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Marfan syndrome: current diagnostic and management strategy

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Abstract

Background. Marfan syndrome (MFS) is a rare genetic disorder and affects connective tissue throughout the body, leading to a variety of symptoms that can vary in severity, including skeletal, ocular, and cardiovascular systems, as well as pulmonary, gastrointestinal, and other systems. The pathogenesis of Marfan syndrome is complex and involves alterations in the structure and function of connective tissue throughout the body.

Aim. To review the genetic, clinical manifestations, and current therapeutic options of Marfan syndrome.

Methods. The literature used for this review was selected using "Google Scholar", "Pubmed", "UptoDate" databases. The search was performed using the following keywords and their combinations: Marfan syndrome, Marfan syndrome management, Marfan syndrome genetics, cardiovascular symptoms in patiens with Marfan syndrome.

Results. Marfan syndrome is a rare genetic disorder affecting approximately 1 in 5,000 individuals worldwide. The disease is inherited in an autosomal dominant manner and caused by mutations in the gene encoding the protein fibrillin-1. One important pathway of pathogenesis is the dysregulation of transforming growth factor-beta signaling, which contributes to the development of connective tissue abnormalities. Another important pathway is oxidative stress that can contribute to the dysregulation of TGF-β signaling, further exacerbating connective tissue abnormalities. Genetic tests and the updated Ghent criteria are used to make the diagnosis. The cardiovascular risks of aortic dilatation and dissection are linked to MFS. Therefore, controlling blood pressure with beta-blockers is the primary objective of medical therapy. Patient should undergo surgery when aortic root maximal diameter is ≥ 50 mm or ≥ 45 mm, when there are additional risk factors.

Conclusions. MFS is autosomal dominant connective tissue disorder, affecting mainly the cardiovascular system, eyes, and skeleton. Early diagnosis, medical treatment to delay the progression of aortic dilatation or possibly halt the pathologic process in the aortic wall, as well as timely elective surgery are the key measures to improve the outcome of this disease as well as the quality of live for affected individuals. Ongoing research is needed to further understand the underlying molecular mechanisms of Marfan syndrome and to develop more effective treatments for this complex disorder.

Keywords: Marfan syndrome, Marfan syndrome management, Marfan syndrome genetics, cardiovascular symptoms in patiens with Marfan syndrome, Marfan syndrome ESC.

1. Introduction

Marfan syndrome is a genetic disorder that affects the connective tissue in the body. It is caused by mutations in the fibrillin-1 gene and is inherited in an autosomal dominant manner. Individuals with Marfan syndrome may manifest a range of physical characteristics, such as tall stature, long limbs, and a curved spine. Additionally, Marfan syndrome can affect the heart, eyes, and other organs, leading to serious health complications if left untreated. Despite its prevalence of 1 in 5,000 individuals, there is still much to be understood about the underlying molecular mechanisms and clinical management of this disorder. In this paper, we aim to provide a comprehensive overview of Marfan syndrome, including its genetic basis, clinical manifestations, and current therapeutic options.

2. Methods

The literature used for this review was selected using “Google Scholar”, “Pubmed”, “UptoDate” databases. The search was performed using the following keywords and their combinations: Marfan syndrome, Marfan syndrome management, Marfan syndrome genetics, cardiovascular symptoms in patiens with Marfan syndrome, Marfan syndrome ESC.

3. Results

3.1. Epidemiology

Marfan Syndrome (MFS) is a rare genetic disorder that affects approximately 1 in 5,000 to 10,000 individuals worldwide [1]. It is considered an autosomal dominant condition, meaning that an affected individual has a 50 % chance of passing the disease-causing mutation to each of their offspring. The incidence of MFS appears to be similar across different ethnic and racial groups [2].

While MFS is a rare disease, it is more common in certain populations. For example, a study conducted in Japan found a higher prevalence of MFS among patients with aortic dissection compared to the general population, with an estimated incidence of 1 in 3,792 individuals [3]. Additionally, a population-based study in Denmark found an increased incidence of MFS among individuals of Faroese descent [4]. These findings suggest that there may be certain populations at a higher risk for MFS, although further research is needed to confirm these observations.

MFS can affect both males and females equally, and symptoms typically appear during adolescence or early adulthood [5]. However, the severity of MFS symptoms can vary widely among affected individuals, even within the same family. This variability is partly due to differences in the location and nature of the disease-causing mutation [6].

3.2. Pathogenesis

The pathogenesis of Marfan Syndrome is complex and involves alterations in the structure and function of connective tissue throughout the body [7]. MFS is caused by mutations in the gene encoding the protein fibrillin-1 (FBN1), which is an essential component of the extracellular matrix (ECM) [8] and the gene is found in the Chromosome 15. Fibrillin-1 is mainly found in elastic fibers, which provide elasticity and structural support to tissues such as the skin, lungs, and blood vessels.

Mutations in FBN1 lead to the production of abnormal fibrillin-1, which can result in the formation of an abnormal ECM. This, in turn, leads to the characteristic features of MFS, including skeletal abnormalities, ocular complications, and cardiovascular manifestations [6]. In addition to FBN1, other genes have been implicated in the

pathogenesis of MFS, including TGFBR1, TGFBR2, SMAD3, and COL3A1 [1].

The pathophysiology of MFS is complex and involves multiple biological pathways. One important pathway is the dysregulation of transforming growth factor-beta (TGF-β) signaling, which plays a critical role in the development and maintenance of connective tissue. Mutations in FBN1 and other genes involved in MFS can lead to excessive TGF-β signaling, which contributes to the development of connective tissue abnormalities [9].

Another important pathway in the pathogenesis of MFS is oxidative stress. Studies have shown that individuals with MFS have increased oxidative stress, which can lead to tissue damage and dysfunction [10]. Oxidative stress can also contribute to the dysregulation of TGF-β signaling, further exacerbating connective tissue abnormalities.

The precise mechanisms by which abnormal ECM and dysregulated TGF-β signaling lead to the characteristic features of MFS are not fully understood. However, it is thought that these abnormalities lead to the progressive weakening of connective tissue throughout the body, which can lead to aortic aneurysms, dissections, and other cardiovascular complications [5]. In addition, abnormalities in connective tissue can lead to skeletal abnormalities such as scoliosis, joint laxity, and bone deformities [11].

3.3. Symptoms

Marfan syndrome affects connective tissue throughout the body, therefore, leading to a variety of symptoms that can vary in severity [9]. The symptoms incude skeletal, ocular, and cardiovascular systems, pulmonary, gastrointestinal and other systems.

3.3.1 Skeletal System. Skeletal features are often the first to appear in patients with Marfan syndrome, and can include a tall stature, long limbs, and a long, narrow face [12]. Other skeletal abnormalities may include scoliosis, pectus excavatum, and joint hypermobility.

3.3.2 Ocular System. Ocular manifestations of Marfan syndrome can include myopia, lens dislocation, and retinal detachment [1]. Ectopia lentis, or lens dislocation, is a hallmark feature of the disease, occurring in up to 60 % of patients [1].

3.3.3. Cardiovascular System. Cardiovascular manifestations of Marfan syndrome are the most serious, and the major cause of morbidity and mortality in affected patients [6]. The most common cardiovascular manifestation is aortic root dilatation, which occurs in over 90 % of patients with Marfan syndrome [1]. This can lead to aortic dissection or rupture, which is a life-threatening condition [13]. Other cardiovascular abnormalities that may occur in patients with Marfan syndrome include mitral valve prolapse, aortic regurgitation, and aortic aneurysm [14].

3.3. 4 Pulmonary System. Marfan syndrome patients may also experience respiratory symptoms, including spontaneous pneumothorax. This is caused by the weakening of lung tissue and can be a potentially life-threatening complication.

3.3. 5 Gastrointestinal System. Gastrointestinal symptoms may include hiatal hernia, which can cause heartburn and difficulty swallowing [15].

3.3. 6 Other. Other less common symptoms of Marfan syndrome include dural ectasia, which can cause back pain and leg weakness [16], and skin manifestations such as stretch marks and hernias [17].

3.4. Diagnosis

According to the ESC guidelines for the diagnosis and management of Marfan syndrome, Marfan syndrome should be diagnosed based on clinical criteria, genetic

testing, and imaging studies. The diagnosis should be confirmed by a multidisciplinary team that includes cardiologists, ophthalmologists, and geneticists. Marfan syndrome is diagnosed using the Ghent criteria. MFS is a multisystem disorder that typically affects the cardiovascular system, skeletal system, and eyes, but may also involve the central nervous system, respiratory system, and skin. According to the 2010 revised Ghent nosology, the diagnosis of MFS can be confirmed if there is isolated aortic root dilatation and a pathogenic variant in the FBN1 gene is detected or if isolated ectopia lentis is described in association with the detection of a pathogenic variant in the FBN1 gene in association with aortic root dilatation [18].

The main cardiovascular manifestation of MFS is aortic root disease leading to aortic regurgitation, aneurysmal dilatation, and dissection [19]. MFS is found in 50 % of patients with aortic dissection younger than 40 years of age and in only 2 % of the elderly with aortic dissection [20]. Risk factors for aortic dissection in MFS include upper aortic diameter > 5 cm, rapid progression of dilation (> 0.5 cm per year), family history of dissection, decreased distensibility of the aorta, and moderate to severe aortic regurgitation (31).

Echocardiography is recommended at initial diagnosis and at six months for evaluation of the aortic root and ascending aorta in patients with Marfan syndrome [21]. Echocardiographic assessment of the aortic root should include measurements at the annulus, sinus, sinotubular junction, distal ascending, arch, and descending thoracic aortic levels. Early and severe disease often includes mitral valve prolapse and regurgitation leading to dilatation, impaired left ventricular function, and pulmonary hypertension [18,35].

Cardiovascular magnetic resonance or computed tomography angiography from the head to the pelvis should be performed in every patient at baseline to visualise the entire aorta and branching vessels [22].

Cardiac arrhythmias are common in patients with Marfan syndrome. Holter monitoring should be performed in symptomatic patients because ventricular arrhythmias, conduction abnormalities, and sudden cardiac death may occur [22]. Careful antihypertensive drug treatment with the goal of a 24-hour ambulatory systolic blood pressure < 130 mmHg (110 mmHg in patients with aortic dissection) is important.

3.5. Treatment

3.5.1 Medical therapy

Beta-blockers are recommended as initial medical treatment for Marfan patients. The beneficial effects of beta-blockers are the reduction of heart rate and left ventricular ejection fraction and the risk of aortic dissection [22,23]. For beta-blockers, dosing should be titrated to maximum effect, usually to a resting heart rate of < 60 bpm if blood pressure permits [23]. Moreover, studies have shown that the additional administration of an angiotensin-2 receptor blocker may reduce aortic root dilatation in patients with MFS. Blockers of the renin-angiotensin system may alleviate the clinical manifestations of MFS by blocking TGF-beta signalling [19]. Other studies have shown that angiotensin-converting enzyme inhibitors (ACE) reduce aortic wall stiffness in MFS [23]. Patients with Marfan syndrome and other forms of thoracic aortic aneurysms who take calcium channel blockers are at increased risk for aortic dissection and the need for aortic surgery [19,25].

3.5.2 Surgical treatment

The 2020 ESC guidelines recommend that surgery is indicated in patients with Marfan syndrome who have aortic root disease with maximal aortic sinus diameter 50 mm. Indications for repair at an external diameter less than 50 mm (aortic root diameter ≥45 mm) include family history of dissection at a low diameter, desire to become pregnant, systemic hypertension, rapid growth (≥3 mm/year) [22].

Cardiac surgery replaces damaged part of aorta and there are two general approaches used for aortic root replacement: composite valve graft and valve-sparing aortic root replacement.

Complete replacement of the aortic root with a composite valve graft consisting of the aortic root and a prosthetic (mechanical or bioprosthetic) aortic valve and reimplantation of the coronary arteries (Bentall procedure) was the surgical procedure of choice for older children and adults in the past. It should be noted that mechanical heart valves require anticoagulation and carry a high risk of thromboembolism and endocarditis [26].

In patients with anatomically normal aortic valves, valve-sparing aortic root replacement with a Dacron prosthesis and reimplantation of the coronary arteries into the prosthesis (David procedure) has been shown to be an appropriate surgical procedure with good results [4]. While anticoagulation may be recommended for some time after surgery, lifelong anticoagulation is not required. Therefore, valve-sparing surgery is a good option for women who want to become pregnant and for other patients in whom long-term anticoagulation is contraindicated [26].

3.6. Genetics

Genetic testing is often used to confirm the diagnosis of Marfan syndrome. If a Marfan mutation is found, family members also should be tested. MFS is inherited in an autosomal dominant manner.

Mutations of fibrillin-1 (FBN1) have been found in > 90 % of cases of MFS. Fibrillin, together with collagen and elastin, is the most important structural component of extracellular connective tissue. FBN1 is located on chromosome 15q21.1 and is comprised of 66 exons. The FBN1 mutation leads to increased production of a protein called transforming growth factor beta (TGF-β), which causes connective tissue problems.

If the aortic root is dilated but FBN1 analysis is negative, testing of TGFBR1 and TGFBR2 genes is recommended.

Genetic variants in the TGFBR1 and TGFBR2 genes have been associated with several inherited connective tissue disorders, including thoracic aortic aneurysms and dissections

TGFBR2 is located on chromosome 3p24.1 and encodes the TGFBR2 protein, which forms a complex with TGFBR1 and binds to TGF-β. This receptor/ligand complex phosphorylates proteins that regulate the transcription of genes related to cell proliferation [2].

4. Conclusions

In conclusion, Marfan syndrome is a rare genetic disorder that affects connective tissue throughout the body, leading to a wide range of symptoms that can vary in severity. Mutations in the FBN1 gene and dysregulated TGF-β signaling contribute to the pathogenesis of the disease, which can lead to cardiovascular complications, skeletal abnormalities, and ocular manifestations. Early diagnosis, medical treatment to delay the progression of aortic dilatation or possibly halt the pathologic process in the aortic wall, as well as timely elective surgery are the key

measures to improve the outcome of this disease as well as the quality of live for affected individuals. Ongoing research is needed to further understand the underlying molecular mechanisms of Marfan syndrome and to develop more effective treatments for this complex disorder.

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