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MARFAN'S SYNDROME: RETROSPECTIVE ASSESSMENT

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ABSTRACT Marfan syndrome (MFS), is an autosomal dominant condition with a reported incidence of 1 in 5000 to 10000 individuals. Clinical severity varies, ranging from isolated features of MFS to neonatal presentation of severe and rapidly progressive disease involving multiple organ systems. The syndrome is associated with ocular, cardiovascular, and musculoskeletal abnormalities, although involvement of lung, skin, and central nervous system may also occur. Decreased life expectancy occurs mainly due to aortic complications. This paper is an attempt to review the pathogenesis, incidence, clinical features and treatment of the syndrome.

KEYWORDS : Marfan's Syndrome, Ocular, Musculoskeletal And Cardiac Abnormalities, FBN1 Mutations.

INTRODUCTION

Marfan syndrome also known as Arachnodactyly, Marfanoid hypermobility syndrome is multi systemic genetic condition that makes connective tissue too loose and elastic. Connective tissue typically provides strength and flexibility to many structures in your body. Because of this, Marfan syndrome can affect several body systems, including heart, blood vessels eyes, bones and joints. It is mainly due to defect in FBN1 gene located on chromosome 15q21 which codes for the connective tissue protein fibrillin. MFS is one of the most common single-gene malformation syndromes[1].

Incidence

Marfan's syndrome is comparatively common, the condition occurring in at least one in every 10000 of the population. Both sexes are equally affected. It exhibits complete penetrance with variable expression.

History

Marfan syndrome was first identified by French pediatrician Antoine Bernard Marfan in 1896. Five and a half year old girl named Gabrielle was presented with unusually long slender limbs and joint contractures. He named the condition dolichostenomelia. In early 1900s Emile Achard and others described features such as spider fingers, eye and heart complications. In 1929 Dr Carrau formally coined the term Marfan syndrome in medical Journal Le Nourisson. In 1991 geneticist Dr Victor Mckusick formally defined the syndrome in 1955 monograph that mutation of gene FBN1 which codes for the protein Fibrillin 1 is responsible. Several of the signs of Marfan's syndrome are not exclusive to the condition, but are also found amongst the general population. So, it has been determined that to make an accurate and correct diagnosis of Marfan's syndrome, at least three of the specific signs or symptoms should be present. If a first-degree relative, i.e. mother, father, brother or sister, also has Marfan's syndrome, two of the characteristic features only are required to make a positive diagnosis. Abraham Lincoln with long height, limbs and facial features was analyzed by historians and geneticist to have suffered from this condition[2].

Etiopathogenesis

25% of the MFS probands disease arises de novo, a clear family history is apparent in the remaining, and thus vast majority, of patients. Yet, it took several extra decades to pinpoint mutations in the fibrillin 1 gene (FBN1; MIM #134797) as the disease cause. FBN1 (chr15q15-15q21.1) encodes a 350-kDa extracellular matrix (ECM) glycoprotein that takes part in the formation of microfibrils, which are of utmost importance for elasticity and structural support of numerous tissues. The encoded protein has a modular structure consisting of 47 epidermal growth factor (EGF)-like motifs, seven transforming growth factor (TGF)- -binding domains as well as a cysteine-rich and proline-rich module. The EGF-like and TGF- -binding domains, respectively, contain six and eight highly conserved cysteine residues, which have a pivotal role in protein structure and stability through covalent formation of three disulfide bridges. Marfan's syndrome is inherited as an autosomal dominant, but some cases arise sporadically as new mutations. Even if the abnormal gene is present, all the typical characteristics may not be seen in any one individual. For example, only the tall stature may occur, without the other specific signs. Recently a particular protein is thought to be one of the affected substances producing some of the clinical signs. Similar features to those seen in Marfan's syndrome can occur in another disorder, homocystinuria. Amino acid assay of the urine is needed to distinguish between the two disorders[3,4].

Clinical Features

Skeletal System

Tall stature: Marfan's syndrome children are tall, being taller than their classmates from an early age. Long slender limbs, which look out of proportion to normal sized trunks make up for this increased height.

Vertebral Column Abnormalities: There can be a scoliosis to the spine in the thoracic region. Also, a kyphosis can occur in this region of the back, giving rise to the appearance of rounded shoulders. Fingers and toes are also particularly long and slender - often giving rise to the name 'spider fingers'! Joints are either very mobile or alternatively can be stiff and contracted. The former is the more common, and is especially noticeable in the wrists, elbows and fingers. Dislocation of joints can occur more readily than normal due to the laxity of the joint capsule and the comparative weakness of the muscles surrounding the joint.

Chest: There are frequently deformities of varying types and degrees in this region of the body.
A high, arched palate is also a consistent feature.

Ocular: The lenses of the eye are dislocated, giving rise to poor vision. In addition to this, myopia (short-sight) is common. Detachment of the retina occurs more frequently than in the general population. Squints and/or nystagmus can also occur, but neither is an invariable characteristic.

Cardiovascular System: The aorta, the large artery passing oxygenated blood from the heart to the rest of the body, is often dilated in its upper part. This can lead to the development of an aneurysm (a 'blowing out' of the blood vessel) in later life. The valves of the heart can also be affected, the mitral or aortic valves being the ones most commonly affected. The valves

can prolapse, causing problems of inadequate blood flow through the heart. These cardiac defects are all part of the connective tissue disorder.

Mental Abilities: Children with Marfan's syndrome have normal intelligence. Occasionally it has been reported that attention span can be limited and also that verbal performance, on testing, can lag behind comprehension. This is by no means always the case, but there is strong evidence that these types of problems do affect Marfan children more frequently than children in the general population. So it is important that regular checks on school performance are made.

Other Features: Subcutaneous tissue can be reduced. This leads to excessive slimness which adds to the 'long, lean look'. Muscles can be weak, so that Marfan's children are not natural sports men and women[5,6].

DIAGNOSIS

In 1996, criteria for diagnosing MFS, known as Ghent nosology, were originally proposed. These criteria relied on major and minor clinical manifestations of the syndrome. Major criteria included ectopia lentis, aortic root dilatation involving the sinuses of Valsalva or aortic dissection, and lumbosacral dural ectasia by computed tomography or magnetic resonance imaging, family or genetic history, and 4 of 8 typical skeletal manifestations. These criteria underwent revision in 2010 due to various limitations, including insufficient validation, limited applicability to children, and an inability to exclude syndromes such as LDS and SGS. The 2010 revised Ghent nosology puts greater weight on aortic root dilatation/dissection and ectopia lentis as the cardinal clinical features of MFS and testing for mutations in FBN1.

Systemic Score

The revised Ghent nosology includes the following scoring system for systemic features:

- Wrist and thumb sign: 3 points
- Wrist or thumb sign: 1 point
- Pectus carinatum deformity: 2 points
- Pectus excavatum or chest asymmetry: 1 point
- Hindfoot deformity: 2 points
- Plain pes planus: 1 point
- Pneumothorax: 2 points
- Dural ectasia: 2 points
- Protrusio acetabuli: 2 points
- Reduced upper segment/lower segment ratio and increased arm span/height and no severe scoliosis: 1 point
- Scoliosis or thoracolumbar kyphosis: 1 point
- Reduced elbow extension (equal to 170 degrees with full extension): 1 point
- At a minimum, 3 of the following 5 features: Dolichocephaly (reduced cephalic index or head width/length ratio), enophthalmos, down-slanting palpebral fissures, malar hypoplasia, retrognathia): 1 point
- Skin striae: 1 point
- Myopia greater than 3 diopters: 1 point
- Mitral valve prolapse: 1 point
- A systemic score equal to 7 indicates significant systemic involvement.

In patients with no family history of MFS, the presence of 1 of any of the following criteria is diagnostic for MFS:

- Aortic criterion (aortic root dissection or diameter Z equal to 2) and ectopia lentis*
- Aortic criterion (aortic root dissection or diameter Z equal to 2) and a causal FBN1 mutation
- Aortic criterion (aortic diameter Z equal to 2 or aortic root dissection) and a systemic score equal to 7*
- Ectopia lentis and an identified causal FBN1 mutation in an individual with an aortic aneurysm

In patients with a family history of MFS, the presence of 1 of any of the following criteria is diagnostic for MFS:

- Ectopia lentis
- A systemic score equal to 7 points*
- Aortic criterion (aortic diameter Z equal to 3 below 20 years old, Z equal to 2 above 20 years, or aortic root dissection)*

For criteria with an asterisk (*), the diagnosis of MFS can be made only in the absence of discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers-Danlos syndrome and after TGFBR1/2, collagen biochemistry, or COL3A1 testing if indicated. Later data suggest that additional gene mutations, including those in SMAD3, TGFB2, and SKI, should also be excluded.

The revised Ghent nosology recommends the following categories for individuals younger than 20 years old with features of MFS who do not meet diagnostic criteria for MFS:

- Nonspecific connective tissue disorder applies if the systemic score is less than 7 or aortic root measurements are borderline (Z less than 3) without an FBN1 mutation.
- Potential MFS applies if an FBN1 mutation is identified in a sporadic or familial case but the aortic root Z-score is less than 3[7].

Management

No specific laboratory test exists with which to make the diagnosis of MFS; however, molecular genetic testing can facilitate diagnosis of MFS in certain clinical situations. Skeletal abnormalities are assessed with radiography, computed tomography (CT), and magnetic resonance imaging (MRI). Ocular abnormalities are assessed with ultrasonography (US), slit-lamp examination, and keratometry. Cardiovascular abnormalities are assessed with electrocardiography (ECG), echocardiography, MRI, and magnetic resonance angiography (MRA). Skeletal system Scoliosis should be noted early before the deformity becomes marked. Scoliosis, if left untreated, can progress to severe chest deformity with subsequent cardiac and respiratory problems. So, early bracing or operative procedures should be done to reduce the possibility of further problems. Any bracing procedures must, however, be done very carefully as respiratory problems can result. In girls, early puberty has been induced by the giving of appropriate hormones. This both reduces final height, and can also prevent the worsening of the scoliosis during the period of rapid growth seen during puberty. Joint contractures occur in a minority of children. Physiotherapy, if given early and consistently, can do much to maintain mobility, which can be at risk due to the joint problems.

Eyes checking on visual acuity early are vital, so that corrective lenses can be given to counteract the myopia which is so common. Squints, if present, will need to be corrected, either orthoptically or surgically to avoid amblyopia. The dislocated lenses, which also reduce vision, should be left in position. In the past lenses have been removed surgically, but it has subsequently been found that this predisposes to retinal detachment.

Cardiovascular system: Beta-blocker drugs, given on a long-term basis, have been found to reduce the rate of dilatation of the aorta. Operative procedures may be necessary to replace the dilated aorta at a later date. Surgery may also be necessary on the abnormal valves in the heart. Endocarditis, an infection of the inner layer of cardiac muscle, is a possible complication. Because of this possibility, antibiotics should be given prophylactically before minor operative procedures, such as dental extractions, for example. Due to the cardiac, visual and skeletal problems which Marfan's children suffer, certain restrictions should be put on their physical activities. For example, body contact sports must be avoided due to the possibility of damage to the eyes, and sports which require the

body to be pushed to its physical limits, such as marathon running and weightlifting, must be avoided. The heart, under these circumstances, has a heavy load to bear, and with the possible abnormalities to be found in Marfan's syndrome, such exertion can lead to cardiac failure. Weak muscles and skeletal problems will also, in many cases, exclude many of the more strenuous physical activities. Mental abilities Children with Marfan's syndrome will be able to manage intellectually very adequately in mainstream schooling, but in some cases visual problems may be sufficient to need special schooling for partially sighted pupils. The possibility of a specific attention deficit must also be remembered and appropriate action taken in school to be aware of, and remedy, the problem[8,9,10].

CONCLUSION

Children with Marfan's syndrome may have a reduced life expectancy due to the cardiac problems. Around 40 to 50 years is the usual life span. Complications due to the aortic abnormalities account for 90% of early deaths. As long as sensible precautions are taken not to overload the cardiovascular system, a normal life can be led within the limits of reduced vision. This, of course, will vary from individual to individual. Genetic counselling before a pregnancy is embarked upon is advisable.

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