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Cardiovascular Management of Marfan Syndrome: Implications for Nurse Practitioners

Jonathan Yip, MN, NP, and Jo-Ann Sawatzky, PhD, RN

ABSTRACT

Marfan syndrome (MFS) is a genetic disorder affecting 1 in 5,000 individuals. The diagnosis is made using a combination of genetic testing and the revised Ghent criteria. MFS is associated with the cardiovascular-related risks of aortic dilation and dissection. Therefore, the main goal of medical therapy is blood pressure control using beta-blockers and lifestyle modification. Prophylactic surgical intervention remains the single, definitive measure in preventing dissection or rupture. Nurse practitioners must be vigilant in caring for this population as these cardiovascular risks can be reduced by early identification and diagnosis and timely intervention.

Keywords: aortic dilation, aortic dissection, cardiovascular complications, Marfan syndrome

Marfan syndrome (MFS) is a heritable disorder of connective tissue. It is a relatively common genetic disorder affecting 1 in 5,000 individuals without gender, racial, or ethnic predilection.[1-3] MFS affects multiple systems of the body, with consequent cardiovascular-, skeletal-, ocular-, integument-, lung-, and dural-related symptoms.[3-5] Based on earlier studies, the cause of MFS was thought to be primarily due to the mutation in the fibrillin-1 (FBN-1) gene on chromosome 15, resulting in abnormal fibrillin structure that causes the connective tissue disorder. More recent studies have shown that the dysfunctional transforming growth factor (TGF)-β cytokine plays a more critical role in extracellular matrix homeostasis or remodeling.[6-8]

The diagnosis of MFS is based on both genetic testing of FBN-1 and physical findings under the revised Ghent criteria. Although MFS manifests in varying degrees of severity, the most life-threatening consequences include aortic dilation and dissection, which can lead to aortic rupture and death. Hence, it is crucial for nurse practitioners (NPs) to have comprehensive knowledge of these complications, as it is not uncommon for NPs to encounter MFS patients in both acute and primary care practice. Currently, the opportunities for early diagnosis and the use of noninvasive serial aortic imaging, as well as advancements in the both medical and surgical management of MFS, have led to significant improvement in the life expectancy of all affected individuals.[3,5] In this study we aim to provide NPs with a comprehensive overview of MFS and offer specific insights for the cardiovascular management of these individuals and their families.

GENETIC OVERVIEW

MFS is the result of a faulty genetic make-up. Earlier studies concluded that MFS was primarily the result of a mutation in the FBN-1 gene on chromosome 15. FBN-1 encodes the extracellular matrix glycoprotein fibrillin, which is a major component of connective tissue microfibrils found throughout the body.[1-3] More recent studies have indicated that the mutated FBN-1 gene also enhances the release of

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TGF-β, which, in turn, plays a critical role in the cardiovascular pathophysiology of MFS.[6,7] TGF-β is a cytokine that functions in the regulation of cell proliferation, differentiation, extracellular matrix formation, cell cycle, and apoptosis.[6,7] It is the mutation in TGF-β receptor 2 gene that results in extracellular matrix homeostasis and/or cardiovascular remodeling, leading to a stiffer and less distensible aorta.[3,6-8]

MFS is an inheritable autosomal dominant disorder, which means that each offspring of an affected parent has a 50% chance of inheriting the altered FBN-1 gene.[1] Although approximately 75% of all cases are found to be inherited, the remaining 25% occur due to spontaneous mutation.[4] To date, > 1,000 different mutations involving the FBN-1 gene have been isolated, with most mutations being unique to a given family.[1,2] However, family members with the same mutation causing MFS can exhibit a wide variation in clinical manifestations. No correlation has been found between the specific type of FBN-1 mutation and the clinical phenotype, which explains the extreme variations in clinical phenotypic presentations of MFS. Furthermore, the mutation in the FBN-1 gene can cause conditions other than Marfan-like disorders.

None of the current genetic testing methods have the ability to identify all mutations of MFS.[4,5] In 10% of patients with a definitive diagnosis of MFS, it is still not possible to find an FBN-1 gene mutation.[5] As a result, genetic testing alone is insufficient to make the diagnosis.

CLINICAL PRESENTATION

The clinical features of MFS can present in many different parts of the body. Although the most commonly affected regions are the skeletal, ocular, and cardiovascular systems, pulmonary, skin/integument, and dural symptoms have also been reported. An affected individual rarely has every feature. The classic clinical appearance of MFS is a tall, thin individual with disproportionally long arms, and usually a longer than normal lower half of the body. Other common external physical characteristics include pectus excavatum (funnel chest) or pectus carinatum (pigeon chest), double-jointed fingers, elongated thumb, long feet and toes with flat or highly arched feet, scoliosis or kyphosis, severe myopia, crowded teeth, and striae atrophiae (stretch marks).[2-4] In addition, common internal characteristics include lens dislocation (ectopia lentis) and a swelling sac around the spinal column (dura ectasia). Cardiovascular involvement results in complications, including the dilation and dissection of aorta, and mitral and/or aortic valve prolapse and/or regurgitation.[2-4] Consequently, due to the highly variable presentation of affected individuals, it is essential for NPs to be familiar with the complex diagnostic process for MFS.

CLINICAL DIAGNOSIS

The diagnosis of MFS was initially identified by Victor McKusick in 1955 as a classification of connective tissue disorder using his Heritable Connective Tissue Disorders monograph.[9,10] Subsequently, a Berlin nosology was created in 1986 by an international panel of experts with the aim of facilitating accurate communication about the condition between health care providers.[11] However, this Berlin nosology was later found to only focus on the physical characteristics associated with MFS, ignoring the genetic aspect of the disease. A newer version of the criteria, called the Ghent nosology, was established in 1996, after identification of the causal gene FBN-1.[12] The Ghent nosology uses clinical findings of 6 organ systems along with family history and molecular findings to diagnose MFS.[12]

Recently, due to further advancements in medical research, Loeys et al[13] published a revised Ghent nosology, with the intent to decrease the risk of premature or misdiagnosis of MFS. The new Ghent nosology is now the gold standard for the diagnosis of MFS. It puts more weight on the cardiovascular manifestations, with aortic root aneurysm and ectopia lentis being the cardinal clinical features. Thus, diagnosing MFS requires comprehensive patient and family history, including information about any family members who may have the disorder or had an unexplained early or sudden death. In the absence of any family history, the presence of these 2 manifestations is sufficient for the unequivocal diagnosis of MFS. In the absence of either of these 2 features, the presence of an FBN-1 mutation or a combination of systemic manifestations is required (Table 1).