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MINI-FOCUS ISSUE ON CARDIOMYOPATHIES AND GENETIC COUNSELING

VIEWPOINT: VOICES IN CARDIOLOGY

Genetic Counseling in Inherited Cardiomyopathies

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Significant advances in genetic testing have provided new opportunities for cardiologists to identify and understand the genetic basis of inherited cardiomyopathies (CMPs). Over the past 10 years, genetic testing has transitioned from research to the clinical arena and is routinely offered in CMP clinics to identify the genetic cause of disease (1). However, this testing also has come with new challenges and responsibilities regarding the use of this information for patients with CMPs and their families.

GENETIC COUNSELING

Genetic counseling is "the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease" (2). All medical professionals, including cardiologists, who treat families with CMPs should have a good knowledge of molecular genetics of CMP and be trained in the principles of genetic counseling (1,3,4). The provision of care for CMP requires a multidisplinary team in which genetics providers play an essential role. Genetic counseling is an integral part of the management for all patients with CMPs and their family members, and specialized CMP centers increasingly have genetic counselors and/or clinical geneticists as a part of the team.

ROLE AND COMPONENTS OF GENETIC COUNSELING

PSYCHOLOGICAL ASPECTS. Communication of information can be carried out by any member of the team with necessary competencies. (**Figure 1**). However, genetic counselors are trained in the genetic basis and psychological impact of disease. At the time of genetic counseling, affected individuals and their families may be struggling with anxiety related to their recent diagnosis, uncertainty about therapy and their longevity, inheritance in other family members, or grief related to the sudden death of a loved one.

Many psychosocial issues should be addressed during counseling. Many feelings may be expressed, such as apprehension about idea of being "labeled" with this condition, guilt about passing on the gene to their children, and feelings related to the impact of the diagnosis on lifestyle, employment, and insurance.

MODE AND RISK OF INHERITANCE. Clinical assessment and family history with construction of a 3- to 4-generation family pedigree helps to confirm the genetic origin and mode of inheritance. In some instances, this may require collection of relatives' medical records or post-mortem reports. Establishing the mode of inheritance identifies relatives who are at risk of disease development. Most CMPs are typically inherited as an autosomal dominant trait as a result of a single gene defect capable of causing the trait (i.e., monogenic origin). Thus, there is a 50% risk for first-degree relatives to be affected by the same condition. Other modes of inheritance, such as autosomal recessive, X-linked recessive, or matrilinear inheritance, may be suspected or identified during assessment of the family history and pedigree. In some X-linked disorders such as Fabry disease, identification of the modes of inheritance may be challenging because female carriers may develop a milder phenotype later in life. In autosomal recessive CMP,

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the phenotype usually manifests by the time the patient is a teenager or a young adult. Genetic testing is recommended even in patients with no family history of CMP or sudden cardiac death because this may reflect a lack of robust family history, incomplete penetrance, or a de novo mutation in the proband.

Knowledge of the mode and risk of inheritability is essential to discuss and guide preconception counseling for family planning. Worsening of symptoms and potential maternal risk of cardiac complications during pregnancy may occur and should be discussed.

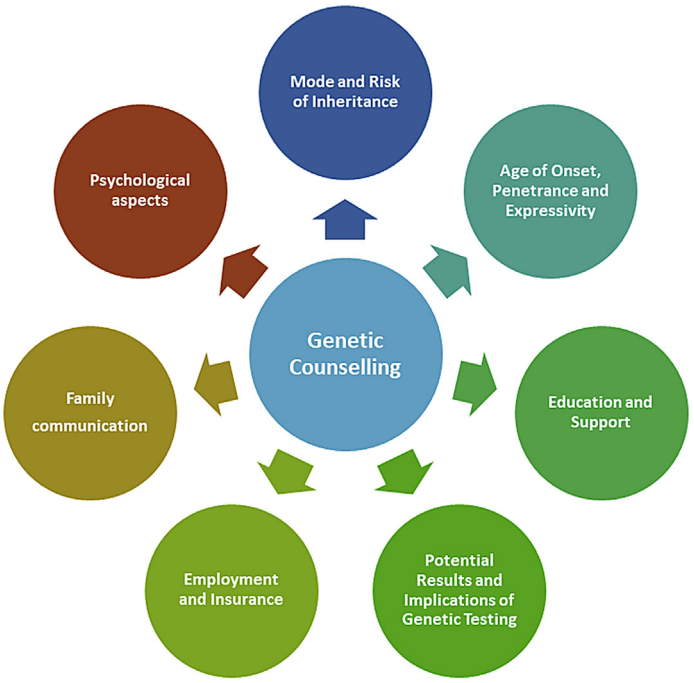
AGE OF ONSET, PENETRANCE, AND EXPRESSIVITY. The age of onset can also vary as a result of incomplete penetrance of the gene causing the mutation. This is commonly seen with autosomal dominant CMP. As a result, a case initially presumed to be sporadic may result from inheritance from a carrier, phenotype-negative, parent. In autosomal recessive CMP, the phenotype usually manifests by the time the patient is a teenager or a young adult.

Initially, the affected individual carrying the mutation may express no phenotype. This can continue for several years until teenage years or young adulthood, or it may persist lifelong. Genetic testing is sometimes able to identify this preclinical subset of mutation carriers. During the second stage of CMP, which may also last for several years, the cardiac phenotype manifests with no symptoms. After a period of clinical stability, symptoms develop, and complications may occur. This variability of phenotype expressivity suggests an interplay of additional genes and environmental factors that "awakens" the phenotype (5–7). Thus, the clinical phenotype can vary from 1 family member to another despite sharing the same genetic mutation. Interestingly, in arrhythmogenic right ventricular cardiomyopathy (ARVC), the phenotype usually shows clinical features as a teenager or young adult that worsen with strenuous exercise. A normal initial clinical assessment in a relative does not exclude the possibility that the phenotype may develop at a later in life. Periodic screening appointments should be offered.

EDUCATION AND SUPPORT. Information about the condition should be provided by the clinical team managing the patient. Clinicians should emphasize that the CMP team is the best setting for airing specific concerns related to their condition.

The provision of written booklets is encouraged for further education. Additional information can be found on the websites of the American Heart Association and the National Heart, Lung, and Blood Institute (8,9). Interaction with patient group forums, such as the Hypertrophic Cardiomyopathy Association (10), should be encouraged. The educational needs of the patient may change over time and should be revisited during consultations.

FIGURE 1 Components of Genetic Counseling



POTENTIAL RESULTS AND IMPLICATIONS OF GENETIC TESTING. The main role of genetic testing in a proband with an undeniable cardiomyopathy is the identification of the causative mutation for genetic screening to their family members. This process of predictive testing is of significant importance in CMP clinics. In ARVC, the identification of a pathogenic variant in ARVC-related genes is a major diagnostic criterion (11). In some situations, genetic testing may change the management (e.g., enzyme replacement therapy for Fabry disease and defibrillator implantation in dilated cardiomyopathy caused by a lamin A/C gene mutation) (3).

Genetic testing is often carried out using multigene panels. The composition of the panels will vary according to the CMP being tested for and from center to center. Chromosomal microarray can be used to evaluate deletions and duplications. Whole exome or whole genome analysis is also used in clinical practise.

Special considerations are in order when counseling children (12). Predictive testing in young children is not encouraged. The child often lacks the capability to comprehend the possible benefits, limitations, and implications of testing and to understand how this

would affect their future. Periodic clinical surveillance should be offered according to guideline recommendations. Testing should be deferred in childhood, and parents should be dissuaded from making decisions until the child is at least an adolescent or adult who can discuss and participate in decision making. In general, this genetic testing should not be carried out unless the child demonstrates a clear phenotype. However, if an older child or adolescent is distressed, or if the test results would have a major impact on life choices, then it may be considered.

If genetic testing is being considered, a thorough explanation of the potential results with benefits, uses, and limitations should also be discussed before genetic testing, to make an informed decision about whether to proceed with testing and obtain informed consent.

- Positive results: In most cases, a positive result does not affect the proband's medical management. Cascade genetic testing should be offered, with testing offered initially to first-degree relatives, to minimize unnecessary tests. Phenonegative genopositive individuals should be offered periodic clinical surveillance to detect the development of CMP.
- Inconclusive results: A variant of uncertain clinical significance (VUS) may be identified (i.e., unknown to be a disease causing or a normal variant). Although some VUSs may eventually be reclassified as pathogenic mutations, many VUSs may represent benign variations that are not disease-causing mutations. A VUS cannot be used to confirm or rule out an inherited condition (13). In these situations, co-segregation studies and follow-up testing of family members may reclassify the VUS as the causative or benign mutation.
- Negative results: A negative result for the proband means that a disease-causing mutation has not been identified. With advances in genetic technology, a pathogenic variant may be identified in the future, and broader genetic testing could be considered at a later date. In this setting, clinical screening and surveillance can still be offered to relatives. When a negative genetic test result is received from a relative of a proband with a known disease-causing mutation CMP, the individual can be discharged from surveillance, and their children are not at risk for the familial mutation.

Before testing, a thorough discussion ensures that the patient understands the provided information, and questions should be encouraged by the genetic counseling provider to address the potential implications of genetic testing. Once the results are available, a discussion should be conducted by genetic counselors/clinical geneticists and the patient. With improvements in technology and the identification of more pathogenic genes, the yield of mutation detection is improving; thus, repeat testing maybe offered in those patients with historical genetic results. Many years after a test has been conducted, repeat contact may be made to determine the need to reclassify an old result (e.g., downgrading from pathogenic to benign or upgrading from VUS to pathogenic). The pathogenicity of any identified variants should be established using the guidelines of the the American College of Medical Genetics and Genomics (14).

EMPLOYMENT AND INSURANCE. Some occupations, such as joining or continuing to work in the armed forces or police force or as an airline pilot, heavy goods truck driver, or professional athlete, carry restrictions in the setting of confirmed CMP. The diagnosis of CMP can result in paying higher premiums for insurance or mortgages following diagnosis. Phenonegative family members may hesitate when it comes to genetic testing because this may have an adverse social impact.

In November 2009, the Genetic Nondiscrimination Information Act (GINA) went into effect to prohibit employers and health insurance companies from bias against individuals on the basis of their genetic test results (15). However, this act does not cover discrimination that could be faced in schools, mortgage lending, or life insurance.

FAMILY COMMUNICATION. Ensuring that the patient comprehends the information given is very important to facilitate communication with the family. The patient is encouraged to inform family members about the inheritance risk and the possibility of clinical evaluation and/or genetic testing (cascade screening). Specific written information should be given to the patient to help relay this information to their relatives. Many factors can affect the dissemination of this information, such as family dynamics, distance, knowledge, and current health of the proband (16). Sometimes the proband expresses no wish to inform the family, and the usefulness of testing in this scenario needs to be reassessed.

CONCLUSIONS

Genetic counseling should be regarded as an essential component of managing CMP. It should be provided by health care professionals appropriately trained in genetic counseling for inherited cardiac conditions. Competent genetic counseling is key to providing the

necessary information and support for patients with CMPs to enable informed decision making and consent throughout all phases of management. This ensures that the expectations of management are met and the results are understood.

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REFERENCES

1. Hershberger RE, Givertz MM, Ho CY, et al. Genetic evaluation of cardiomyopathy-a Heart Failure Society of America practice guideline. J Card Fail 2018;24:281–302.

2. Resta R, Biesecker BB, Bennett RL, et al. A new definition of genetic counseling: National Society of Genetic Counselors' Task Force report. J Genet Couns 2006;15:77–83.

3. Charron P, Arad M, Arbustini E, et al. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2010;31:2715–26.

4. Mital S, Musunuru K, Garg V, et al. Enhancing literacy in cardiovascular genetics: a scientific statement from the American Heart Association. Circ Cardiovasc Genet 2016;9:448–67.

5. Pasipoularides A. Linking genes to cardiovascular diseases: gene action and gene-environment interactions. J Cardiovasc Transl Res 2015;8:506–27.

6. Day SM. Exercise in hypertrophic cardiomyopathy. J Cardiovasc Transl Res 2009;2:407–14.

7. Prior D, La Gerche A. Exercise and arrhythmogenic right ventricular cardiomyopathy. Heart Lung Circ 2019 Dec 26 [E-pub ahead of print].

8. National Heart, Lung, and Blood Institute. Available at: https://www.nhlbi.nih.gov. Accessed February 18, 2020.

9. American Heart Association. What is cardiomyopathy in adults?. Available at: https://www.heart.org/en/health-topics/cardiomyopathy/what-is-cardiomyopathy-in-adults. Accessed February 18, 2020.

10. Hypertrophic Cardiomyopathy Association. Available at: www.4hcm.org. Accessed February 18, 2020.

11. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533–41.

12. Botkin JR, Belmont JW, Berg JS, et al. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet 2015;97:6–21.

13. Morales A, Hershberger RE. Variants of uncertain significance: should we revisit how they are evaluated and disclosed? Circ Genom Precis Med 2018;11:e002169.

14. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–24.

15. Genetic Nondiscrimination Information Act (GINA) of 2008. Available at: https://www.genome.gov/24519851/genetic-information-nondiscrimination-act-of-2008. Accessed February 18, 2020.

16. Cirino AL, Seidman CE, Ho CY. Genetic testing and counseling for hypertrophic cardiomyopathy. Cardiol Clin 2019;37:35–43.

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