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Brief Report

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Expectancy and Delivery in Individuals with Syndrome-Marfan

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ABSTRACT

Marfan syndrome (MFS) is an autosomal dominant condition with a reported incidence rate of 1 in 3000 to 5000 individuals. The majority of cases of MFS are caused by a mutation in the fibrillin-1 gene (FBN1). Transforming growth factor β (TGF-β) plays an important role in Marfan syndrome. The identification of the FBN-1 mutation will help identify potentially affected family members and promote prenatal diagnostic testing. β blockers decrease myocardial contractility and pulse pressure and may also improve the elastic properties of the aorta. Angiotensin II-receptor blockers attenuate the clinical manifestations of MFS.

KEY WORDS: Marfan syndrome; Aortic root enlargement; Ectopia lentis; Fibrillin-1; Beta blockers; Dural ectasia; Protrusio acetabuli.

INTRODUCTION

Marfan syndrome (MFS) is primarily inherited in an autosomal dominant manner and in some cases with a recessive manner, which affects one person in every 3000-5000 people in the general population.[1,2]

In the majority of patients due to gene mutations on fibrillin-1 [fibrillin-1 gene (FBN-1)], located in chromosome 15q-21.1q and comprises 65 exons.[2] Fibrillin-1 is an extracellular cysteine-rich protein that participates primarily in manufacturing and maintaining the structure of the microfibrils on the extracellular matrix of the elastic and non-elastic connective tissue.[3]

Mutations on the fibrillin-1 gene interrupt the normal structure of these micro fibrils thus inducing abnormal protein structure in which they participate. This may lead to an infringement of biomechanics (structure that can meet the functional role) connective tissue. The disturbance of homeostasis of connective tissue, for example, in blood vessel walls can cause strong solution of the connecting elastic fibers after intense expression of metalloproteinases (such as metalloproteinases -2 and -9) of the matrix, and increasing the hyaluronic acid can lead to degradation of these elastic fibers and other components of the matrix.[4] It is also reported to increase the activity of transforming growth factor-β [transforming growth factor beta (TGF-β)] interactions and loss of cell-matrix (cell-matrix interactions).[5]

Clinically the MFS may be manifested by a series of events from various organs and systems:

a. Dermal super elasticity transparent skin and stretch marks in skin areas such as the spine, the upper limbs, the inguinal regions and the leg.[6]

b. Regarding the musculoskeletal system general laxity of ligaments leading to hyper

extensibility and instability with frequent joint dislocations and subluxations, prolapse of the femoral head,[7] valgus posterior segment combined with abduction of the anterior and shortening of the average part of the edge of the leg,[7] of the ends arachnodaktylia hands (especially long thin fingers) and the chest wall may be observed as distortion asymmetry and tropidoeidis (pectus carinatum) or funnel-shaped (pectus excavatum) thorax.[7] In the spine, scoliosis and spondylolisthesis are described.[8]

c. In the nervous system, dural ectasia (inflation of the bag of the dura and the vertebral canal together possibly swelling sheaths spinal nerves)[9] affects the spinal canal in all degrees of the spine, often in the lumbosacral region and can manifest with headache, back pain, damage of muscle power and limiting the sensation of the legs and pain in the anal region and external genital organs are deteriorating in the supine and enhances the prone (face down) bed.[10] Each patient escorted by Marfan syndrome with related clinical signs should be tested for possible dural ectasia using computational or MRI.[11]

d. In the eyes, ectopia (dislocation or abnormal axis) of the eye lens (ectopia lentis) the most common bilateral and symmetric but non-progressive[12,13] myopia, retinal detachment (possibly bilateral)[14,15] strabismus and glaucoma.[16]

e. In the cardiovascular system, involvement of the root of the aorta may result in aneurysmal dilatation/separating walls and insufficiency of the aortic valve.[17] Abdominal aortic root was reported in approximately 50% of children and 60%-80% adult patients, often combined with a failure of the aortic valve, and has been reported abdominal wall and the thoracic and abdominal aorta and the pulmonary artery (the root), the carotid and intracranial arteries.[18,19] The aorta showed a significant limitation in its luminal elasticity and durability, factors that increase with increasing age.[20-23] No significant correlation has been observed between aortic root infection with infection of other organs or systems such as the eye or the frame.[18] Cardiac involvement has also been observed with the most common mitral valve prolapse reported in 40%-54% of patients with Marfan syndrome.[24,25] Mitral valve infringement usually results in mild or moderate deficiency, although cases have been observed with severe infestation of spontaneous rupture of the tendon string.[24]

f. Respiratory system blisters (bullae) in the pulmonary parenchyma (most commonly detected in the upper lobes), rupture of which may lead to spontaneous pneumothorax.[1,6,26]

MRI provides the ability to detect the presence and extent of the aneurysm of the aorta and of these aneurysms relationship with the vessels of the aortic arch.[27]

Samples from the aortic root wall of tunica media reveal fragmentation of elastic fibers, cystic necrosis, fibrosis and loss of smooth muscle fibers that reflect the damage and repair process.[28-32]

Genetic testing on the fibrillin-1 gene mutations help in the detection of the affected patient's family members and promote prenatal diagnosis. The absence of mutations in a person suspected of MFS does not exclude the diagnosis, which should be based on medical history, clinical assessment and imaging evaluation. With regards to the relatives of patients with MFS the recommendations of the American College of Cardiology/ American Heart Association/American Association for Thoracic Surgery- 2010 state that[33]:

a. First-degree relatives of patients with the gene mutation associated with aneurysms and/or aortic separation (for example FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) should receive genetic testing and prenatal counseling. Patients with this type of mutations should undergo imaging evaluation of the aorta.

b. The risk of children of the above relatives depends on whether they present the syndrome or not. In the case of a parent with MFS, the risk of having a child with this syndrome is estimated at 50%.

c. If neither of the parents have MFS then the risk is estimated at <50% (because probably a mutation in these parents may be *de novo*). This percentage is however higher than those of the general population because there are rare cases of somatic and germline mosaicism which can lead to the evolvement of MFS even without the existence of the syndrome in the parents.

d. Parents with aneurysms and/or aortic separation without the known mutation, imaging of the aorta is recommended to first degree relatives to disclose those with the asymptomatic disease. If one or more first-degree relatives have aortic dilatation, aneurysm or aortic separation then imaging of the aorta is suggested for second-degree relatives.

Pregnancy and Childbirth

Pregnant women with MFS, particularly those with an increased diameter of the root of the aorta, possess an increased risk of separation or rupture of the aorta including additional obstetric complications throughout pregnancy and more frequently during the third semester.[34-38] The risk of aortic separation or other serious complications such as endocarditis or development of heart failure has been estimated at approximately 1% in case the aortic root diameter being (ACTS) ≤40 mm.[36,37,39] This risk increases significantly for ACTS>40 mm and/or rapid increase in diameter of the aortic.[39,40] It also increases the risk of complications in pregnant women with a history of aortic dissection.[41] With relation to the above data, it might prove to be crucial to estimate the risk of separation or rupture of the aorta by

transthoracic echocardiography (estimation of the dimensions of the aortic root and ascending aorta and the possible infection of the heart valves presence) before proceeding with childbearing. If additional imaging is required, magnetic or computed tomography is recommended.[39]

Preventive surgical intervention maybe required before attempting procreation. According to the guidelines of the European Society of Cardiology (ESC) 2011 it is recommended for ACTS ≥45 mm (or >27 mm/m^2),[39,42,43] and according to the guidelines of the American College of Cardiology/American Heart Association/American Association of Thoracic Surgeons (ACC/AHA/AATS) 2010 it is recommended for ACTS exceeding 40 mm. As for pregnancies that are likely to follow it should be noted that despite the fact that successful surgical correction greatly reduces the risk of dissection of the ascending aorta, the risk to the remaining parts of the aorta persists.[36,41,43-45] During pregnancy women with MFS should be monitored clinically and sonographically even those with ACTS ≤40 mm.[35-37] This monitoring should be individualized:

1. The recommendations of the European Society of Cardiology (ESC)-2011 require ultrasound imaging every 4-8 weeks throughout gestation in patients with abdominal aortic root or the ascending aorta (ACTS >40 mm).[39]

2. The recommendations of the American College of Cardiology/American Heart Association/American Association of Thoracic Surgeons (ACC/AHA/AATS)-2010 require measuring the dimensions of the root of the aorta and the ascending aorta by means of ultrasound.[40]

3. Recommendations 2011 ESC and 2010 ACC/AHA/AATS require MRI control for pregnant women with dilation of the aortic arch, descending thoracic aorta and abdominal aorta. MRI without gadolinium administration (contrast medium) is preferred for the evaluation of the size of the aorta, although there is data (however inadequate) showing that the risk to the fetus from administration of gadolinium is low.[44]

Certainly, the imaging of the thoracic aorta requires trans esophageal scanning without the use of irradiation or administration of contrast agents.

The administration of β-blockers can be used as therapeutics because they reduce abdominal aorta and the risk of dividing the aneurysm.[39,43] It is preferable to administer either labetalol or metaprolol compared to atenolol since atenolol can negatively affect fetal growth. Also angiotensin-II blockers should not be used because they adversely affect the fetus. Constant low blood pressure should be achieved (not exceeding systolic pressure value of 130 mmHg) throughout pregnancy.[39]

In accordance with the 2011 ESC guidelines, surgery will be required in the case of a ACTS ≥50 mm rapidly evolving.[39] If ACTS >45 mm termination of pregnancy may be required followed by surgical intervention, before the embryo matures.[43]

It is generally known that women with MFS have an increased risk of complications during childbirth such as premature rupture of membranes or postpartum bleeding.[45,46] An increased risk of dissection of the aorta has also been observed after birth. Regular and careful monitoring with follow-up scans of the aorta are required in high-risk patients during the after birth period. Women with MFS who have aneurysmal dilatation of the aortic root (ACTS ≥40 mm) or a history of aortic dissection should plan their delivery in specialized Cardiothoracic Surgery Units.[39]

According to the recommendations of the European Society of Cardiology, women with a diameter of the ascending aorta <40 mm without other clinical signs have an increased risk of aneurysm rupture; a slow delivery by vaginal route is preferred, prolonged or delayed second stage combined with a Valsalva maneuver to minimize delivery exertion. Epidural anesthesia is also recommended, provided that dural ectasia is excluded by magnetic resonance imaging or computed imaging. This is a necessary step in order to avoid complications during the epidural anesthesia.[47]

Women with MFS with an ascending aorta diameter ≤45 mm, vaginal delivery is recommended, whilst women with a diameter of the ascending aorta >45 mm, a cesarean section is preferred.[39] Cesarean section is preferred for women with a high risk of complications during childbirth. In aortic dissection Type A, when the fetus is considered viable, childbirth by caesarean section is recommended, with a consequent or subsequent prompt surgical correction of this vascular lesion.

According to the guidelines in 2010 ACC/AHA/AATS for type A separation of the aorta (ascending aorta) during the first or second trimester of pregnancy urgent surgical correction and fetal monitoring are required, while during the third trimester of pregnancy delivery caesarean section and then surgical correction. For type B aortic separation or acute separation in the aortic arch, drug therapy is preferred unless surgical intervention is required for the treatment of sub-acute escape from the aorta or aortic rupture. It should be noted that hypothermia and prolonged cardiopulmonary bypass can cause fetal loss.[48]

CONCLUSION

The Marfan syndrome (MFS) is a syndrome that is inherited in an autosomal dominant manner primarily and it may be manifested by a series of events from various organs and systems. It affects one person in every 3000-5000 people in the general population. In the majority of patients it is caused by gene mutations of fimprillinis 1 [fibrillin 1 gene (FBN1)] and in some cases it was reported that such mutations are inherited as recessive manner.

MRI provides the ability to see the presence and extent

of the aneurysm of the aorta and of these aneurysms relationship with the vessels of the aortic arch. Samples from the wall of the aortic root in tunica media can reveal fragmentation of elastic fibers, cystic necrosis, fibrosis and loss of smooth muscle fibers that reflect the damage and repair process.

Genetic testing on the mutations on the fibrillin-1 gene assists in locating the patient's affected family members and augment prenatal diagnosis. MFS final diagnosis should be based on genetic prenatal testing, medical history, clinical examination and imaging evaluation.

Before any childbearing attempt, a trans-esophageal ultrasound should be performed for the assessment of the risk in aortic separation or rupture of the aorta. Should further monitoring be required, a magnetic or computed tomography can help in the final evaluation the aorta.

A very careful detailed and regular monitoring plan with a possible immediate therapeutic intervention should be followed during gestation, since childbearing women with MFS, particularly those with an increased diameter of the root of the aorta, demonstrate an increased risk of separation or rupture of the aorta including obstetric complications notably during the third trimester:

a. During pregnancy women with MFS should be monitored clinically and sonographically exclusively those with a diameter of the root of the aorta (ACTS) ≤40 mm.

b. It is highly probable, patients with ACTS ≥40-45 mm to require preventive surgical intervention before conceiving.

c. β-blockers reduce aortic luminal dilatation and the risk of a dividing aneurysm. Metaprolol and labetalol are preferably administered, since atenolol can affect fetal development. Likewise, angiotensin-II blockers should not be used because they adversely affect the fetus. A systolic blood pressure value of no more than 130 mmHg is suggested throughout pregnancy.

d. Surgical intervention will most likely be required in an ACTS ≥50 mm.

e. Women with MFS with aneurysmal dilatation of the aortic root (ACTS ≥40 mm) or a history of aortic dissection should plan their delivery in Cardiothoracic Units.

f. Female subjects with MFS and an ascending aorta diameter ≤45 mm are advised to deliver by the vaginal route; childbearing women having an ascending aorta diameter >45 mm, caesarean section is the suggested way of giving birth.

g. Epidural anesthesia is allowed, provided that dural ectasia is excluded by MRI or computed tomography.

h. Postpartum dissection of the aorta has been observed; regular and careful monitoring should be performed weeks after delivery in high-risk patients.

AUTHORS' CONTRIBUTIONS

All authors participated in writing the paper and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human participants or animals performed by any of the authors.

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