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Educational Case: Genetic Mutations and Multifactorial Inheritance: Dilated Cardiomyopathy

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

Keywords
pathology competencies, genetic mechanisms, developmental and functional abnormalities, mutations, cardiovascular, cardiomyopathy, dilated cardiomyopathy, disease mechanisms, genetic diseases, inherited diseases, organ system pathology

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Primary Objective

Objective GM1.1: Types of Mutations. Describe different types of mutations that can occur in human disease, and discuss how each of these can produce abnormalities in DNA transcription and/or alterations in the type or amount of protein produced.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Secondary Objectives

Objective GM1.5: Multifactorial Inheritance and Environmental Factors. Discuss and give examples of disorders associated with multifactorial inheritance and describe how environmental factors can interact with genetic factors to produce or modulate disease.

Competency 1: Disease Mechanisms and Processes; Topic GM: Genetic Mechanisms; Learning Goal 1: Genetic Mechanisms of Developmental and Functional Abnormalities.

Objective CH1.2: Cardiomyopathy. Compare and contrast the clinicopathologic features of dilated, restrictive, and hypertrophic cardiomyopathies.

Competency 2: Organ System Pathology; Topic CH: Cardiovascular—Heart; Learning Goal 1: Heart Failure

Patient Presentation

A 26-year-old male presents to the emergency department with complaints of a 5-month history of progressive dyspnea that became more severe over the past 6 days and prompts this evaluation. Medical history is significant for at least 6 upper respiratory infections over the past 2 years. Family history is significant for 4 cardiac-related deaths in ages between 24 and 38 years involving the 3 last generations of his family, as well as a 29-year-old paternal cousin with heart failure. There is no significant history of alcohol ingestion, toxin exposures, or

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illicit drug abuse. Physical examination discloses bilateral basal lung rales, displaced apical impulse to the left, systolic apical murmur, hepatomegaly of 6 cm below the right midclavicular line, and bilateral low extremity pitting edema extending to 5 cm above the ankles. Recorded vital signs are blood pressure = 105/65 mm Hg, Respiratory Rate = 28 per minute, Heart Rate = 138 per minute, and temperature = 98.9°F.

Diagnostic Findings

Echocardiogram shows marked cardiac enlargement, dilation of all chambers, 35% left ventricle ejection fraction, and left ventricle thrombi. Imaging studies show normal cardiac valves and patent coronary arteries. Laboratory studies reveal moderate B-natriuretic peptide elevations and mild troponin and liver enzyme elevations.

Questions/Discussion Points

What is Your Preliminary Diagnosis and Its Differential?

Dilated cardiomyopathy is the primary diagnosis, based on the clinical findings consistent with heart failure, cardiac enlargement of all chambers, imaging studies showing normal valves and patent coronaries, and functional studies describing decreased ejection fraction. The differential diagnosis based on the clinical findings includes other types of cardiomyopathy such as restrictive or hypertrophic, as well as multiple diseases included within the syndrome of dilated cardiomyopathy per se. Dilated cardiomyopathy can be further categorized as familial and inherited or as acquired. Acquired etiologies include myocarditis; toxins such as cocaine, amphetamines, or heavy metals; autoimmune; endocrine diseases such as hypothyroidism or hyperthyroidism; thiamine deficiency; and ischemic heart disease.[1,2]

What Clinical Considerations Should Follow a Diagnosis of Cardiomyopathy?

When suspecting a cardiomyopathy, the initial considerations are morphologic and functional, which help classify them as dilated, restrictive, hypertrophic, or one of the more unusual types of cardiomyopathy such as right ventricle arrhythmogenic or left ventricle noncompaction cardiomyopathy. Occasionally, these features may overlap or may not be fully developed, such as when you evaluate inherited genetic diseases early in their development.

The extent of organ involvement should be recorded. The manifestations may be limited to only the heart, but the disorder may affect other organs as well, such as skeletal muscle, kidneys or liver as part of the disease process, or may it affect other organs secondarily.

Constructing a pedigree tree may be very useful in determining the inheritance pattern. When evaluating the pedigree, it is possible that the information may be unknown or not investigated at the time of initial presentation. Genetics/familial considerations include autosomal dominant or recessive, X-linked, mitochondrial, or sporadic inheritance patterns which can easily be determined with the family history evaluation.[3]

Etiology of the cardiomyopathy should be investigated. This may include genetic, viral following a myocarditis, autoimmune, toxic, or unknown causes of cardiomyopathy.

The stage of heart failure at the time of presentation should be recorded using criteria of the American Heart Association or New York Heart Association.

What Pathophysiologic Mechanisms Are Involved in the Development of Dilated Cardiomyopathy?

Defects of force transmission, force generation, or calcium handling result in systolic dysfunction, cell death, and fibrosis, producing the dilated cardiomyopathy phenotype. Mutations involving δ-sarcoglycan may cause defects of force transmission; in a similar fashion, defects of force generation may be caused by mutations encoding for sarcomere proteins such as β-myosin.[4] Even in nonfamilial cases of cardiomyopathy, inherited genetic susceptibilities may determine how the cardiac muscle responds to environmental factors such as alcohol or viral myocarditis.

What Are the Inheritance Patterns of Dilated Cardiomyopathy? Can You Give Some Examples?

Approximately 30% to 48% of dilated cardiomyopathies are inherited or familial. Most of the inherited cases are autosomal dominant; but autosomal recessive and X-linked patterns have also been reported. Causative genes predominantly encode for sarcomere (ie, titin [TTN], actin, myosin, troponin) or cytoskeletal (ie, dystrophin, desmin, lamin) proteins. Dystrophin is the same protein involved in the X-linked Duchenne or Becker muscular dystrophies. Less commonly, an X-linked inheritance pattern may be identified in newborns and children as part of the Barth syndrome, which is caused by mutations of the gene tafazzin, which codes for an acyltransferase. Twenty percent of autosomal dominant, dilated cardiomyopathies identified genetically affect genes coding for TTN, a protein that provides structure, flexibility, stability, and chemical signals to the sarcomere.[5] These mutations result in an abnormally short TTN protein.[6] About 8% of all genetic dilated cardiomyopathy cases are caused by deletions or sequence variations of the LMNA gene that, when mutated or deleted, encode for an absent or abnormal lamin A/C protein. Most of these cases also have an associated atrioventricular block clinically, and in this circumstance, implantation of intracardiac defibrillator may be a consideration. Rare autosomal recessive cases result from mutations encoding for troponin I.

How Should You Proceed With the Genetic Evaluation of This Case?

Perform a careful pedigree analysis of all possible affected family members taking into consideration and annotating all possible involved cardiac and extracardiac clinical features. Inherited cardiomyopathies are phenotypically variable in regard to the age of presentation, expressivity, or disease

progression. Mixed forms that do not fit into a single traditional category have been described as several instances of dilated cardiomyopathy have been associated with an arrhythmogenic phenotype. Incomplete penetrance and variable expressivity warrant a high index of suspicion, particularly for first-degree relatives. You may consider genetic testing for first-degree family members, with the caveat that the yield may be much lower than in the cases of hypertrophic cardiomyopathy. The sensitivity of genetic sequencing panels for familial dilated cardiomyopathy cases is 25% but rises up to 40% if the cardiomyopathy coexists with conduction defects. A truncated TTN protein caused by TTN frameshift, nonsense, or splice mutations have been reported in approximately 25% of familial dilated cardiomyopathy cases. Titin encompasses 363 exons with an established role in muscle assembly and function. At present, there seems to be no clear correlation between genotype and phenotype probably because this large gene can undergo extensive alternative splicing. These splicing variants beg for a more refined interpretation of genetic findings.[7] Truncating mutations have also been associated with sporadic cases, suggesting increased susceptibility to environmental effects. The significance of genetic variations is unknown in many instances. Frequently, a genotype–phenotype correlation will be of limited clinical utility in the treatment of the patient, but some instances warrant genetic characterization.

Teaching Points

- Clinical evaluation including complete pedigree analysis is essential in the evaluation of genetic disorders such as dilated cardiomyopathy.
- Penetrance and expressivity are important considerations, especially when evaluating first-degree relatives.
- A truncated protein that fails to transmit or generate force within or across the sarcomere or adequately handle calcium can result from frameshift, nonsense, or splice mutations.
- The clinical significance of mutations is frequently unknown.
- Many dilated cardiomyopathy cases are familial; most commonly autosomal dominant disorders, but autosomal recessive and X-linked inheritance patterns can also be observed.
- Dilated cardiomyopathy clinical presents with heart failure and cardiac enlargement; imaging studies showing normal valves and patent coronaries and a decreased ejection fraction.

Authors' Note

The opinions expressed herein are those of the authors and are not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), or the United States Army, Navy, or Air Force.

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References

1. Jefferies JL, Towbin JA. Dilated cardiomyopathy. *Lancet*. 2010; 375:752-762.
2. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. *Lancet*. 2017. doi:10.1016/s0140-6736(16)31713-5; pii: s0140-6736(16)31713-5.
3. Arbustini E, Narula N, Dec GW, et al. The Moge(s) classification for a phenotype–genotype nomenclature of cardiomyopathy. *Global Heart*. 2013;4(N8):355-382.
4. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. *N Engl J Med*. 2011;364(17):1643-1656.
5. National Institutes of Health, National Library of Medicine. Familial Dilated Cardiomyopathy. Genetics Home Reference. [Online]. 2017.
6. Norton N, Li D, Rampersaud E, et al; National Heart, Lung, and Blood Institute GO Exome Sequencing Project and the Exome Sequencing Project Family Studies Project Team. Exome sequencing and genome-wide linkage analysis in 17 families illustrate the complex contribution of TTN truncating variants to dilated cardiomyopathy. *Circ Cardiovasc Genet*. 2013;6(2):144-153.
7. Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. *Genome Med*. 2017; 9(1):20. doi:10.1186/s13073-017-0410-8.