Marfan Syndrome: the Nowadays of a Century-old Disease

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The review emphasizes the actuality and importance of Marfan syndrome research worldwide. The hundred years old disease has been described mainly by its skeletal, ocular and cardiovascular manifestations, and constitutional type. The underlying gene mutations have been discovered in 1991. The surgical treatment of aortic root dilatation and dissection using Dacron tube reconstruction in emergency and prophylactic surgery has been published in 1955. Nowadays international foundations, database networks subjected Marfan syndrome as a rare disease with privileged research programs. The clinical Ghent nosology of pleiotropic criteria is accepted world-wide (1996). The research programs are focused on international proposals.

Keywords: Marfan syndrome, former, recent, incursions

Marfan syndrome (MFS), named after Antoine Marfan who first described its skeletal disorders in a 5 years old child (1896). It is a genetically inherited, autosomal dominant disease of the connective tissues, characterized by multiorgan-system pleiotropism [1].

The most severe consequences of the disorder are the cardiovascular complications. The dilatation and dissection of the proximal aorta occurs in 75-80% of the cases, which unpredictably may lead to parietal rupture and sudden death [2, 3].

MFS exposes the individual to medical, emotional, financial and social stress; all of these factors are reflected in everyday activities and quality of life [8]. The progression of the untreated disease is catastrophic; 50% of these patients die before getting emergency care, the mortality rates being around 75-80% per week. Children and young adults are the most affected age groups. Life expectancy of untreated Marfan syndrome is 32 years [4].

Based on demographic statistical data the incidence of MFS is estimated to 1-2 cases / 100,000 individuals yearly. The prevalence, calculated by extrapolated statistical analysis (with limited relevance), is 2000 cases / 10 million individuals [5, 6].

The WHO ranked the MFS as a RARE DISEASE, and granted a scientific research program for the years of 2008-2013, emphasizing the research of the genetic, therapeutic, epidemiological and social aspects of the disease.

In the first decade of the last century the goal was the description of the genotype involved with the phenotype, mainly with the skeletal, ocular, cardiovascular (1943) manifestations, and dominant inheritance (1931).

In 1955 McKusick [7] established that the cardiovascular complications of MFS are connective tissue inherited disorders.

The MFS's associated gene mutation was discovered and indentified by Dietz in 1991 [9], the Fibrillin1 (FBN1) mapping in chromosome 15q21. The gene mutations result in disintegration of elastic fibers in the aortic media, mucinous degradation and potential dilatation, cleavage and rupture of the weakened aortic wall, interacting with hemodynamic wall stresses.

Developmental molecular biology demonstrated about 600 mutations of the FBN1 gene, where the possible complications cannot be prevented, of 25% resulting "de novo mutations" [10, 11, 12, 13].

The FBN1 is regulated, activated and signaled by Transforming Growth Factor beta receptor genes. The overexpression of these genes increases the mutated FBN1 genes and increases the severity of the elastofibbrillolitic processes in the aortic wall.

In 1991 Dietz [10] developed the "knock-in mouse" ("Marfan mouse model"), in which the pathophysiological mechanism of aortic dilatation is caused by the extensive TGF beta receptor 1 signaling. Potentially the regulation with pharmaceutical drugs, the extracellular matrix signals regulation effects to inhibit the elastic fiber fragmentation in the ascending aorta.

Under experimental conditions, beta blockers and angiotensin II receptor blockers had a beneficial effect on the evolution of ascending aorta aneurysms. The clinical prophylactic pharmacotherapy of aortic dilatation in Marfan syndrome is supposed to decrease, but not block the rate of dilatation. There is no available data regarding the effect of long term use on dilated aortic root remission.

The crucial turning point in cardiovascular complications of the MFS is the successful aortic surgical strategy, which is mandatory for survival. The pioneer of aortic replacement techniques was Michael F. DeBakey (1908-2008) who developed the impregnated woven Dacron graft, in 1955 being the first to publish about its usage in replacement surgery in an aortic root dissection case [14]. A historical coincidence: the oldest famous survivor of a self-diagnosed aortic dissection in 2006 was BE DeBakey who at the age of 97 by the time underwent surgery using

the technique described by him, i.e. Dacron tube aortic reconstitution.

Decades of aortic root surgery involved many technical and tactical challenges, hypothermia and selective brain protection, and conditions requiring lifelong follow-up, management and care [14].

The paramount procedure for ascending aorta dilatation and dissection is the Bentall and Bono tubular valve (St. Jude mechanical valve) Dacron reconstruction technique, validating its efficiency and durability in the treatment of MFS with a four decade experience (1968) [15].

The emergency operations are the only way for survival in acute aortic dissections. The surgical mortality decreased from 72% (in 1972) to about 10% (in 2009) [16].

Prophylactic, elective surgery with reconstruction of the ascending aorta before imminent rupture has a mortality rate between 0% and 2%.

The prognosis of operated MFS patients with a regular follow-up control and management is good, increasing their potential life-expectancy to the population average of 70-74 years (2009) [17].

The MFS literature is almost endless, the scientific articles, fundamental and clinical results prove the actuality of the syndrome. Presentations, database summarizations, analyses and meta-analyses, as well as the representative task force guidelines make appropriate conclusions [18, 19, 20, 21, 22]. The consensual nature of MFS research has a national and worldwide advantage.

Actually, two important factors enforced the international aspect of MFS: the informative, database and organization networks, and the worldwide accepted MFS nosology as clinical diagnostic classification, based on pleiotropism criteria.

The international MFS study structures:

- ISMS (International Symposium on MFS) organized 2-3 yearly meetings in the form of itinerary sessions. The 1st was in 1988 (Baltimore, USA), 8th in 2010 (Warrenton, Virginia, USA)
- IFMSO (International Federation of Marfan Syndrome Organizations), founded in 1992 at the 2nd ISMS (San Francisco, USA) [23]
- IRAD (International Registry of Acute Aortic Dissections, 1996) summarized the data of representative centers of 20 countries in a common database with analyses, demographics, conclusions and statistical evaluations.
- EMSN (European Marfan Support Network), a coalition of support organizations for people with MFS and related disorders.
- EURODIS (European Rare Disease Organization)
- Ophornet: a database promoting the optimal preventive and treatment of rare diseases; affiliated countries: HU, RO
- NMF (National Marfan Foundation), nonprofit, with country-specific research and help programs.
- GSNW (International Genetic Support Network)
- GARD (Genetic and Rare Disease Information Center).

The international constellations stipulate a universally accepted clinical nosological coding for the diagnosis of MFS.

Table I. The Ghent nosology criteria

Organ system	Major criteria	Minor criteria
Skeletal system: (affected in 95%)	In case of the presence of four concomitant manifestations: – pectus carinatum – pectus excavatum – reduced segment ratio – wrist and thumb signs – scoliosis > 20° – spondylolisthesis – reduced elbow extension – protrusio acetabuli	– moderate pectus excavatum – joint hypermobility – gothic palate with jamming teeth – facial discrepance: * dolichocephaly * retrognathia * enophthalmus, * malar hypoplasia * slating palpebral fissures
Ocular system: (affected in 18%)	– ectopia lentis (subluxation)	– flat cornea (keratometria) – axialis elongation of bulbus – hypoplastic iris / ciliary muscle (reduced myosis)
Cardiovascular system: (affected in 68–77%)	– dilatation of ascending aorta (with – involvement of the sinus Valsalvae) ±regurgitation – disseciton (tear) of the ascendant aorta	– mitral prolapse ± regurgitation – dilatation of main pulmonary artery without valvular disease peripheral pulmonary stenosis or other evident cause < 40 years – mitral anulus calcification < 40 years – dilatation or dissection of the descendent aorta < 50 years
Pulmonary system: (affected in 1–5%)		– spontaneous PTX – pulmonary apical blebs – striae, stretch-marks (without weight gain, pregnancy or enforcement) – recurring incision hernias
Skin and connective tissue underneath:		
CNS (Dura):	– lumbosacral dura ectasia	
Family anamnesis/genetic contribution:	– diagnosed MFS at direct family member (parent, child) – known presence of FBN1 mutation – presence of haplotype around FBN1 inherited by descent and unequivocally associated with diagnosed MFS in the family	

The diagnosis is based on the involvement of pleiotropic organ-system manifestations and considers phenotype-based signs and family history (if individual genetic screening is not accessible).

The criteria of clinical diagnosis are supported by genetic investigations (with clinico-genetic value). The major criteria are highly specific of MFS, the minor ones are only partly representative.

- The Berlin nosological criteria (1986) [25] was incomplete, and missed or excluded about 20% of Marfan patients.
- The revised Ghent criteria (University of Ghent, Belgium) by De Paepe et al. (1996) concretized in stringent nosological criteria, and were based on the six organ system's objective manifestations. It had a 96% value to include or exclude MFS without family history and genetic contributions, asserting the MFS diagnosis based on two major and 1–2 minor criteria [26, 27].
- The Loeys simplification (2010) of the Ghent nosology considers that in absence of family history, the aortic root aneurismal dilatation and ectopia lentis are the cardinal clinical features, and these two are unequivocal for the clinical diagnosis of MFS [28].

Table I lists the Ghent six organ-system major and minor criteria. Some of these manifestations occur only in adults, thus they are less apparent in children.

Genetic studies of Marfan-like disorders demonstrated that they arise from new mutations of fibrillin 1 and transforming growth factor beta receptor I, II genes, mapped on different chromosomes, were only partially detected. The common characteristics of MFS and related disorders are the autosomal dominancy, and overlapping signs and characteristics, as Marfanoid habitus, skeletal manifestations and possible aortic root dilatation, with potential for parietal rupture. In urgent surgery differential diagnosis is not always necessary, because the management and surgical procedures are the same [29, 30, 31]. The rate of aortic dissection in Marfan related disorders is 3-17%. The following syndromes are of relative interest in MFS pathology:

- Loyes-Dietz syndrome (LDS), type I and III
- Ehlers-Danlos syndrome (EDS) (cutis laxa)
- Stickler syndrome (SS) (arthro-ophtalmopathy)
- Beals syndrome (CCA) (Congenital contractural arachnodactyly)
- Shprintzen-Goldberg syndrome (SGS) (familial craniosynostosis)
- Familial Thoracic Aortic Dissection (TAAD)
- MASS: Mitral valve-Aorta-Skin-Skeletal phenotype

Presently, the MFS is a priority for clinical and fundamental research, and focused national and transnational advices:

- Proper communication between patients, family, healthcare community, medical professionals, education, public relations
- Encounter the main areas of research: clinical-genetic, therapeutic, epidemiological and social.
- Share information about MFS worldwide and facilitate communication among medical professionals, research centers and researchers.
- Multi-department workgroups for prophylactic therapy of progression of aortic root dilatation.

The hundred years of research had a supreme result, the increased life expectancy in Marfan syndrome.

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