Critical analysis of aortic dysmorphism in Marfan Syndrome

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Abstract

Introduction: Marfan syndrome (OMIM #154700) was described for the first time in 1896 by Antoine Bernard-Jean Marfan. It is characterized by its autosomal dominant inheritance pattern, affects 1:5000 of those born alive, and involves the gene that codifies the structural protein fribrillin-1. Fibrillin-1 is critical for the formation of the elastic system backbone and for the negative regulation of the cytokine transforming growth factor beta 1 (TGF-β1). In the syndrome this fibrillar component causes the degeneration of the fibers of the elastic system, which no longer sequesters matrix TGF-β, causing disorganization of the collagen fibers and vascular smooth muscles. The disease affects mainly the cardiovascular system, cardiovascular problems being the main cause of death. This is because arteries have large amounts of elastic fibers that rupture in an adverse process, causing mainly dissections and aneurisms, which have been better clarified in experimental studies with mice. **Objective:** The objective of this study was to conduct an etiopathogenic and molecular review to describe the advances in the understanding of blood vessel dysmorphism in the syndrome, especially of the aorta. **Materials and Methods:** For this purpose the literature of the last 35 years was extensively reviewed. **Conclusion:** The origin of the aortic dysmorphism in the syndrome stems from a number of events that begin with the mutation of the gene fibrillin-1, causing fragmentation of the aortic elastic fibers. Excess cytokine TGF-β increases the amount of metalloproteinases and of vascular smooth muscle cell apoptosis, leading to matrix remodeling and increasing the susceptibility of the vessel to an aneurysm or dissecting process.

Keywords: Marfan syndrome, arterial wall, morphology, extracellular matrix, aneurysm, dissecting aneurysm.

1 Introduction

Marfan syndrome (OMIM #154700) is an autosomal dominant inheritance condition described in 1896 by the French pediatrician Antoine Bernard-Jean Marfan. The syndrome is linked to the gene fibrillin-1 (*FBN1*) that codifies the protein fibrillin-1 (OMIM *134797), whose *locus* is located at 15q21.1. Mutations of the gene *FBN1* were associated with the disease in 1991. Accurate molecular diagnosis is challenging because of the more than 1500 described mutations. The proteins fibrillin-1 and fibrillin-2 form the backbone of the elastic system for elastin deposition and by extension, of the elastic fibers. Abnormalities of the gene *FBN1* lead to structural changes in the protein fibrillin-1, causing degeneration of the elastic system and disorganization of the collagen fibers and vascular smooth muscle of the aorta. Aortic microfibrils (fibrillin-1 and fibrillin-2) regulate the expression of the transforming growth factor beta (TGF-β) and so mutations of the gene *FBN1* increase the amount of circulating and tissue cytokine, compromising vascular smooth muscle and the integrity of the extracellular matrix.

Since arteries have large amounts of elastic fibers, the cardiovascular system is affected in more than 90% of the patients, causing mainly aortic dilation, aneurysm, and dissection. Given the challenge of understanding the intrinsic mechanisms of the disease, studies in experimental models in mice have advanced the understanding of the syndrome's pathophysiology and improved the available treatments.

2 Materials and Methods

A systematic search of the literature published between 1980 and 2014 was conducted in the following electronic databases: Web of Science, MedLine, LILACS, Scielo, and Oxford Journals, in addition to a manual search in book chapters, theses, and references of the selected studies in English, Spanish, and Portuguese using the keywords: "síndrome de Marfan" [*Marfan syndrome*], "morfologia" [*morphology*], "matriz extracelular" [*extracellular matrix*], "aneurisma" [*aneurysm*], and "aneurisma dissecante" [*aneurysm, dissecting*].

The exclusion criteria were: repeated studies in the various databases, studies without the keywords in the title, and studies with the keywords in the title but without the subject of interest in the abstract.

3 Results and Discussion

After the original description of the disease made by Antonie Bernard-Jean Marfan, other explanations of the condition emerged, such as one provided by Weve, who believed that the disease was caused by a disorder of the mesodermal structures (BEIGHTON, 1993). After Weve's theory, researchers looked for the etiopathology of the syndrome, assuming the disorder was caused by collagen fibers, and later, by elastin (BYERS, SIEGEL, PETERSON et al., 1981; BORRESEN, BAMFORTH, TSIPOURAS et al., 1985; TSIPOURAS, BORRESEN, BAMFORTH et al., 1986; AHTI, PALOTIE, KAITILA et al., 1987; KAINULAINEN, SAVOLAINEN, PALOTIE et al., 1990; TSIPOURAS, SARFARAZI, DEVI et al., 1991). With the discovery of the microfibril fibrillin-1 in 1986 (SAKAI, KEENE and ENGVALL, 1986) Hollister, Godfrey and Sakay (1990) Lee, Godfrey, Vitale et al. (1991), Magenis, Maslen, Smith et al. (1991), and Dietz, Pyeritz, Hall et al. (1991b) found an association between the syndrome and the gene *FBN1* using *in situ* hybridization techniques. In that same year Dietz, Cutting, Pyeritz et al. (1991a) described the first mutation in patients with the syndrome, and in 1993 Pereira, D'Alessio, Ramirez et al. concluded the sequencing of the gene.

The genomic organization of the gene *FBN1* (*locus* in 15q21.1) was elucidated by Pereira, D'Alessio, Ramirez et al. (1993) and Corson, Chalberg, Dietz et al. (1993), who divided the gene with 200Kb (BIERY, ELDADAH, MOORE et al., 1999) into 65 *exons*, with an mRNA containing 9663 nucleotides.

The codified protein, fibrillin-1, is a calcium-binding glycoprotein rich in cysteine, with intra- and interstrand disulfide bonds (HANDFORD, 2000) discovered in 1986 by Sakai, Keene and Engvall in human fibroblast cultures. Using electron microscope and in situ hybridization techniques, fibrillin-1 was identified in the extracellular matrix of the skin, lungs, kidneys, vascular compartment, cartilage, tendons, muscles, cornea, and zonule of Zinn (SAKAI, KEENE, GLANVILLE et al., 1991).

Pereira, D'Alessio, Ramirez et al. (1993) and Corson, Chalberg, Dietz et al. (1993) divided the protein into five domains: A, B, C, D, and E. Domain A contains *exon* 1, the cleavage site; domain B has *exons* 2-10; domain C has *exon* 10, rich in proline; domain D, the largest domain, has *exons* 11-63; and domain E has *exons* 64 and 65 (ROBINSON and GODFREY, 2000; ONLINE…, 2014).

Domains B-D consist of repeated *motifs* (specific amino acid sequence characteristic of a biochemical function) separated into three groups. The first *motif* is the *epidermal growth factor-like motif* (EGF) that repeats 47 times in this segment, and in 43 of those times, the molecule presents a calcium-binding variation, the *calcium binding EGF-like motif*. The second *motif* is the *latent transforming binding protein* (LTBP) with eight cysteine residues, analogous to that of the molecule *latent transforming growth factor β1* (LTGFβ1). The third *motif* is a fusion between parts of the EGF *motif* and the LTBP *motif*, forming the *fibmotif* (Figure 1) (PEREIRA, D'ALESSIO, RAMIREZ et al., 1993; CORSON, CHALBERG, DIETZ et al., 1993; ASHWORTH, KIELTY and McLEOD, 2000; LIMA, SANTOS, FERNANDES et al., 2010).

Fibrillin-1 is a critical glycoprotein for the formation of the elastic fiber system (SHERRATT, WESS, BALDOCK et al., 2001) and for the negative control of the cytokine *transforming growth factor β 1* (TGF-β1) (Figure 1) (SENGLE, TSUTSUI, KEENE et al., 2012; BYERS, 2004; KIELTY, 2006).

In the formation of the system of elastic fibers, fibrillin-1 interacts with other fibrillar components such as fibrillin-2, fibronectin-4, fibulin-8, and with the MAGP (glycoproteins associated with microfibril) (ADAMTS10, ADAMTSL, and
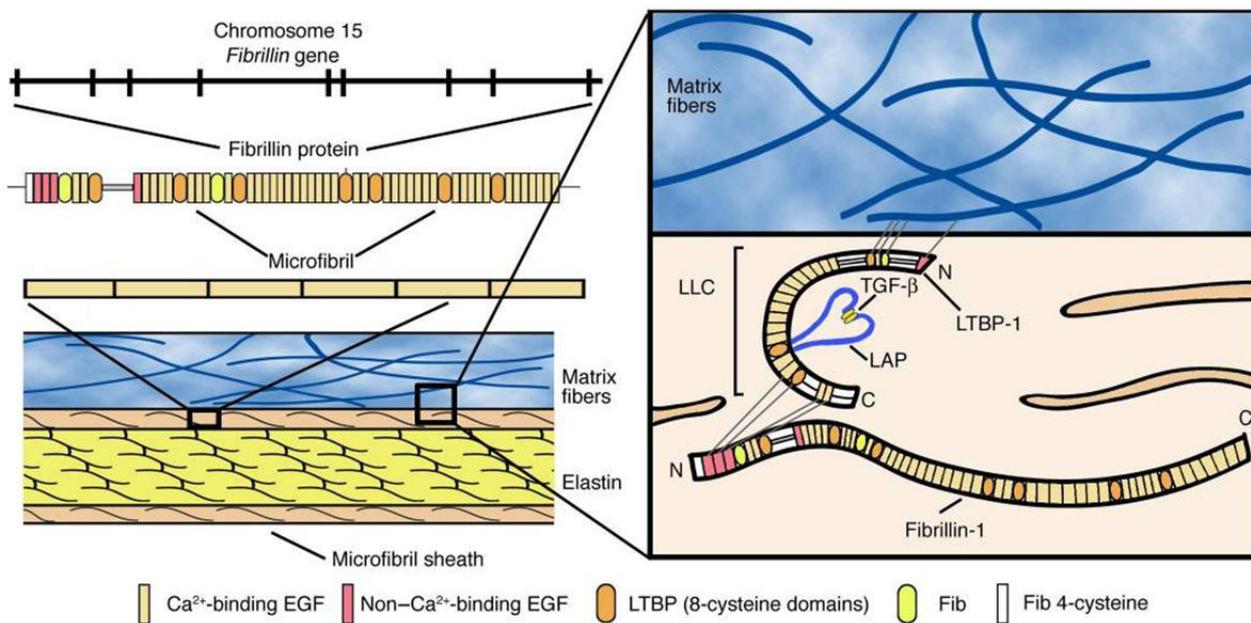
Figure 1. *Extracted from Byers (2004)*. The protein fibrillin-1 is codified from the mRNA transcribed from the gene *FBN1* at 15q21.1. Next, the protein is processed and binds with other fibrillar components forming microfibrils, which in turn interact with elastin, constituting mature elastic fiber. In another segment the image illustrates association between the elastic fiber and the extracellular matrix. Finally, fibrillin-1 is associated with the cytokine TGF-β1, and the latter, with the extracellular matrix.

ADAMTS; KIELTY, SHERRATT and SHUTTLEWORTH, 2002; BALDWIN, SIMPSON, STEER et al., 2013), forming the fibrillar component of elastic fibers. As the tropoelastin molecule interconnects with the fibrillar components, they form arrangements classified into three types of fiber: oxytalan, elaunin, and mature elastic (JUNQUEIRA and CARNEIRO, 2013).

Oxytalan fibers consist of microfibril bundles with a diameter of 10 nm composed of various glycoproteins, including fibrillin. They are found in the zonule of Zinn in the eyes, in periodontal ligaments, esophageal submucosa, and certain places of the skin, where they connect the elastic system to the basal lamina (FERRAZ DE CARVALHO and KÖNIG JUNIOR, 1982; FERRAZ DE CARVALHO, 1987; INOUE, HARA and SATO, 2012; BALDWIN, SIMPSON, STEER et al., 2013; JUNQUEIRA and CARNEIRO, 2013).

Elaunin fibers have a disorganized deposit of tropoelastin between the microfibrils (oxytalan fibers). They are found around the sweat glands, in the skin, esophageal submucosa, and juxtacanalicular tissue of Schlemm's canal (HANN and FAUTSCH, 2011; BALDWIN, SIMPSON, STEER et al., 2013; JUNQUEIRA and CARNEIRO, 2013).

In mature elastic fibers, tropoelastin builds up until it fills the entire bundle of microfibrils. They are the most numerous fibers of the elastic system, found mainly in blood vessels (BALDWIN, SIMPSON, STEER et al., 2013; JUNQUEIRA and CARNEIRO, 2013).

Given the LTBP *motifs*, the cytokine TGF-β1 anchors on fibrillin-1, which then controls its bioavailability keeping it latent (LTGF-β1) (KAARTINEN and WARBOURTON, 2003; BYERS, 2004) (Figure 1.). Mutations in the gene fibrillin-1 change the formation of the elastic fiber system, making them fragile and fragmented (ROBINSON and GODFREY, 2000). There is also a likely change in the molecule that prevents the cytokine TGF-β1 from binding to fibrillin-1, leaving too much of it active in the tissue and circulating blood (NEPTUNE, FRISCHMEYER, ARKING et al., 2003; MATT, SCHOENHOFF, HABASHI et al., 2009).

The cytokine TGF-β is involved in many physiological phenomena (PARDALI and DIJKE, 2012; DOBACZEWSKI, CHEN and FRANGOGIANNIS, 2011). It is also a strong activator of mast cells, metalloproteinases (MMP), fibroblast contractibility, and apoptotic process of the vascular smooth muscle cells (HANS, FENG, NAURA et al., 2011; HEISSIG, RAFII, AKIYAMA et al., 2005; CHUNG, YUENG, SANDOR et al., 2007; MARGULIS, NOCKA, WOOD et al., 2009).

The frailty of the elastic fibers and the excess cytokines in the extracellular matrix aggravate the disease phenotype. The cardiovascular system is affected in more than 90% of the patients, since arteries contain a large amount of elastic fibers (PYERITZ, 2000; STUART and WILLIANS, 2007; HOLM, HABASHI, DOYLE et al., 2011; CHIU, WU, CHEN et al., 2014).

The aorta is an elastic artery divided into three structural components: tunica intima, tunica media, and tunica externa. The tunica intima is rich in thick elastic fibers. The tunica media contains perforated elastic laminae organized concentrically. The smooth muscle cells, collagen fibers, proteoglycans, and glycoproteins are found between these elastic fibers. The tunica externa contains collagen fibers surrounding the vessel, with small vessels in their periphery (*Vaso vasorum*) (JUNQUEIRA and CARNEIRO, 2013).

Stuart and Willians (2007), found that 60% to 80% of the patients with Marfan syndrome presented aortic dilation, later developing dissection; in 76% of the cases, the pulmonary artery was also dilated, but rarely dissected; 52%-68% of the cases presented primary prolapse of the mitral valve that later evolved into arrhythmias; 80%-100% of the cases experienced dilation in the descending aorta after dissection; 4% of the cases presented prolapse of the tricuspid valve; 20%-30% of these evolved to arrhythmias; less than 1% presented aneurysm in the coronary arteries; 4% presented atrial septal defect; and 36% presented left ventricular dysfunction (children). Recent studies show that the greatest concern with Marfan syndrome patients is still aortic dilation and dissection because of its fatality (TSAI, LIN, HSU et al., 2009; JONDEAU, DETAINT, TUBACH et al., 2012; CHIU, WU, CHEN et al., 2014).

Marshall, Carlson, O'Malley et al. (2013), found circulating fibrillin-1, showing that the elastic fibers of the arteries are not only fragmented but also have a fragile backbone, losing its main component and facilitating the establishment of a dissecting process.

Excess TGF-β1 promotes a positive regulation of metalloproteinases (MMP), whose function is to degrade matrix elements. In the syndrome activated MMP deteriorate the mechanical properties of the aorta, decreases its contractility, increases apoptosis, and increases osteopontin in the smooth muscle cells, making the vessel susceptible to aneurysms, dissections, and even rupture (CHUNG, YUENG, SANDOR et al., 2007; HANS, FENG, NAURA et al., 2011; HOLM, HABASHI, DOYLE et al., 2011; HABASHI, DOYLE, HOLM et al., 2011; BALDWIN, SIMPSON, STEER et al., 2013).

According to CHUNG, YUENG, and SANDOR et al., 2007, contraction of the vascular smooth muscle cells regulates the resistance to traction of the aortic wall. Excess TGF-β1 reduces αSM-actin expression, which reduces vessel integrity and αSM-actin function, leaving the aorta even more susceptible to aneurysms and dissections associated with the syndrome (CHUNG, YUENG, SANDOR et al., 2007; SYYONG, CHUNG, YANG et al., 2009; HOLM, HABASHI, DOYLE et al., 2011; BALDWIN, SIMPSON, STEER et al., 2013).

Given the complexity of Marfan syndrome, experimental models in mice were necessary (HAMILTON and YU, 2012). The first experimental models were MgΔ and MgR (PEREIRA, ANDRIKOPOULOS, TIAN et al., 1997; PEREIRA, LEE, GAYRAUD et al., 1999), both with low gene expression, thereby characterizing the syndrome only in homozygosis (PEREIRA, LEE, GAYRAUD et al., 1999; JUDGE, BIERY, KEENE et al., 2004).

Later researchers found that these models did not provide reliable methods to test the interference of the negative domain of the mutant allele (JUDGE, BIERY, KEENE et al., 2004). Hence, in order to perfect the experimental models, Judge, Biery, Keene et al. (2004), discussed the formation of the experimental model C1663R, which substitutes one of the six cysteine residues by a *motif calcium-binding epidermal growth factor like* (cbEGF-like). This mutation is very common in humans with Marfan syndrome. However, the experimental model does not present the cardiovascular phenotype, which is the greatest concern in practice. Thus, researchers created the murine C1039G model, characterized by the substitution of cysteine by glycine in the residue 1039 of the EGF *motif* of the gene (HABASHI, JUDGE, HOLM et al., 2006).

This model has the backbone and cardiovascular phenotypes commonly found in the affected patients (LIMA, SANTOS, FERNANDES et al., 2010).

The most recent model is the MgΔ^{LoxPneo}, a variant of the mgΔ model with deletion of the resistant neomycin cassette. Consequently, the fibrillin-1 gene presents a deletion between *exons* 19-24 (LIMA, SANTOS, FERNANDES et al., 2010). This new model manifests the negative domain of the disease, phenotypic variability with backbone changes, and chronic pulmonary inflammation.

Based on experimental models, the pathophysiological mechanisms of the disease were better clarified, which can improve treatments and surgical techniques, increasing patient longevity and quality of life.

4 Final Considerations

The origin of the aortic dysmorphism was much better clarified by studies with experimental murine models. A priori, it stems from a number of events that begin with the mutation of the gene that codifies the protein fibrillin-1, causing fragmentation of the aortic elastic fibers. Unbalance of the cytokine TGF- β1 occurs along with this event, increasing the amount of metalloproteinases and vascular smooth muscle apoptosis, making the vessel susceptible to aneurysms and dissections. Therefore, we notice that despite the monogenic nature of the anomaly, hence a the genetic etiopathogenesis, many other subsequent situations occur at the expense of incorrect secondary events in the intracellular cascade mediated by fibrillin-1, culminating in the various morphological anomalies, especially in the cardiovascular compartment.

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