive family history for cardiomyopathy, and extracardiac manifestations such as skeletal neuromuscular disease and dysautonomia are warning signs for possible genetic cardiomyopathy.[3-6]

Currently, due to the easy of access to next-generation sequencing (NGS) panels for the diagnosis of cardiomyopathies, in addition to their advantages, it has become attractive for cardiologists to request these tests. Collaboration with a geneticist is essential for these interpretations, in addition to other specialties in the systemic follow-up of patients with genetic disease, providing guidance for appropriate treatment, further sources of clinical research, and gene therapies (Figure 1). However, when requested, it is fundamental that the possible results are explained, in addition to the consequences for the family. This takes place during genetic counseling, with a qualified professional. Depending on the patient's clinical presentation, such as the presence of dysmorphisms and systemic alterations, other tests may be necessary, such as karyotyping and exome sequencing.[7] The advantages and limitations of genetic testing are displayed in Figure 2. The interpretation of the genetic test result may need to be revised by the geneticist, due to a relatively low positivity rates, namely, 30% to 50% in cases of hypertrophic cardiomyopathy, 20% to 30% in dilated cardiomyopathy, and 50% in arrhythmogenic right ventricular cardiomyopathy, in addition to the high rate of variants of uncertain significance (VUS), which may influence correct diagnosis.[3-5]

Genetic counseling

Genetic counseling is a necessary process to assist patients in understanding and adapting to the medical and psychological implications and genetic contributions of certain diseases. It is fundamental to integrate personal and family medical history in order to assess the chance of occurrence or recurrence of a disease, patterns of inheritance, management of genetic tests, prevention of pathologies, and promotion of choices and adaptation to the risk or condition.

Training of professionals for genetic counseling is necessary for adequate support to individuals and their families. All patients with hereditary cardiomyopathy should be consulted by a medical geneticist for guidance. Not all detected genetic variants are clinically significant, and caution should be exercised in their interpretation.

Genetic counseling involves the following aspects:

1. Collection of personal and family medical history to construct the pedigree.

2. Before the genetic test, it is essential to choose the appropriate type of test and explain the family members who will be involved and the possible results, including positive, negative, and uncertain (VUS), for guidance on diagnostic limitations.

Keywords

Genetic Testing; Genetics; Genetic Counseling; Cardiomyopathies.

Mailing Address: Diane Xavier de Ávila •
Complexo Hospitalar de Niterói - Rua La Salle,12. Postal Code 24020-096, Niterói, RJ - Brazil
E-mail: dianeavilamed@gmail.com, dianeavilamed@cardiol.br
Mansucript received April 09, 2023, revised manuscript April 14, 2023, accepted April 14, 2023

DOI: https://doi.org/10.36660/abchf.20230023

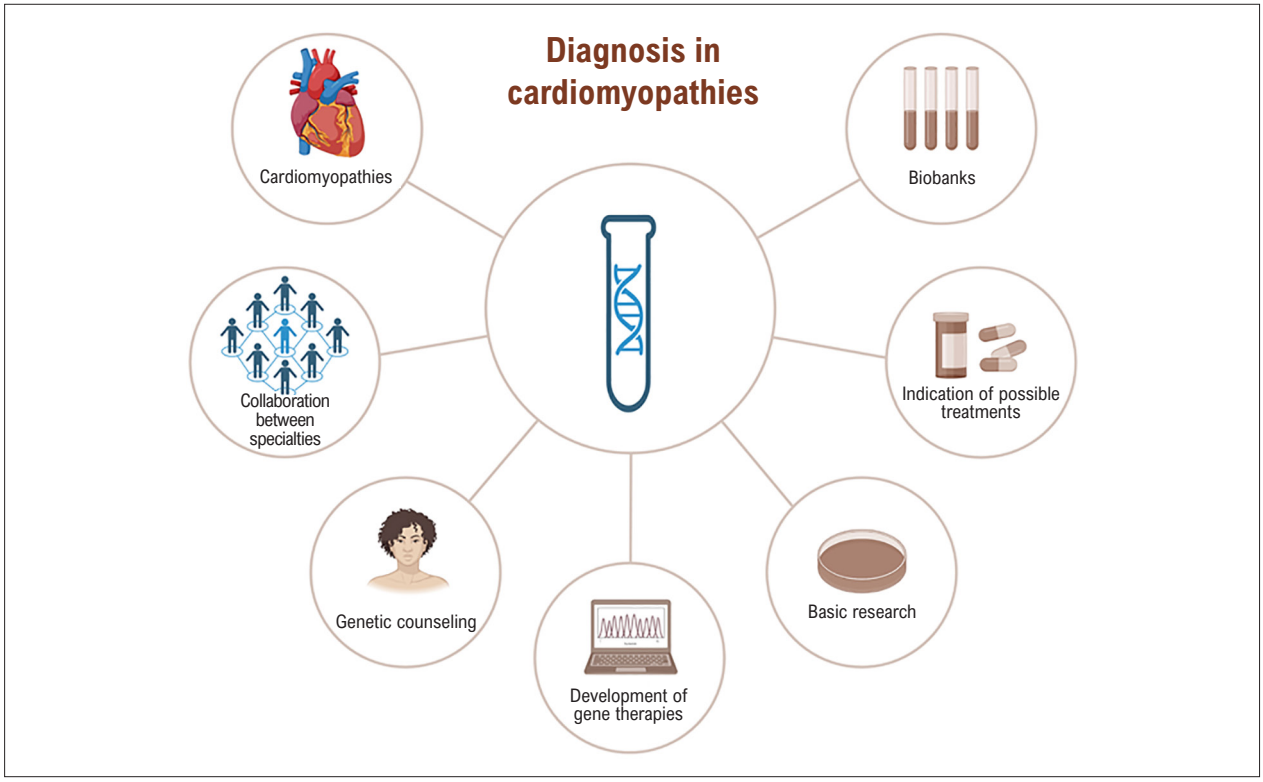

Figure 1 – *Implications of genetic testing.*

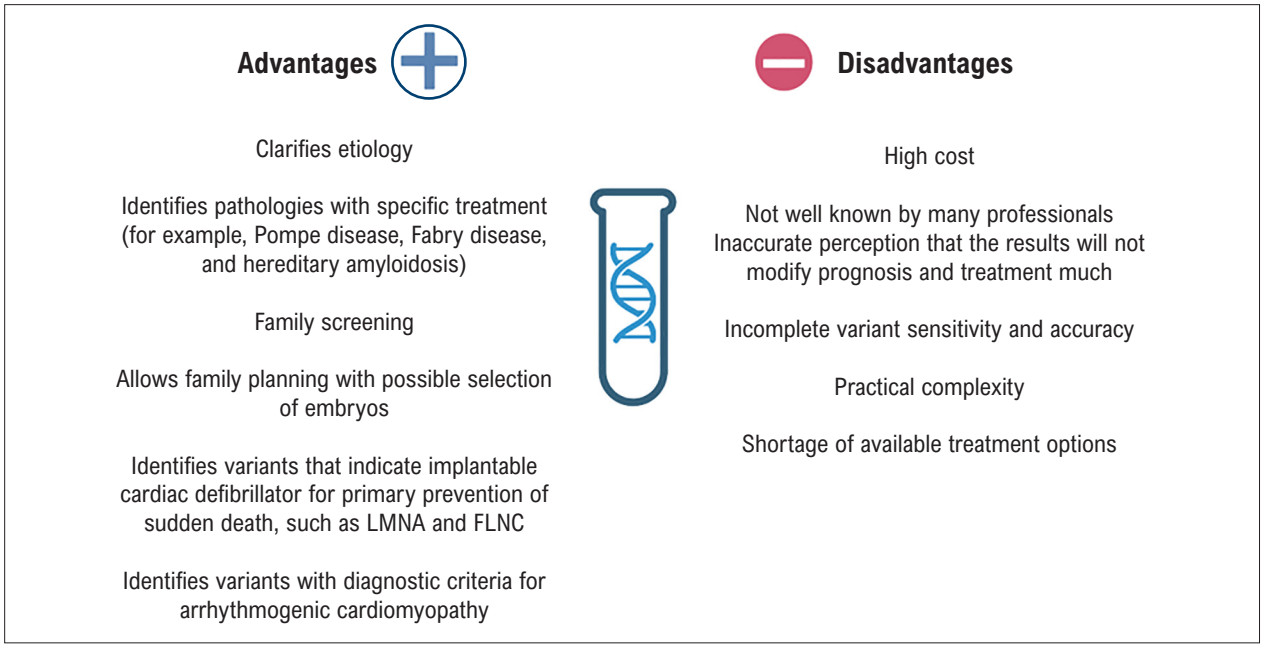

Figure 2 – *Advantages and limitations of genetic testing.*

3. After the genetic test, guidance on test results, risk estimation, communication, and support for the patient and the family members involved.

It is important to emphasize the basic principles of genetic counseling. The priority is for patients to maintain their autonomy in decision making, even though the name "counseling" might suggest giving advice. The consultation should always be non-directive, that is, without standard protocols.[8] It is also essential to maintain patients' right to privacy, even among their family members, regarding

the results obtained from molecular tests, which can often create conflicts.

The importance of a pedigree

The patient must undergo a detailed family history of at least three generations, with the construction of a pedigree every time a cardiomyopathy is identified in any of the phenotypes (level of evidence A).[9] This takes place during the consultation with the clinical geneticist, but cardiologists should become familiar with this preparation.

The pedigree makes it possible to observe the pattern of inheritance, whether autosomal dominant, recessive, or X-linked and, thus, identify which individuals are at risk of developing the disease and should undergo clinical investigation in search of the phenotype, in addition to family genetic screening. This approach is important, given that even asymptomatic individuals can develop cardiomyopathy, and, in some cases, the first symptom can be ventricular arrhythmias with a risk of sudden death.[7,10]

The pedigree in Figure 3 provides an example of a family where there is possibly an autosomal dominant disease, with a high risk of sudden death, making genetic investigation mandatory. This begins with the patient with symptoms, and, after the positive result, the indication to investigate first-degree relatives is evaluated, in the case below, the patient's brother.

Conclusion

With recent advances in cardiogenetics, clinical geneticists participate in the management of patients with cardiomyopathies, collaborating directly with cardiologists. It is important for cardiologists to become accustomed to constructing pedigrees, and it is essential for genetic counseling to be carried out by a medical geneticist before requesting tests. Properly conducted genetic counseling and pedigree can determine early treatment and, consequently, better outcomes for each family.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Ávila DX, Nunes F, Germer R, Torbey AFM.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

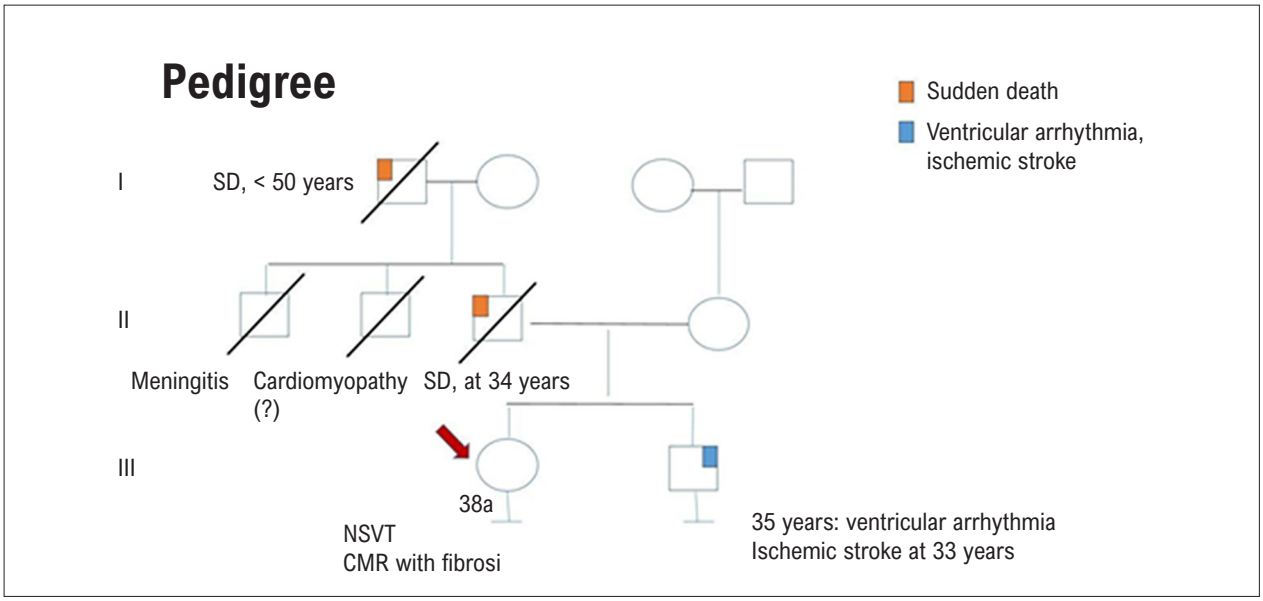

Figure 3 – *Pedigree of 38-year-old patient X (arrow) who underwent the panel for cardiomyopathies in general. A heterozygous variant in the filamin C (FLNC) gene was detected. She complained of palpitation with non-sustained ventricular tachycardia documented on 24-hour Holter and resting cardiac magnetic resonance imaging, with extensive foci of delayed enhancement with diffuse mesocardial and subepicardial distribution, compatible with non-ischemic fibrosis. As important family history, her father died suddenly at 34 years of age and her grandfather at age 50. In addition, her brother had similar complaints. CMR: cardiac magnetic resonance imaging; NSVT: non-sustained ventricular tachycardia; SD: sudden death.*

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