What is new in the Marfan syndrome?

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Available online 22 October 2004

Abstract

The Marfan syndrome is an autosomal dominant disorder of connective tissue, caused by mutations in the FBN1 gene on chromosome 15. More than 500 mutations have been identified and almost all are unique to an affected individual or family. Genotype–phenotype correlations in the Marfan syndrome have been complicated by the large number of unique mutations reported, as well as by clinical heterogeneity among individuals with the same mutation. A relatively unknown cardiovascular manifestation of Marfan syndrome is dilatation of the main pulmonary artery. Of 50 patients with Marfan syndrome, MR imaging showed in 74% patients an enlarged pulmonary artery root above the upper limit of normal. Aortic elasticity determined by measurement of local distensibility and flow wave velocity with MR imaging is decreased in non-operated patients with Marfan syndrome. Aortic distensibility of the thoracic descending aorta appeared to be the strongest predictor for descending aortic complications. Over the past 30 years improvement of diagnostic modalities and aggressive medical and surgical therapy, have resulted in considerable improvement of life expectancy of patients with Marfan syndrome. Further studies are needed to investigate the role of modulating genes and genotype-phenotype correlations. Long-term follow-up studies may reveal the prognostic significance of aortic elasticity and may identify patients at risk of aortic complications.

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Keywords: Marfan syndrome; FBN1; Fibrillin-1

The Marfan syndrome is an autosomal dominant disorder of connective tissue, caused by mutations in the FBN1 gene on chromosome 15q21 encoding a large glycoprotein called fibrillin-1, a main component of extracellular microfibrils found in a wide range of tissues [1].

The Marfan syndrome is characterised by highly variable clinical manifestations in primarily skeletal, ocular and cardiovascular organ systems [2]. Prevalence has been estimated at 2–3 per 10,000 and about 25–30% of cases represent new mutations [3,4]. Prognosis is mainly determined by progressive dilatation of the aorta, potentially leading to aortic dissection and death at a young age [5]. Prophylactic surgery and treatment with β-adrenergic blocking agents have improved life expectancy substantially, from 47 years in 1972 to 61 years in 1995 [6,7,8,9]. Early identification of patients with Marfan syndrome is therefore of considerable importance.

1. Genetics

Marfan syndrome is the result of mutation in the FBN1 gene [1] (Fig. 1). More than 500 mutations have been identified and almost all are unique to an affected individual or family [10]. FBN1 consists of 65 exons, with almost every domain of fibrillin-1 being encoded by an individual exon. The locations of the mutation are spread throughout the FBN1 gene. The majority of mutations are missense mutations (about two-thirds of all FBN1 mutations) that alter a single amino acid out of the 2.871 amino acids that constitute the protein [11]. Most of these missense mutations occur in EGF-like domains and are predicted to disrupt calcium binding and/or the secondary structure of the domain [12]. About 20% of all reported mutations caused a frameshift with a downstream premature termination codon and approximately 12% of all mutations found to date are splice site mutations [11].

Genotype–phenotype correlations in the Marfan syndrome have been complicated by the large number of
unique mutations reported, as well as by clinical heterogeneity among individuals with the same mutation [13,14]. At present it is still not possible to find a mutation in approximately 30% of the patients with a definite diagnosis of Marfan syndrome [15]. Moreover, mutations in the \( FBN1 \) gene have also been found in patients with other fibrillinopathies. Some associations have emerged, however. Skipping of exons 24–32 correlates with the most severe, neonatal forms of Marfan syndrome [16,17,18]. Mutations that change a cysteine residue or a residue that is crucial for calcium binding in one of the cbEGF-like domains usually cause classic Marfan syndrome [19,20]. A significant subset of mutations located in exons 59–65 (the last seven exons of \( FBN1 \)) seem to be associated with mild phenotypes [21]. Hutchinson et al. [22] suggested that differences in normal \( FBN1 \) expression could contribute to the clinical variability seen in families with Marfan syndrome, and should be considered as a potential modifier of phenotype.

Until recently, three models of the pathophysiology of Marfan syndrome have been proposed. Initially, a dominant negative model of pathophysiology was hypothesized, in which the mutant fibrillin monomer disrupts assembly of normal fibrillin-1 into microfibrils or is itself misincorporated into the microfibril [23]. The level of mutant protein modulates the severity of the disease. Two other models are disturbance of tissue homeostasis of elastic fibers, and increased susceptibility of fibrillin to proteolysis [24,25].

Recently in a study by Neptune et al. [26], a fourth model of pathophysiology has been proposed. It was shown that mice deficient in fibrillin-1 had marked dysregulation of transforming growth factor-\( \beta \) (TGF-\( \beta \)) activation and signaling, resulting in apoptosis in the developing lung. Perinatal antagonism of TGF-\( \beta \) attenuated apoptosis and rescued alveolar septation in vivo.

This pathogenetic mechanism might also underlie other manifestations of Marfan syndrome, including myxomatous changes of valve leaflets and bone overgrowth. If this model could be confirmed in humans, some pathologies might become amenable to perinatal treatment.

Because of the intragenic heterogeneity molecular genetic screening is hampered to a considerable extent, and diagnosis is still based mainly on clinical major and minor features, as defined by a multidisciplinary council of experts in the field, known as the Ghent nosology [13] (Table 1).

In the Ghent nosology, dural ectasia was added to the major criteria for Marfan syndrome. In a recent study, quantitative criteria for dural ectasia were established using magnetic resonance (MR) imaging [27]. Dural sac-vertebral body ratio was calculated at all lumbosacral levels from L1 through S1. A dural sac-vertebral body ratio at L3\( \geq 0.47 \) or at S1\( \geq 0.57 \) could identify Marfan syndrome with 95% sensitivity and 98% specificity. No other major criterion

![Fig. 1. Schematic representation of the domain organization of fibrillin-1.](image)

Table 1: Diagnostic criteria for Marfan syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Family history</td>
<td>independent diagnosis in parent, child, sibling</td>
<td>none</td>
</tr>
<tr>
<td>Genetics</td>
<td>mutation ( FBN1 )</td>
<td>none</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>aortic root dilatation</td>
<td>mitral valve prolapse</td>
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<tr>
<td></td>
<td>dissection of ascending aorta</td>
<td>calcification of the mitral valve (&lt;40 years)</td>
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<tr>
<td>Ocular</td>
<td>ectopia lentis</td>
<td>dilation pulmonary artery</td>
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<tr>
<td></td>
<td>(4 needed):</td>
<td>dilation/dissection of descending aorta</td>
</tr>
<tr>
<td></td>
<td>pectus excavatum</td>
<td>(2 needed): flat cornea, myopia, elongated globe</td>
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<tr>
<td></td>
<td>needing surgery</td>
<td>(2–3 major, or 1 major and 2 minor signs):</td>
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<tr>
<td></td>
<td>pectus carinatum</td>
<td>moderate pectus</td>
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<tr>
<td></td>
<td>pes planus</td>
<td>excavatum</td>
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<tr>
<td></td>
<td>wrist and thumb sign</td>
<td>high narrowly arched palate</td>
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<tr>
<td></td>
<td>scoliosis &gt;20(^\circ) or</td>
<td>typical face</td>
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<tr>
<td></td>
<td>spondylolisthesis</td>
<td>joint hypermobility</td>
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<tr>
<td></td>
<td>arm span-height ratio &gt;1.05</td>
<td></td>
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<tr>
<td></td>
<td>protrusio acetabulae (X-ray, MRI)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>diminished extension elbows (&lt;170(^\circ))</td>
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<tr>
<td>Skin</td>
<td>spontaneous pneumothorax apical bulla</td>
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<tr>
<td></td>
<td>unexplained stretch marks (striae)</td>
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<tr>
<td></td>
<td>recurrent or incisional herniae</td>
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<tr>
<td>Central nervous</td>
<td>lumbosacral dural ectasia (CT or MRI)</td>
<td></td>
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<td>system</td>
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reaches the sensitivity and specificity of dural ectasia for Marfan syndrome.

2. Cardiovascular manifestations

The most common cardiovascular manifestations of Marfan syndrome include mitral valve prolapse and regurgitation, but aortic dilatation, especially of the aortic root, is the most common cause of morbidity and mortality. Dilatation of the sinus of Valsalva is found in 60–80% of adults with Marfan syndrome. Elastic fibers, composed of elastin deposited in microfibrils, are relatively more prevalent in the ascending aorta than in any other region of the arterial tree [28]. This histological feature, coupled with the repetitive stress of left ventricular ejection, probably accounts for aortic dilatation usually occurring primarily in the aortic root [29,30]. The rate of dilatation is heterogeneous and unpredictable [31,32]. Beta-blockers have been shown to reduce the rate of aortic dilatation and to improve survival in patients with Marfan syndrome during a follow-up of more than 10 years [7]. Echocardiography in the parasternal long-axis view is mostly used for measurement of the aortic root. MR imaging is particularly useful for imaging of the entire aorta, for patients with deformation of the chest wall and asymmetrical aortic roots [33].

A relatively unknown cardiovascular manifestation of Marfan syndrome is dilatation of the main pulmonary artery. Normal values for the pulmonary artery root have been established recently [34]. Of 50 patients with Marfan syndrome, MR imaging showed in 37 (74%) patients an enlarged pulmonary artery root above the upper limit of normal, 34.8 mm. Dilatation of the pulmonary artery was more prominent in the root than in the distal main pulmonary artery, similar to the dilatation process in the aortic root in patients with Marfan syndrome. There was a good correlation between pulmonary and aortic root diameter, indicating that pulmonary root dilatation seems to increase with progressive involvement of the cardiovascular system. Until now, pulmonary artery aneurysm and dissection are rare, but they may become of more clinical relevance in the near future because of increased longevity in patients with Marfan syndrome.

Although not included in the diagnostic criteria for Marfan syndrome, it has been speculated that a fibrillin defect in the myocardium may predispose patients with Marfan syndrome to LV dilatation and reduced LV function [4,35,36]. Recently, in a study of 36 patients with Marfan syndrome without significant valvular regurgitation, LV dimensions were found within the normal range [37]. No abnormal change in LV dimension was observed during an average follow-up period of 10.8 years. Mean ejection fraction was 60±4% (range 50–69%) and there was no change in ejection fraction over time. The authors concluded that LV dilatation and dysfunction do not occur in most patients with Marfan syndrome in the absence of important valvular regurgitation.

3. Aortic elasticity

The risk of aortic dissection rises appreciably with increasing aortic size, but it may occur at any point in the course of the disease [38,39]. As an additional potential predictor for aortic dissection noninvasive aortic elasticity has been investigated in patients with Marfan syndrome [40,41,42].

Groenink et al. [41] demonstrated decreased aortic elasticity determined by measurement of local distensibility and flow wave velocity with MR imaging in non-operated patients with Marfan syndrome (Fig. 2).

After aortic root replacement, both patients presenting with dissection at the time of the operation and electively operated patients with Marfan syndrome deserve intensive attention because aneurysms and dissection of the aorta may develop distal to the site of the graft [7,43].

In a population of 117 patients with Marfan syndrome no significant differences in aortic elasticity could be demonstrated between 39 patients with and 78 without aortic root replacement [44]. This agrees with the observation of Finkbohner et al. [42] that the incidence of surgery for aneurysm or dissection in the thoracoabdominal region...
minal aorta is similar (16%) in electively operated and non-operated patients with Marfan during a follow-up period of 25 years. Patients after elective aortic root replacement are probably not at higher risk for aortic complications in the residual aorta than non-operated patients [44].

The prognostic significance of aortic elasticity has been investigated in a prospective follow-up study of 78 non-operated patients with Marfan syndrome (Nollen et al., preliminary data). After a 6-year follow-up period 31 aortic complications—defined as aortic dissection or mean aortic growth >1 mm/year—had occurred in 25 (33%) of the patients. Twenty (26%) of 78 patients developed complications of the aortic root. In 11 (14%) patients complications occurred in the descending aorta (2 dissections, 9 aortic growth >1 mm/year). Multivariate analysis showed that for complications of the aortic root, the initial aortic root diameter was the major independent predictor. Aortic distensibility of the thoracic descending aorta appeared to be the strongest predictor for descending aortic complications. This means, that follow-up of patients with Marfan syndrome, should not only concern aortic diameters, but also aortic elasticity especially in the descending aorta, in order to identify patients at risk in the near future (Nollen et al., preliminary data).

4. Aortic surgery

Until recently, composite replacement of the aortic valve and ascending aorta was the standard operation for aortic root aneurysm in patients with Marfan syndrome. Over the past 30 years, composite valve graft has become a low risk operation and a very durable one for these patients. In a recent report by Gott et al. [45] on the results of aortic root replacement in 675 patients with Marfan syndrome, the operative mortality was 1.5% for elective operations and 11.7% for emergency operations. Five- and ten-year survival after aortic root replacement was 84% and 75%, respectively [45].

Aortic root replacement in patients with Marfan syndrome has been associated with a considerable higher risk of redissection and recurrent aneurysm than in patients with another etiology of aortic disease [46]. Presence of dissection, either acute or chronic, at the time of first operation is a significant predictor of subsequent repeat aortic operation [42]. Other risk factors for reoperation are hypertension and smoking [42].

For those patients wishing to avoid anticoagulation therapy two types of valve-sparing operations have been introduced in the early 1990s: reimplantation of the aortic root (David’s procedure), and remodelling of the aortic root (Yacoub’s procedure) [47,48]. Either type of valve-sparing aortic root replacement appears to be safe, reproducible, and associated with reasonable 5–10 years results for selected patients, at least in institutions with cardiac surgeons who have considerable personal experience with this procedure [49]. Survival was excellent in a recent report from the Toronto group, although 25% of the patients had severe aortic regurgitation 10 years after valve-sparing aortic root replacement [50]. The long-term results of valve-sparing aortic root replacement, and the overall incidence of all valve-related and aorta-related complications in large numbers of patients with Marfan syndrome are still unknown.

A relatively unknown postoperative complication, both after aortic valve-sparing operations and after composite aortic valve replacement is coronary ostial aneurysm [51] (Fig. 3). In a series of 40 patients with Marfan syndrome who underwent MR imaging 3 months to 19 years after elective aortic root surgery 27 (43%) patients had coronary ostial aneurysms. Coronary ostial aneurysms were more frequently seen in patients ≤35 years of age at operation versus those >35 years of age. Time after operation, did not influence the prevalence of coronary ostial aneurysms. Therefore, it seems likely that coronary ostial aneurysms are not progressive and develop due to perioperative stretch of the weakened wall of the coronary ostium. Follow-up studies, however, are needed to confirm this.

Over the past 30 years improvement of diagnostic modalities and aggressive medical and surgical therapy, have resulted in considerable improvement of life expectancy of patients with Marfan syndrome.

Further studies are needed to investigate the role of modulating genes and genotype-phenotype correlations. Long-term follow-up studies may reveal the prognostic significance of aortic elasticity and may identify patients at risk of aortic complications.

References


