Journal of Contemporary Medical Education, 2023
VOL 13, NO. 1, PAGES 01

PERSPECTIVE

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Pathogenesis of Marfan Syndrome and its Diagnosis

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ARTICLE HISTORY
Received: 02-Jan-2023, Manuscript No. JCMEDU-22-87768;
Editor assigned: 06-Jan-2023, Pre-QC No. JCMEDU-22-87768 (PQ);
Reviewed: 20-Jan-2023, QC No. JCMEDU-22-87768;
Revised: 27-Jan-2023, Manuscript No. JCMEDU-22-87768 (R);
Published: 03-Feb-2023

Description

Marfan syndrome (MFS) is a multisystem genetic disorder that affects connective tissue. Those with this condition tend to be tall and thin, with long arms, legs, fingers and toes. They also usually have exceptionally flexible joints and abnormally curved spines. The most serious complications involve the heart and aorta, with an increased risk of mitral valve prolapse and aortic aneurysm. The lungs, eyes, bones and spinal cord are also usually affected. The severity of symptoms varies. Marfan syndrome is caused by a mutation in FBN1, one of the genes that makes fibrillin, resulting in abnormal connective tissue. It is an autosomal dominant disorder. In about 75% of cases it is inherited from a parent with the condition, while in about 25% it is a new mutation. Diagnosis is often based on the Ghent criteria.

Pathogenesis

Marfan syndrome is caused by mutations in the FBN1 gene on chromosome 15, which encodes fibrillin 1, a glycoprotein component of the extracellular matrix. Fibrillin-1 is essential for the proper formation of the extracellular matrix, including the biogenesis and maintenance of elastic fibers. The extracellular matrix is critical both for the structural integrity of connective tissue, but also serves as a reservoir for growth factors. Elastic fibers are found throughout the body, but are especially abundant in the aorta, ligaments, and ciliary zonules of the eye; as a result, these areas are among the most affected. It can also be caused by a number of intravenous crystal treatments in individuals prone to the disorder.

A transgenic mouse was created carrying a single copy of mutant fibrillin-1, a mutation similar to that found in a human gene known to cause Marfan syndrome. This mouse strain recapitulates many features of the human disease and promises to provide insight into disease pathogenesis. Depletion of normal fibrillin 1 causes Marfan-related disease in mice.

Transforming growth factor beta (TGF-β) plays an important role in Marfan syndrome. Fibrillin-1 directly binds the latent form of TGF-β, keeping it sequestered and unable to exert its biological activity. The simplest model suggests that decreased levels of fibrillin-1 allow increased levels of TGF-β due to insufficient sequestration. Although it is not proven how elevated levels of TGF-β are responsible for the specific pathology seen in the disease, it is known that an inflammatory response occurs releasing proteases that slowly degrade elastic fibers and other components of the extracellular matrix. The importance of the TGF-β pathway was confirmed by the discovery of a similar Loeys–Dietz syndrome involving the TGFβR2 gene on chromosome 3, a TGF-β receptor protein. Marfan syndrome has often been confused with Loeys-Dietz syndrome due to the considerable clinical overlap between the two pathologies.

Diagnosis

Diagnostic criteria for Marfan syndrome were internationally agreed upon in 1996. However, Marfan syndrome is often difficult to diagnose in children because they usually do not show symptoms until they reach puberty. Diagnosis is based on family history and a combination of major and minor indicators of the disorder that rarely occur in one individual in the general population for example: four skeletal features with one or more features in another body system, such as eye and cardiovascular in one individual. The following conditions can result from Marfan syndrome, but can also occur in people without any known underlying disorder.

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