Masterarbeit

Marfan Syndrome

Cardiovascular Aspects and Pregnancy

A literature review and discussion of current perspectives

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Abstract

Background: Marfan syndrome (MFS) is an autosomal dominant inherited connective tissue disorder, affecting several organ systems, with the most notable in skeletal, ocular, cardiac, and dural systems. In most cases the syndrome is caused by mutations in the *FBN1* gene on chromosome 15, encoding a member of the fibrillin family of proteins. Fibrillin-1 is an extracellular matrix glycoprotein that serves as a structural component of microfibrils, which provide force-bearing structural support in elastic and non-elastic connective tissue throughout the body. Cardiovascular manifestations are the major cause of mortality in MFS, with a prevalence of 80% of patients suffering from cardiac events once in their lifetime. The most common cardiac features include aortic dilatation and dissection, and mitral valve prolapse and regurgitation. The expression of clinical features in MFS varies widely and the diagnosis of MFS offers a challenge for health physicians and genetic experts. The Ghent nosology provides criteria for diagnosis and management of MFS, established by a panel of experts. Woman with MFS considering pregnancy carry an even higher risk for cardiac complications and need proper management and counselling before, during and after pregnancy. Though plenty of literature and studies regarding MFS have been published, there are still issues in regard of diagnosis, management and counselling. **Method**: The thesis is based on literature research and a discussion of current available data. The publications were acquired from Pubmed. **Results**: Due to molecular genetic testing techniques, such as Sanger sequencing and next generation sequencing, an internationally available gene map has been established which provided huge improvement for diagnosis and genotype–phenotype correlations in MFS. However, concrete predictions about a patients individual risks are still not possible to be made. Counselling and proper management of patients with MFS is still showing deficiencies. Beside the common monitoring and frequent medical observations, the prevention of psychologic diseases, such as depression, should be focused on and a patient should be supported individually to his needs.

Zusammenfassung

Hintergrund: Das Marfan Syndrom (MFS) ist eine autosomal vererbte systemische Bindegewebserkrankung mit einer hohen klinischen Variabilität. Die häufigsten Symptome treten an Skelett, Augen und Kardiovaskulären System auf. In den meisten Fällen liegt die Erkrankung einer Mutation im Fibrillin-1-Gen zugrunde, welches für Fibrillin-1, ein für das Bindegewebe essentielles Protein codiert. Kardiovaskuläre Ereignisse, wie Aortendissektion und Aneurysmen oder Mitralklappeninsuffizienz haben eine Prävalenz von 80% in Patienten mit MFS und können im Laufe des Lebens zu lebensbedrohlichen Komplikationen führen. Das Ausmaß der klinischen Symptome in betroffenen Personen kann stark variieren und die Diagnose des Syndroms konfrontiert Ärzte oftmals mit Schwierigkeiten. Eine Gruppe von Experten erstellte dafür eine Richtlinie mit einer Reihe von Kriterien für die Diagnose des MFS, die sogenannte Genter Nosologie. Frauen mit MFS die eine Schwangerschaft in Betracht ziehen oder bereits schwanger sind tragen ein besonders hohes Risiko für kardiovaskuläre Komplikationen während und nach der Schwangerschaft und benötigen deshalb eine entsprechende medizinische Beratung und Betreuung. Trotz jahrelanger Forschung und einer großen Menge an verfügbarer Literatur bezüglich des Syndroms, gibt es immer noch Defizite im Bereich der Diagnosestellung, Beratung und Therapie. **Methode:** Die Arbeit basiert auf Literaturrecherche und einer Diskussion über Ergebnisse von verfügbaren Studien und Publikationen in Bezug auf das MFS. Die Publikationen wurden von Pubmed erworben. **Ergebnisse:** Dank des Fortschritts im Bereich der molekular-genetischen Tests wurde bereits ein international verfügbares Gen-Panel erstellt, welches mehrere tausend Mutationen die in Verbindung mit dem Syndrom gestellt wurden, beinhaltet. Dieses ermöglicht Ärzten und Genetikern, basierend auf der Art der Mutation, eine Vorhersage über den Krankheitsverlauf eines Patienten zu stellen. Eine sichere Vorhersage ist auf Grund der hohen klinischen Variabilität, auch innerhalb einer Familie, normalerweise aber nicht möglich. Im Bereich einer ausreichenden und individuellen Beratung bestehen immer noch Defizite und besonders der psycho-soziale Effekt den eine genetische Erkrankung mit sich bringen kann sollte in eine angemessene Therapie mit einbezogen werde.

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, 10.10.2019

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1. General Introduction

Hereditary connective tissue disorders are relatively rare diseases affecting the extracellular matrix that supports organ systems (Aalberts, 2014). The extracellular matrix consists mainly of collagens and has numerous functions, such as supplying support for neighbouring cells and regulation cell behaviour. In the cardiovascular system the extracellular matrix is of major importance, providing compliance and elasticity to the heart, valves and vascular tree. Hence, cardiovascular abnormalities represent the major clinical aspect in connective tissue disorders, such as aortic root dilatation, mitral valve prolapse, aortic aneurysm or aortic dissection. Connective tissue disorders encompass two broad and pathogenically unrelated categories of diseases (Ryan, 2019). The first is genetic diseases, such as Marfan syndrome (MFS), Ehlers-Danlos syndrome or fibromuscular dysplasia, the second is autoimmune diseases, such as systemic lupus erythematosus, Sjögren syndrome or systemic sclerosis. Genetic as well as autoimmune causes of connective tissue disorders can lead to severe clinical manifestations in the cardiovascular and other organ systems.

MFS is one of the most common inherited disorders of connective tissue (Murken *et al.*, 2017). It is an autosomal dominant condition occurring once in every 10,000 to 20,000 individuals. There is a wide phenotypic variability of symptoms in MFS with the most notable occurring in eye, skeleton, connective tissue and cardiovascular systems. 25-35% of diagnosed cases are caused by a de novo mutation in the *FBN1* gene. So far, more than 3000 different mutations in the *FBN1* gene have been detected, hence the probability of various families carrying the same mutation is quite small (Isekame *et al.*, 2016). The *FBN1* gene provides instructions for making a large protein called fibrillin-1 (Murken et al., 2017). Fibrillin-1 is an extracellular matrix glycoprotein that serves as a structural component of calcium-binding microfibrils, which are essential for the structure of elastic and non-elastic connective tissue throughout the body.

The features of MFS can become apparent anytime between infancy and adulthood. Depending on the onset and severity of signs and symptoms, MFS can be fatal early in life. However, with proper treatment and management of the disease, many affected

individuals have lifespans that can be compared to that of the general population (Isekame *et al.*, 2016).

The aim of this thesis is to discuss current available literature regarding MFS and connected issues such as cardiovascular manifestations and risks, in general and during pregnancy. Other typical features of the syndrome, such as ocular or skeletal will be described and further discussed in relation with diagnostic criteria. The most common genetic mutations of MFS will be reviewed, as well as recently rare findings of variants or untypical phenotypic features. The sources used for this thesis consist primarily of studies and publications acquired from Pubmed.

1.1. Clinical features

MFS is part of a broad phenotypic continuum associated with heterozygous *FBN1* pathogenic variants that ranges from mild to severe clinical conditions (Dietz, 2019). The cardinal manifestations of MFS, including the ocular, skeletal and cardiovascular systems have a high degree of clinical variability. In general, clinical manifestations run true within families, suspecting that the genetic variant is the predominant determinant of phenotype.

Ocular findings in MFS include myopia, the most common ocular feature which often progresses rapidly during childhood, and ectopia lentis, a displacement of the lens from the center of the pupil. Patients with MFS are also at increased risk for retinal detachment, glaucoma and early cataract formation (Dietz, 2019).

Skeletal characteristics in MFS include excessive linear growth of the ling bones and joint laxity, disproportionally long extremities and overgrowth of the ribs (*figure1*). Scoliosis is also a common feature and can be mild or severe and progressive. Joint laxity and excessive linear overgrowth lead to the characteristic thumb and wrist signs in MFS patients. Flat feet (*figure 2*) can be the result of inward rotation of the medial aspect of the ankle. Patients may also suffer from reduced mobility of the joints and digits. Usually those skeletal findings develop during early childhood and tend to progress during periods of rapid growth. Facial findings include long and narrow faces with deeply set eyes, downward slanting of the palpebral fissures, flat cheek bones and a small and receding chin. Patients with MFS are not necessarily tall compared to the general population standard, but they are usually taller than predicted for their family (Dietz, 2019).

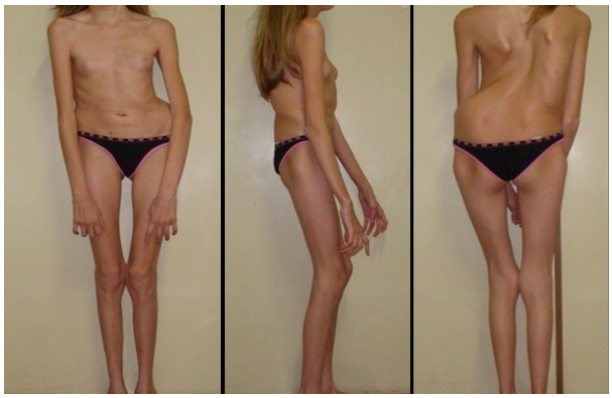

Figure 1: MFS patient, showing excessive linear growth, disproportionally long extremities and scoliosis.

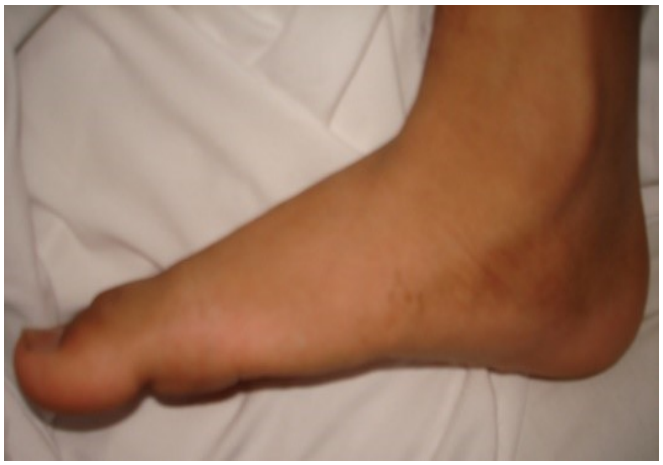

Figure 2: Flat foot of MFS a patient.

Cardiovascular manifestations are the major source of morbidity and early mortality in patients with MFS. Cardiovascular features include dilatation of the aorta, aortic tear and rupture, mitral valve prolapse, tricuspid valve prolapse and enlargement of the

pulmonary artery. Aortic dilatation usually progresses with age. Histologic examination shows fragmentation of elastic fibers, loss of elastin content and accumulation of amorphous matrix components in the aortic media. Those features can result in aortic dissection. Commonly the progression rate of dilatation of the aorta ascends with age, although it is unpredictable and individual in each patient. Cardiovascular aspects in connection with MFS will be further discussed in chapter 3 (Dietz, 2019).

Other features of MFS are dural ectasia, which can lead to bone erosion and nerve entrapment, manifestations in skin, such as hernias and skin stretch marks, and spontaneous pneumothorax due to the developing of long bullae especially of the upper lobes (Dietz, 2019).

The phenotype of MFS is likely to highly vary. Some people experience only mild effects, while others develop life-threatening complications. In most cases, the disease tends to worsen with age.

The diagnosis of Marfan syndrome relies on a set of defined clinical criteria, the Ghent nosology, developed to facilitate proper recognition of the syndrome and improve the patient management and counselling. To decrease the risk of premature or missed diagnosis, an international panel of experts revised the criteria in 2010. The new diagnostic criteria put more attention on the cardiovascular manifestations of the disorder. The criteria of the Ghent nosology will be further discussed in chapter 2.3.

1.2. History of MFS

MFS was first described in 1896 by the French paediatrician Antoine Bernard-Jean Marfan, who described a case of a 5-year old girl with disproportional ling limbs and long slender fingers and toes (Hetzer, Gehle and Ennker, 1995). By the 1930s cardiovascular and ocular findings have been found to be linked to the disease as well as a dominant inheritance due to the familial pattern of the phenotype. The cause of premature mortality has not been mentioned until 1940, when aortic root diseases have been brought in compliance with the disease Marfan has described. In 1986 the diagnostic criteria for the MFS were codified by a group of experts, who set up a

guideline of recommendations for the diagnosis and treatment of the syndrome. Those so called Berlin criteria picture the syndrome as a clinical and phenotypic spectrum and are still widely used today. All along this spectrum, various non-Marfan conditions were overlapping, such as autosomal dominant mitral valve prolapse syndrome, various Ehlers-Danlos types, Stickler syndrome, familial aortic dissection and others, which often led and still do lead to problems in the diagnosis of MFS (Hetzer, Gehle and Ennker, 1995).

In 1955, Victor McKusick coined the term “heritable disorder of connective tissue” in a paper on the cardiovascular manifestations of the Marfan syndrome. The year after, he published the first of four editions of a monograph entitled “Heritable Disorders of Connective Tissue”, including a chapter devoted to MFS. Finding the cause of MFS was a long way of biochemists and genetics, whose research included the clinical features and phenotypes, as well as the actual genetic defect (Hetzer, Gehle and Ennker, 1995).

In the 1950s it was clear that the aortic media is distinctly abnormal in the MFS. The histopathology, termed “cystic medial necrosis” by Erdheim in 1930, proved to be a misnomer, given that there is neither necrosis nor cysts. The most striking feature was recognized to be fragmentation and disarray of the elastic fibres (Hetzer, Gehle and Ennker, 1995).

Another hallmark of MFS is ectopia lentis, with the lens typically displaced upward and zonules stretched but intact. McKusick, knowing of the evident importance of the zonules in keeping the lens in place, made the following prescient prediction in 1956: “What the suspensory ligament of the lens has in common with the media of the aorta is obscure. If known, the basic defect of this syndrome might be understood.” It took more than 30 years to get an idea of what that common link was, and another four years to prove it (Hetzer, Gehle and Ennker, 1995).

In the 1990s mutatuions in the *FBN1* gene were discovered to be the cause of the typical features of MFS. Dietz and colleagues found a single nucleotide change in the *FBN1* gene that had the result of altering an arginine residue to a proline. That change was proven to be harmful for three reasons: first, the altering of the secondary structure of proteins, second, the region in which the mutations occurred are highly conserved, and third, the arginine remnant was found to be vital for a hydroxylation reaction predicted to occur as a post-translational modification of fibrillin. Most telling however,

was the population evidence, considering that the mutation was not found in healthy humans (Hetzer, Gehle and Ennker, 1995).

In more than a century of research and medical development, the knowledge about MFS has increased tremendously. Currently, MFS id known as a clinically heterogeneous disorder, due to the great variability of gene expression caused by mutations in the *FBN1*, and in rare cases by mutations in the transforming growth factor (TGF)-β receptor 1 (*TGFBR1*) or -2 genes (*TGFBR2*).

2. Genetics and diagnosis of MFS

2.1. Inheritance

MFS is inherited in families in an autosomal dominant manner. In autosomal dominant inheritance, a genetic condition is present when the child inherits one copy of a mutated gene from one parent. Hence a child of a parent with the mutated gene has a 50% chance of inheriting the mutation (*figure 3*). Men and women are equally likely to carry these mutations and sons and daughters are equally likely to inherit them (Murken *et al.*, 2017).

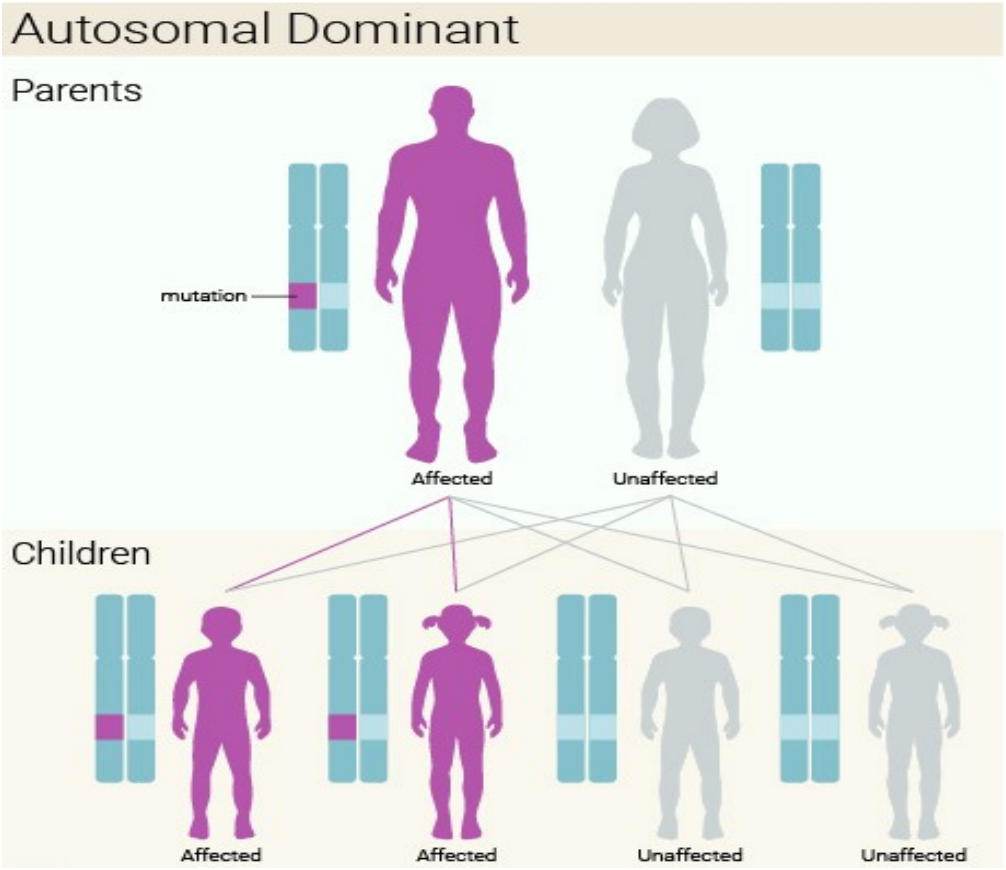

Figure 3: Autosomal dominant inheritance. The figure shows a 50% chance of children inheriting the mutation of one of their parents. In this case the father is heterozygote mutation carrier, men and women are affected equally.

Approximately 75% of individuals who have MFS have a parent who is affected by the condition. While MFS is not always inherited, it is always heritable. Approximately 25% of children with MFS are born to parents who do not show features of the MFS, and are affected due to a de novo mutation. In that case, the chance for future siblings to be born with MFS is less than 50%, but still higher than the general population risk of 1 in 10,000, because in some cases a Marfan gene mutation may be present in some percentage of the germline cells of one of the parents, either testes or ovaries (*https://www.genome.gov, 2017*).

2.2. Molecular genetics

2.2.1. Fibrillin-1 gene (*FBN1*)

- Genetic Location: 15q21.1 (*Figure 4*).
- Molecular Location: 48,408,306-48,645,788

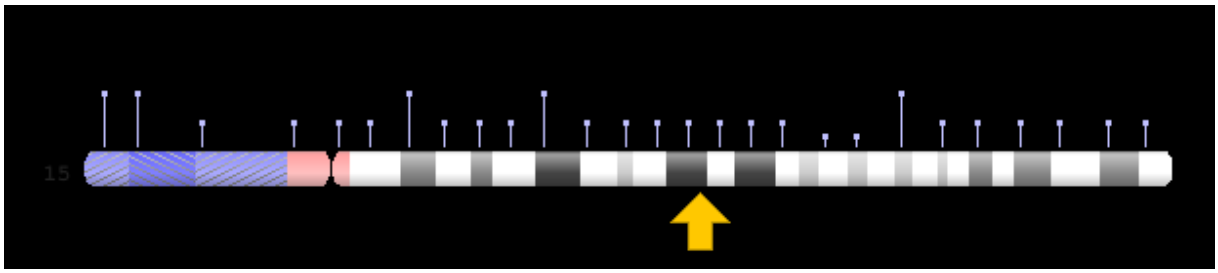

Figure 4: Genetic location of the FBN1 gene on chromosome 15q21.1.

The *FBN1* gene is located on chromosome 15 and spans about 200kb genomic DNA with 65 exons and a transcript size of 10kb (Robinson and Godfrey, 2000). The mRNA possesses 9663 nucleotides with an open reading frame of 8613 nucleotides and 5' and 3' untranslated regions of 134 and 916nt.

The gene is responsible for the production of the two proteins fibrillin-1 and the protein hormone aprosin *(https://ghr.nlm.nih.gov, 2019)*. Fibrillin-1 is a cysteine-rich glycoprotein and part of the structural supporting calcium binding micrifibrils in the extracellular matrix in connective tissue, elastic and non-elastic throughout the body. The hormone aprosin is secreted by white adipose tissue and plays a role in the regulation of the glucose homeostasis *(https://ghr.nlm.nih.gov, 2019)*.

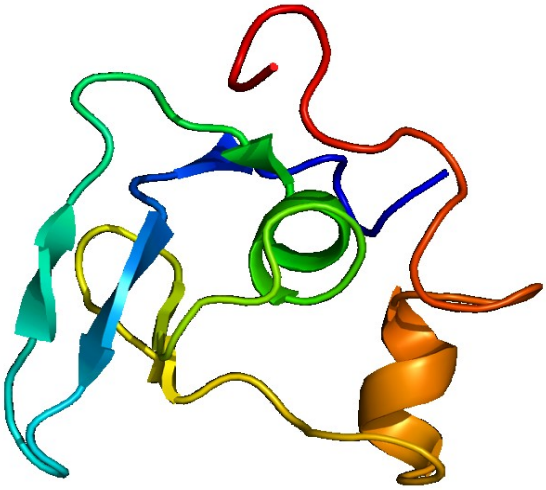

Figure 5: Structure of fibrillin-1 protein.

Fibrillin-1, shown in *figure 5*, is a major component of the 10-12nm microfibrils, which are thought to play a role in tropoelastin deposition and elastic fiber formation in addition to possessing an anchoring function in connective tissues. Fibrillin-1 mutations have also been found in patients with related disorders of connective tissue, but do not have the clinical features of MFS (Robinson and Godfrey, 2000).

In most cases MFS is caused by a mutation in the *FBN1* gene on chromosome 15, commonly affected by missense point-mutations. Those missense mutations lead to a structural change of profibrillin. Furthermore, the integration of wrong amino acids results in a faulted gene product and leads to a restricted productivity and quality of profibrillin-1. The pathological profillibrin-1 is the primary stage of fibrillin-1, whose amino acids are therefore also affected. In addition the proteolysis of fibrillin-1 is increased, which leads to a lower quantity of the protein than in healthy organisms. Thus, mutations in *FBN1* lead to deleterious biochemical effects and aberrant signalling pathway activation within the aorta and other affected tissues. Fibrillin is a latent transforming-growth-factor-β binding protein. Patients with MFS usually have higher values of free TGF-β in their extracellular matrixes (Robinson and Godfrey, 2000).

In 2000, Robinson and Godfrey published a study about the importance of *FBN1* mutations in MFS and other related connective tissue disorders and type 1 fibrillinopathies. They reported that mutations in the closely related *FBN2* gene were found in patients with congenital contractural arachnodactyly and they assumed that other mutations in relation to connective tissue disorders and fibrillinopathies will be

discovered in the future, which we now know became true. In 2009 Faivre et al. analysed a series of 198 probands with a pathogenic *FBN1* mutation (Faivre *et al.*, 2009). The vast majority of probands carried a mutation within the exons 24-32. It was shown in previous studies that variants in that genetic region are predictive for severe cardiovascular phenotypes. Within a total of 1013 patients with a *FBN1* mutation, 198 probands carried the mutation in exons 24-32 und were therefore further investigated. They compared mutations leading to a premature termination codon with in-frame mutations and found a significantly higher probability of developing ectopia lentis and mitral valve insufficiency in the latter. Patients with premature termination codons rarely displayed a neonatal or severe MFS presentation. In addition, a high phenotypic heterogeneity could be described in the case of recurrent mutations ranging from neonatal to classical MFS phenotype. They concluded that mutations in exons 24-32 in *FBN1* appear to cause severe phenotypic manifestations in patients, however other factors such as the type of mutation or modifier genes might be relevant too. In comparison to that, Gao et al. reported that mutations of premature termination codons were associated with an increased risk of major cardiovascular involvements and that the cardiovascular involvement in patients with mutations in exons 43-65 was as high as it was in mutations in exons 24-32 (Gao *et al.*, 2019).

Zhang et al. recently found two rare missense mutations in *FBN1* with atypical cardiovascular manifestations in a patient affected by MFS (Zhang *et al.*, 2018). They investigated the genetic data of a patient diagnosed with MFS showing typical skeletal and ocular features but atypical manifestations in the cardiovascular system, such as dilatation of the four cardiac chambers and a large saccular aneurysm of the non-coronary sinus of Valsalva. Following gene sequencing two novel heterozygous mutations of the *FBN1* gene were found. They highlighted the importance of gathering the complete family history and the value of clinical connections while investigating patients with unusual features.

2.2.2. Transforming growth factor-β receptor (*TGFBR1/2*)

The *TGFBR1* is located on chromosome 9q22.33 and contains 9 exons (Laer, Dietz and Loeys, 2014). The gene provides instructions for producing a protein called *transforming-growth-factor-β* (TGFβ). The cytokine TGFβ is known to have an impact on cell proliferation and cell differentiation. It is found throughout the body but is primary present in tissues that make up the skeleton, regulating the growth of bone and cartilage, a tough, flexible tissue that makes up the majority of the skeleton during early development. TGFβ is also involved in the formation of blood vessels, the development of muscle tissue and body fat, wound healing, inflammatory processes in the immune system, and the prevention of tumor growth. The absence of fibrillin, which acts as a latent transforming-growth-factor-β binding protein, leads to higher values of free TGFβ in extracellular matrixes, which furthermore increases the negative impact on connective tissues affected by the *FBN1* mutation (Laer, Dietz and Loeys, 2014).

Mutations in *TGFBR2*, which is located on chromosome 3p and contains 8 exons (Laer, Dietz and Loeys, 2014), encoding TGFβ type II receptor, were first described in 2004 in patients with thoracic aortic root aneurysms and skeletal features of the MFS (Jondeau *et al.*, 2016). Subsequently, mutations in both *TGFBR2* and *TGFBR1* (TGFβ type I receptor) were described to be associated with early onset on aggressive thoracic aortic disease with MFS-like skeletal features, but also hypertelorism, craniosynostosis, developmental delay, cleft palate and bifid uvula, congenital heart disease and aneurysms, and dissections throughout the arterial tree with marked arterial tortuosity. This condition was termed Loes-Dietz syndroms (LDS), a Marfan like genetic connective disorder (Jondeau *et al.*, 2016).

Jondeau et al. reported that patients with *TGFBR1* and *TGFBR2* mutations show similar prevalence of systemic features and same global survival. They evaluated data of a total of 441 patients in 228 families from around the world. Mutations in the *TGFBR2* gene were 50% more frequent than mutations in *TGFBR1*. The two populations were similar in terms of age and sex distribution. Patients with either *TGFBR1* or *TGFBR2* mutations were similar in most phenotypic features and of note, 20% of patients met the clinical criteria of MFS which underlines the phenotypic overlap

of MFS patients with *FBN1* mutations and patients with *TGFBR* mutations. De Cario et al. published a sudy regarding the role of *TGFBR1* and *TGFBR2* genetic variants in MFS (Cario *et al.*, 2017). They investigated 75 unrelated patients with MFS and related disorders, of which 63% carried a pathogenic *FBN1* mutation. In addition ten common polymorphisms were identified within *TGFBR2* and six in *TGFBR1*. The association with cardiovascular manifestations of those polymorphism was evaluated. Due to the collected data, they concluded that variants in *TGFBR1* and *TGFBR2* might play a role in modulating the severity of cardiovascular manifestations in MFS. Another study by You et al. examined the connection of vascular smooth muscle cells (VSMC) dysfunction and augmented TGFβ in patients with MFS (You *et al.*, 2019). VSMCs were isolated from tissue of the ascending aorta of both MFS patients and control donors. They reported a much higher TGFβ1 level in tissue of MFS than in control muscle cells, and that TGFβ1 induced VSMC senescence through excessive reactive oxygen species. Cozijnsen et al. reported the pathogenic effect of a *TGFBR1* mutation in a family with Loeys-Dietz syndrome (Cozijnsen *et al.*, 2019). Their aim was to investigate the pathogenic effect of a *TGFBR1* mutation in relation to thoracic aortic aneurysms and dissections. The c.1043G>A *TGFBR1* mutation was found in the index patient, a deceased brother and five other pre-symptomatic family members and confirmed that the detected mutation shows increased myogenic differentiation of the patients fibroblasts.

2.2.2.1. Loeys-Dietz syndrome

LDS was first described by Loeys and Dietz in 2005 (Laer, Dietz and Loeys, 2014). The syndrome is an autosomal dominant aortic aneurysm syndrome characterized by multi-systemic involvement. Hypertelorism, bifid uvula or cleft palate and aortic aneurysm with tortuosity are some of the most common clinical features of LDS. Although LDS shows clinical overlap with the characteristics of MFS, it can be clinically distinguished from the latter. Shared features include aortic root aneurysm, pectus deformities, scoliosis and arachnodactyly. Typical findings for LDS but not for MFS are craniosynostosis, hypertelorism, cleft palate or bifid uvula, cervical spine instability, club feet, and most importantly widespread arterial aneurysms with tortuosity and early

aortic rupture. The two major genes suspected to be associated with LDS are *TGFBR1* and *TGFBR2,* whereas one third of the yet identified *TGFBR* mutations were identified in *TGFBR1*, the others were found in *TGFBR2*. Despite the loss of function nature of these mutations, the TGFβ signalling in aortic tissues of patients was found to be increased, rather than decreased (Laer, Dietz and Loeys, 2014).

2.3. Ghent nosology

Since Antoine-Bernard Marfan described the case of a 5-year old girl with skeletal manifestations of the disease, important progress has been made in the specification of the MFS (Loeys *et al.*, 2010). The diagnosis of MFS relies on defined clinical criteria, outlined by international experts to facilitate an accurate recognition of this genetic syndrome and to improve the counselling and management of patients with MFS. Victor McKusick first established a classification of connective tissue disorders in 1955, which were presented in the publication of his monograph 'Heritable connective tissue disorders'. In 1986, the diagnosis of MFS was codified on the basis of clinical criteria in the Berlin nosology (Paepe *et al.*, 1996), with the aim to enable an accurate communication about the disease between healthcare providers, researchers and patients (Loeys *et al.*, 2010). Weaknesses have emerged in these criteria over the time, accentuated by the advent of molecular testing and the following identification of *FBN1* as the causal gene for MFS. New diagnostic criteria were put forth in 1996, due to the fact that the Berlin criteria allowed a misdiagnosis of MFS in individuals with a family history of MFS, who had only non-specific connective tissue findings themselves and did not carry the genetic mutation connected with MFS. These revised criteria, called the Ghent criteria, were more stringent, mitigating over-diagnosis of MFS and providing better guidelines to differentiate MFS from related or overlapping conditions. MFS is, above else, associated with the risk of aortic dissection or aneurysm and often led to misdiagnosis, which can lead to restricted career aspirations or insurance benefits. Additionally, financial burden due to frequent medical care, anxiety or situational depression, unfounded marital or reproductive decisions and loss of health due to exercise restriction are all consequences that should be prevented. The challenge is to balance such concerns with the maintenance of good health and proper

medical management. It also important to avoid the diagnosis of MFS when clinical or molecular examinations reveal different diagnoses that could be even more severe and ask for even more specialised and careful counselling. The Ghent nosology lists a set of major and minor criteria in the skeletal, ocular, cardiovascular and pulmonary system as well as the dura, skin and integument. The diagnosis of MFS requires the involvement of at least two major and one minor of the mentioned organ systems. In the case of a known *FBN1* mutation the presence of at least one major and one minor criteria in different organ systems is sufficient to make a diagnosis (Loeys *et al.*, 2010).

The current Ghent criteria have excellent specificity to identify patients with *FBN1* mutations and allows the detection of such mutations in 97% of MFS patients who fulfil the Ghent criteria. However, the criteria have been criticised for taking deficient account of the age dependent nature of some clinical manifestations, which makes the diagnosis in children more difficult, as well as for including some rather non-specific physical manifestations. Also, *FBN1* mutations can be present in familial ectopia lentis who also show lens dislocation or skeletal features, but have fewer cardiovascular risk than seen in classic MFS. For that, the criteria allow the diagnosis of familial ectopia lentis in the absence of a second major Marfan manifestation (Loeys *et al.*, 2010).

Loeys et al. published a proposal for a new nosology including five alterations to the current criteria. First, more weight should be given to cardinal features such as aortic root dissection and ectopia lentis. Second, a more prominent role should be assigned to molecular genetic testing of *FBN1*, *TGFBR1* and *TGFBR2*. Third, some of the less specific minor criteria should be removed to avoid the use of obligate thresholds that lack clear validation. Fourth, additional diagnostic considerations and testing should be formalised if a patient shows unexpected findings next to those listed in the criteria. Last, the nosology should provide context specific recommendations for patient counselling and follow-up (Loeys *et al.*, 2010).

To address some of the current issues, in 2010 an international panel of experts in the diagnosis and management of MFS was convened in Brussel considering modifications of the Ghent criteria, as well as factors including the specialised nature, availability and cost of diagnostic tests, the need for a better definition of certain diagnostic categories, management guidelines for various patient groups who do not yet fulfil the diagnostic criteria and the definition of features triggering alternative diagnoses.

2.3.1. Cardiovascular criteria

Aortic root aneurysm and dissection is a key diagnostic criterion in the new nosology. Aortic root aneurysm is defined as enlargement of the aortic root at the level of the sinuses of Valsalva. The largest correctly measured root diameter, either measured in systole or diastole, should then be corrected for age and body size. Echocardiography as well as computed tomography or magnetic resonance imaging can be used for examinations of the aorta (Loeys *et al.*, 2010).

Mitral valve prolapse is also included in the systemic score and a common feature in MFS patients. It should be defined by echocardiography as protrusion of one or both of the mitral valve leaflets.

Dilatation of the pulmonary artery is seen in MFS, however, it was not defined as a major criteria of the revised nosology due to the lack of research regarding thresholds and the diagnostic utility of this finding.

Aortic enlargement or dissection distant from the aortic root may occur in MFS and appears to be progressing with the onset of age and improved management of disease at the aortic root. In adult patients with a clinical suspicion of MFS but with no present aortic root enlargement intermittent imaging of the descending thoracic aorta is indicated and recommended. If LDS is suspected, systemic vascular imaging from head to pelvis is recommended, because of the high frequency of tortuosity, aneurysms and dissections throughout the vascular tree (Loeys *et al.*, 2010).

2.3.2. Ocular criteria

Myopia and ectopia lentis are suspected to be the most prominent ocular features in MFS. The diagnosis of ectopia lentis, shown in *figure 6*, is based on a slit-lamp examination after maximal dilatation of the pupil, and reflects failure of supporting structures called ciliary zonules. The dislocation of the lenses in any directions is very common in MFS, but most typically is an upward dislocation. For a definitive diagnosis of ectopia lenis, the eye exam should be repeated later if only minimal subluxation was revealed (Loeys *et al.*, 2010).

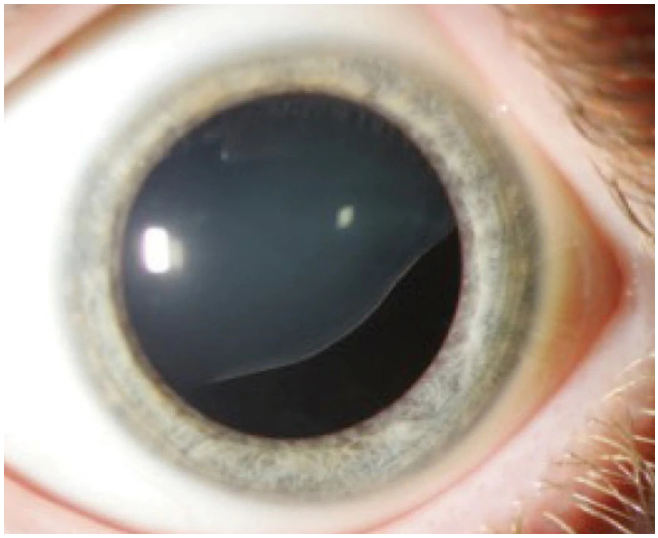

Figure 6: Ectopia lentis in MFS.

Other features seen in MFS are increased globe length and corneal flattering, but they are not routinely measured due to unclear specificity. Myopia is usually monitored as it is a common manifestation of MFS and tends to show early onset, high severity and rapid progression. However, as myopia is a common finding in the general population the Ghent criteria attributed less importance to it in the diagnosis of MFS (Loeys *et al.*, 2010).

2.3.3. Systemic criteria

Based on expert opinion and available literature clinical features of MFS in other organ systems were evaluated for their specificity and diagnostic utility and many of the minor criteria of the old Ghent criteria were eliminated in the revised nosology. High importance was given to the combination of the typical wrist and thumb signs shown in *figure 7*.

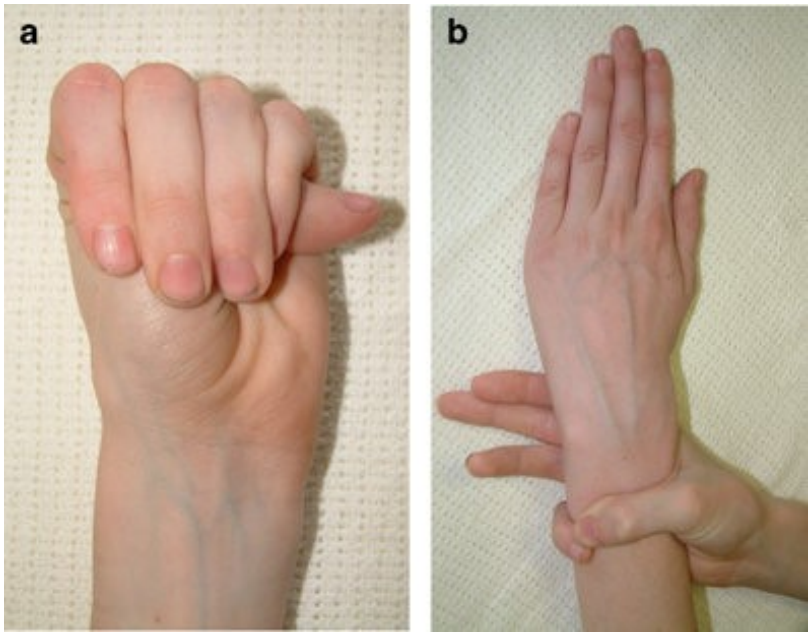

Figure 7: Typical thumb and wrist signs of MFS (a) positive thumb sign: entire thumbnail protrudes beyond ulnar border of hand (b) positive wrist sign: thumb and fifth finger overlap when encircling the wrist.

The thumb sign is positive if the entire distal phalanx of the adducted thumb extends beyond the ulnar border of the palm. The characteristic wrist sign is present if the tip of the thumb covers the entire fingernail of the fifth finger when wrapping around the contralateral wrist (Loeys *et al.*, 2010).

Other specific manifestations are anterior chest deformity, hindfoot deformity, spontaneous pneumothorax, dural ectasia, acetabular protrusion or pectus carinatum. Some subjective qualifiers requiring surgery of the old criteria have been eliminated, and the examiner should be confident that a positive finding of pectus excavatum or chest wall asymmetry is extending beyond normal chest contour in the general

population before assigning significance on it. The combination of hindfoot valgus and forefoot abduction with lowering of the midfoot is another criteria that should be distinguished from the more common flat foot without significant hindfoot valgus. Spontaneously occurring pneumothorax is remaining a clinical feature, as it was in the old criteria. Dural ectasia is a sensitive but not specific sign of MFS, and is no longer seen equally of importance than lens dislocation and aortic root enlargement. For the detection of lumbosacral dural ectasia standard methods such as computed tomography or magnetic resonance imaging should be applied. Furthermore, dural ectasia is often seen and even more common in LDS. The combined presence of reduced upper to lower segment ratio and increased arm span to height ratio in the absence of scoliosis is of significance, but ethnic differences should be considered, due to different distributions and lower ratios, in for example the Asian population. However, neither of these ratios provide an accurate measurement of bone overgrowth in the presence of significant scoliosis or kyphosis. Facial characteristics include dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia and malar hypoplasia, of which at least three must be shown in the patient. The criteria of joint hypermobility, highly arched palate and recurrent or incisional herniae have been removed from the current nosology, due to a lack of perceived specificity (Loeys *et al.*, 2010).

2.3.4. Differential diagnoses

Conditions that occur to have overlapping manifestations in the cardiovascular, skeletal and ocular system with MFS include conditions with aortic aneurysms, such as LDS, bicuspid aortic valve, familial thoracic aortic aneurysm, Ehlers-Danlos syndrome or arterial tortuosity syndrome. Ectopia lentis can be seen in ectopia lentis syndrome, Weil-Marchesani syndrome, homocystinuria or Stickler syndrome and other systemic features of MFS may also occur in Shprintzen-Goldberg syndrome, congenital contractural arachnodactyly, LDS, mitral valve prolapse syndrome or MASS phenotype. The latter stands for mitral valve, aorta, skin and skeletal and is a connective tissue disorder similar to MFS. These syndromes should be highly

considered while managing the diagnosis of a patient suspected to have MFS (Loeys *et al.*, 2010).

2.3.5. Conclusion

The diagnostic evaluation of MFS is highly complex, due to the variability of phenotypes of affected individuals, the age dependency of manifestations and its extensive differential diagnosis. The criteria of the Ghent nosology aim to emphasize simplicity of use and the desire for early diagnosis, but also accuracy of the diagnosis to avoid misdiagnosis and the mentioned consequences in chapter 2.3. There are still ongoing concerns about delayed diagnosis and the use of diagnostic categories, as well as follow-up and management principles that should be further discussed.

2.4. Screening analyses and counselling

As already pointed out in chapter 2.3 MFS can be challenging for doctors to diagnose because of the many differential diagnoses showing similar signs and symptoms. Even among members of the same family, the features and symptoms of MFS vary widely, both in their specificity and in severity. Certain combinations of symptoms and family history must be present to confirm a diagnosis of MFS. In some cases, a person may have some features of MFS, but according to the ghent criteria not enough of them to be diagnosed with MFS.

If MFS is suspected, one of the first recommended tests is the echocardiogram. This test uses sound waves to capture real-time images of the heart in motion. It checks the condition of the heart valves and the size of the aorta. Other heart-imaging options include computerized tomography scans and magnetic resonance imaging (Loeys *et al.*, 2010).

If diagnosed with MFS, a patient needs to have regular imaging tests to monitor the size and condition of the aorta. Managing cardiovascular manifestation will be further discussed in chapter 3.

Furthermore, annual ophthalmological evaluation for the detection of ectopia lentis, cataract, glaucoma and retinal detachment is essential. In order to prevent amblyopia early monitoring and aggressive refraction is required for children with MFS. Lens opacity with poor visual function, anisometropia or refractive error not amenable to optical correction, impending complete luxation and lens induced glaucoma or uveitis are indications for surgical lens extraction (Loeys *et al.*, 2010).

2.4.1. Genetic testing

In addition to the clinical screening methods, genetic testing should be used to confirm the diagnosis of MFS. The usual genetic examination includes screening of the *FBN1* gene, as well as *TGFBR1* and *TGFBR2*. If a Marfan mutation is found, it is recommended that family members, even without phenotypic features of MFS, undergo genetic testing. However, the financial and psychosocial implications for these individuals should be considered. The choice of mutation screening technique depends mainly on success rate and cost of the technique (Child, Aragon-Martin and Sage, 2016). Sanger sequencing is commonly used but cannot detect large deletions or duplications in the DNA sequence unless it is combined with the multiplex ligation-dependent probe amplification technique. This combination has improved an accuracy of 99% in the field of genetic mutation screening. Lately, techniques such as whole exome or genome sequencing are becoming more prominent, however each variant needs to be subsequent confirmed by the Sanger sequencing. Other genes, called modifier genes, are suspected to influence the severity of the MFS phenotype. Hence in future, the next generation sequencing will not only screen the whole *FBN1* gene, but also allow the study of other modifier genes which may help us to understand the genotype–phenotype correlation in patients with MFS (Child, Aragon-Martin and Sage, 2016).

As a result of intense international collaborative clinical and molecular genetic research in the past 23 years, an internationally available gene map has been established containing thousands of different mutations suspected to cause MFS. This has effected huge improvement for diagnosis and genotype–phenotype correlations. Long-term predictions and management programmes can now be based on the identified mutation type and compared to previous studies and research (Child, Aragon-Martin and Sage, 2016).

2.5. Genotype/Phenotype Correlations

Although MFS is inherited in an autosomal dominant way, the syndrome shows a wide phenotypic variability (Landis, Veldtman and Ware, 2017). For example the age of onset, severity and rate of progression of thoracic aortic dilatation is currently unpredictable. These gaps in knowledge faces medical professionals with problems in clinical decision making, considering the time of surgery, frequency of follow-ups, physical activity restrictions and drug management (Landis, Veldtman and Ware, 2017).

Mutations in *FBN1* can cause a reduction of fibrillin produced in the cells that can lead to quantitative defects, changes of the structure or stability of the protein and altering the ability of fibrillin to be exported to the extracellular matrix. Mutations in *FBN1* that

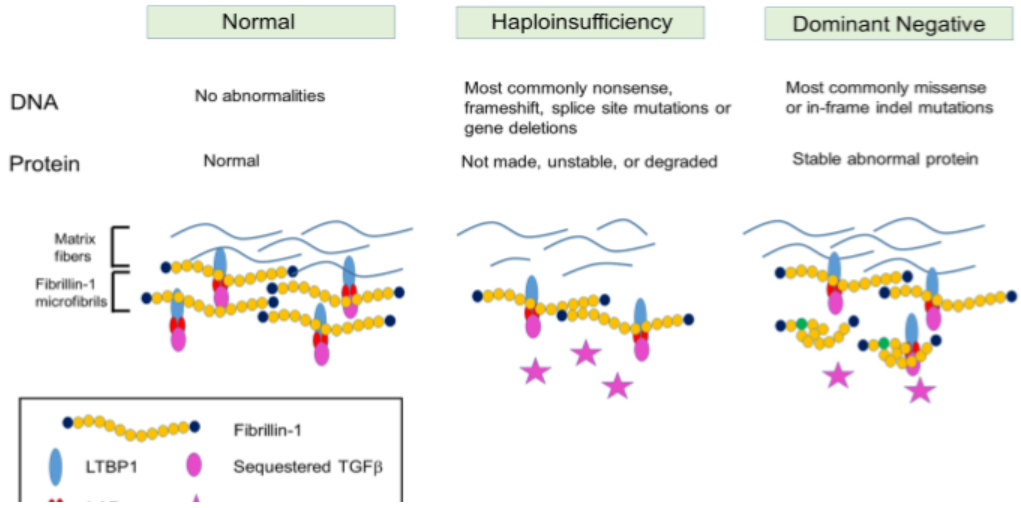

Figure 8: Genetics and pathogenesis in MFS. A schematic overview of the effect of haploinsufficiency or dominant negative mutations on fibrillin (Landis et al., 2017).

result in haploinsufficiency lead to reduced amounts of fibrillin, hence fewer microfibrils and increased activated TGFβ levels due to decreased TGFβ sequestration. In contrast, dominant negative mutations in *FBN1* result in qualitative defects of the protein that may affect the function such as folding or protein–protein interactions, leading to a disorganisation of the extracellular matrix, altered structure of the matrix and increased TGFβ levels (*figure 8*) (Landis, Veldtman and Ware, 2017).

Conceptually, dominant negative mutations should result in more phenotypic variability because mutations at different regions of the protein will have various effects, whereas haploinsufficient mutations should be suspected to have more consistent phenotypes (Landis, Veldtman and Ware, 2017). Franken et al. investigated the impact of the mutation type in *FBN1* on aortic diameters, dilatation rates and cardiovascular events, such as aortic dissection and mortality (Franken *et al.*, 2017). Their study included 190 patients with MFS of which 39% carried a haploinsufficient and 61% a dominant-negative mutation. After a follow-up of five years, patients with haploinsufficient mutations had higher rates of aortic root dilatations and tended to be at higher risk for dissection (Franken *et al*., 2017).

Another study by Faivre et al. examined a study population of 1191 probands diagnosed with MFS and tried to find a genotype-phenotype correlation in MFS patients, concentrating on inframe mutations, patients with nonsense, frameshift, splicing, missense, or inframe deletions/insertions and missense mutations that led to an elimination or creation of cysteine (Faivre *et al.*, 2007). They found a higher risk of ectopia lentis in patients with mutations eliminating or creating a cysteine. Mutations that lead to a premature termination codon in *FBN1* were found to cause more severe skeletal and skin conditions than inframe mutations and mutations in exons 24-32 were associated with more severe phenotypes in general, including skeletal and ocular features, cardiovascular events and early age of onset (Faivre *et al*., 2007).

3. Cardiovascular aspects in MFS

Cardiovascular manifestations represent the major morbidity and early mortality factors in patients with MFS, including dilatation of the aorta at the level of sinuses of Valsalva, a predisposition for aortic tear and rupture, mitral valve prolapse, tricuspid valve prolapse and enlargement of the proximal pulmonary artery (Dietz, 2019).

3.1. Aorta

The aorta in patients with MFS presents a variety of abnormalities, all of which share the feature of dilatation (Hetzer, Gehle and Ennker, 1995). The ascending aorta often shows severe fusiform dilatation of the lumen and thinning of the aortic wall. MFS displays a number of abnormalities of the thoracic and abdominal aorta, ranging from aortic stiffness to aortic aneurysm and dissection (Pepe *et al.*, 2016). Aortic dilatation and aneurysm foundation in MFS is caused by cystic medial necrosis, in which the medial layer of the aorta shows fewer cells and a lacunar appearance (Isekame *et al.*, 2016). Histologic examinations showed fragmented elastic fibers, a loss of elastin content, and accumulation of amorphous matric components in the aortic media (Dietz, 2019). A reduced content of elastic fibers in combination with continual force of the left ventricular cyclic torsion applied to the aortic root is associated with the main reason of why dilatation is starting at the aortic sinus (Isekame *et al.*, 2016). Aortic root dilatation is the most common cardiovascular manifestation occurring in patients with MFS, and can lead to severe conditions such as aortic aneurysm or aortic dissection. Isekame et al. reported aortic dilatation in 60-80% of MFS patients and aneurysm in 50-60%. The progressing aortic dilatation is usually ascending with age, although the growth rate is individually and depends on the severity of phenotypic conditions in each patient. It has been reported though that patients with Loeys-Dietz syndrome have a higher yearly growth rate of dilatation than patients with MFS.

The aortic diameter in MFS patients is used for monitoring the progression rate of the disease, including the factors body surface area, age and sex, which makes a general diagnosis if a patient's condition is severe or not even harder(Isekame *et al.*, 2016).

Aortic dissection, the worst case of aortic manifestations, occurs if a tear forms within the intima of the dilated aorta (*figure 9*). It is defined as disruption of the medial aortic layer provoked by intramural bleeding and results in separation of the aortic wall layers and a formation of a false lumen. Aortic dissection can be followed by myocardial infarction as well as ischaemia of the mesenteric and femoral arteries. Patients experiencing aortic dissection usually feel chest pain, back pain or abdominal pain, depending on which part of the aorta is affected. Sudden death by aortic dissection can be prevented by careful und regularly monitoring of the aorta and proper clinical management, such as aortic root surgery (Isekame *et al.*, 2016).

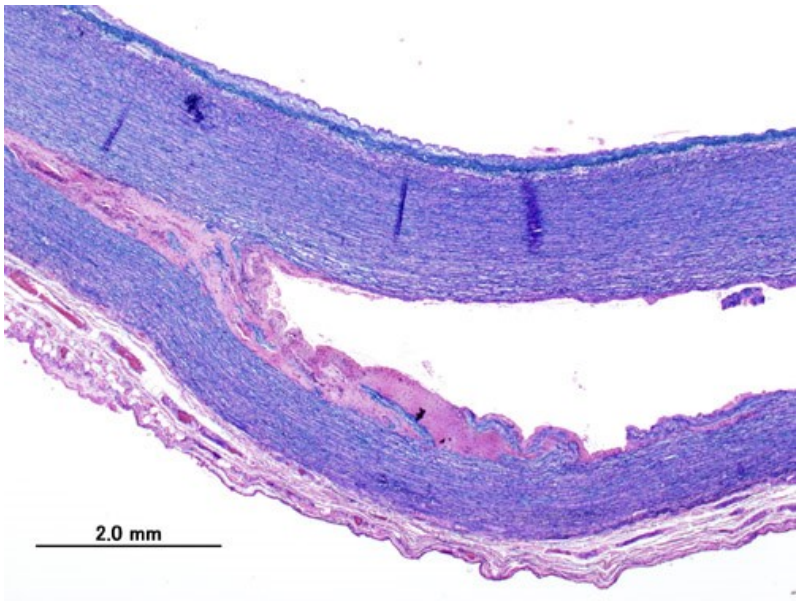

Figure 9: Histopathology of an aortic dissection.

Faivre et al. published a study investigating the cardiovascular manifestations in men and women carrying a *FBN1* mutation (Faivre *et al.*, 2010). The investigated a total of 1013 probands with pathogenic *FBN1* mutations, among whom 965 patients had data suitable for the analysis. The percentage of patients with ascending aorta dilatation increased steadily with increasing age and reached 96% by the age of 60. The presence of aortic events reached 74% by 60 years and was rare before the age of 20 and men were at higher risk compared to woman. They concluded that regular monitoring of the aorta is crucial in patients with *FBN1* mutations and that aortic

dilatation and dissection should trigger suspicion of a genetic background (Faivre *et al.*, 2010).

3.2. Aortic valve

The histopathology of the aortic valves in patients with MFS show a basically normal structure, without excessive fragmentation of the elastin component or excessive increase of the mucoid layer (Hetzer, Gehle and Ennker, 1995). However, aortic root dilatation causes aortic regurgitation, subsequent zonular dilatation and myxomatous valvular degeneration (Isekame *et al.*, 2016). The increasing regurgitant volume is linked to an increase of blood volume ejected with each left ventricular contraction. Thus the left ventricular volume becomes larger to maintain the cardiac output and the left atrium enlarges. This chronic overload of volume can lead to myocardial damage and failure of the reimbursing mechanisms, such that cardiac output cannot be preserved. Subsequently the entire left ventricle is affected and causes a global reduced motility (Isekame *et al.*, 2016).

3.3. Mitral valve

The mitral valves of MFS patients display elongated and thickened valve leaflets. Once affected as part of the MFS, the mitral valves show diffuse floppiness associated with excessive dilatation of the valve annulus (Hetzer, Gehle and Ennker, 1995). The histopathology shows a degenerative process of the supportive tissue and destruction of the fibrous layers of the leaflet (*figure 10*). The defective connective tissue and myxomatous degeneration is linked to increased TGFβ signalling (Isekame *et al.*, 2016). In the case of severe mitral valve regurgitation the left ventricle and left atrium become volume-overloaded and can result in heart failure. Mitral valve elongation and myxomatous thickening can lead to mitral valve prolapse and regurgitation (Pepe *et al.*, 2016).

Mitral valve prolapse counts for the most common valvular manifestation in MFS with a prevalence of 28-75% in comparison to 2.4% in the general population. The prevalence of mitral prolapse is reported to be even higher among children with Marfan syndrome than among adults (Gu *et al.*, 2015). Mitral valve prolapse can be surgically repaired, however, the risk of aortic dissection after surgery is increasing due to rapid postoperative increase in cardiac output (Pepe *et al.*, 2016).

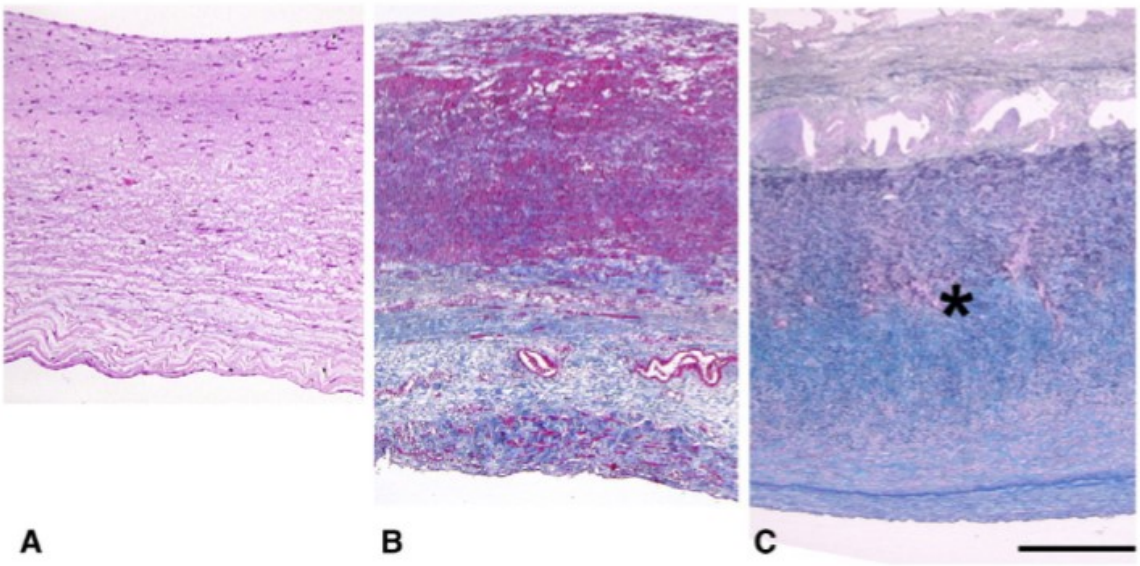

Figure 10: Comparison of normal (A), Marfan (B) and mitral valve prolapse (C) valve morphology. The trilaminar structure of normal mitral valve is lost in Marfan disease showing degenerative tissue and loss of elastic lamellae (Prunotto, Primo and Bongiovanni, 2010).

Faivre et al. reported in their study, mentioned in chapter 3.1, that the prevalence of mitral valve prolapse and mitral valve regurgitation increased steadily with age, without significant difference between genders. In a retrospective study by Gu et al. the prevalence of multiple valve-involvement in MFS compared to echocardiographic and histologic findings was established (Gu *et al.*, 2015). They reviewed echocardiograms of 73 MFS patients who underwent cardiovascular surgery and available tissue histology. Histologic findings were available in 29 patients and all of whom revealed myxomatous degenerations. Thickened aortic valves was seen in 4 patients, mitral valve involvement in 18 and tricuspid valve involvement in 8. Among the 73 patients 66 had moderate or severe aortic regurgitation, although their aortic valves did not

show significant histologic changes. Histologic findings were most common in mitral valves. Tricuspid valve involvement was rarely seen, however there was a prevalence of diffuse valvular disease (Gu *et al.*, 2015).

3.4. Tricuspid valve and pulmonary artery

Tricuspid valve thickening, prolapse and regurgitation are common findings in MFS patients, occurring due to degeneration of the tricuspid valve (Isekame *et al.*, 2016). Publications about tricuspid valve involvement in MFS are rather rarely at the common time. Gu et. al reported tricuspid valve involvement and diffuse valvular disease in 12% of their study population (Gu *et al.*, 2015). In those patients with tricuspid valve involvement, valvular thickening, myxomatous degeneration, and prolapse with chordal elongation involving all three leaflets were examined. In addition in all of these patients the mitral valves were affected and concurrently involved, which underlines that the surgical evaluation of MFS should include the examination of the tricuspid valve (Gu *et al.*, 2015).

Pulmonary artery dilatation is a minor criterion for MFS, usually occurring at the level of the root (Isekame *et al.*, 2016). In the general population the diameter of the pulmonary artery is 24-27mm, in MFS patients the mean root diameter of 35mm was reported. The dilatation of the pulmonary artery is suspected to be linked to the ascending aortic disease and can result in pulmonary aortic aneurysm pulmonary hypertension. Lundby et al. aimed to establish the prevalence of pulmonary artery dilatation in MFS (Lundby *et al.*, 2012). They examined the diameter of the pulmonary artery in 87 patients with diagnosed MFS via computed tomography and magnetic resonance imaging and found a widening of the trunk of the pulmonary artery in 54% of the patients. Of those 54%, 85% had signs of disease of the ascending aorta and further analysis showed that surgery of the ascending aorta and a high body surface area may be associated with dilatation of the pulmonary artery. Another study by Sheikhzadeh et al. investigated the frequency of pulmonary artery dilatation in adult patients with MFS using echocardiography (Sheikhzadeh *et al.*, 2014). Their study was performed in a retrospective cross-sectional observational controlled way in four

tertiary care centers. The study population included 123 healthy adults and 98 patients with MFS at the average age of 40 years. Measured pulmonary artery diameter revealed a normal distribution without correlation to age, sex, weight, or body surface area. Pulmonary artery dilatation was found in 69.4% of the MFS patients, in comparison to 4.9% in the control group. They concluded that no clinical features of MFS relate to the pulmonary artery diameter, however that there is high prevalence of pulmonary artery dilatation and aneurysm in MFS. Considering the results of these two studies, it is still debatable whether dilatation of the pulmonary artery is correlating with features such as aortic dilatation or circumstances such as age and body weight. However, MFS patients have a high risk of dilatation of the pulmonary artery and developing aneurysms (Sheikhzadeh *et al.*, 2014).

3.5. Left ventricular dilatation and dysfunction

Left ventricular systolic and diastolic dysfunction in adult MFS patients is considered to be due to valvular insufficiency and left ventricular overload (Pepe *et al.*, 2016). The dimensions and configuration of the left ventricular are usually inconspicuous in MFS patients (Isekame *et al.*, 2016). However, left ventricular dilatation and dysfunction may occur in case of progressed mitral valve or aortic dilatation due to volume-overload. Although mitral valve collapse is a major cause for heart failure, some patients appear to develop ventricular dysfunction independently, without the presence of significant valvular regurgitation. Approximately 25% of MFS patients show asymptomatic reduction in left ventricular ejection fraction, suggesting impaired systolic function and underlying cardiomyopathy. Impaired left ventricular fraction is suspected to be often responsible for sudden cardiac death. Aortic root stiffness as well as extracellular matrix remodelling increase left ventricular overload and may contribute to impaired left ventricular function. The left ventricular dysfunction has been found to be related to the type and severity of mutation, suggesting possible primary cardiomyopathy in MFS (Pepe *et al.*, 2016).

Meijboom et al. evaluated left ventricular dimensions and function in using echocardiography in 234 patients with MFS (Meijboom *et al.*, 2004). In most patients

left ventricular dimensions and systolic function was found to be normal and involvement of the left ventricle was only present in a small group of the study population. Their study provided data concerning left ventricular dimensions and systolic function of a large population of MFS patients without significant valvular regurgitation. Only 7% showed dilation of the left ventricle, however none of those fulfilled criteria for idiopathic dilated cardiomyopathy. In comparison to that, Yetman et al. observed left ventricular dilatation in 68% of their study population of MFS patients, but including patients with valvular regurgitation (Meijboom *et al.*, 2004).

3.6. Arrhythmia and sudden cardiac death

The most common arrhythmias in MFS are premature atrial or ventricular beats (Isekame *et al.*, 2016). It is presumed that fibrillin-1 deficiency in patients with MFS causing microfibril abnormality in the matrix of the myocardium, is affecting the conduction of impulses. Savolainen et al. reported that the prevalence of cardiac arrhythmia, prolonged atrioventricular conduction and ventricular repolarisation abnormalities are higher in patients with MFS than in the general population. Most arrhythmias do not cause severe life threatening complications, however, Yetman et al. reported that 4% of MFS patients with ventricular arrhythmia died because of that reason. It is also suspected that left ventricular dysfunction and special exon mutations in *FBN1* cause an increased risk of ventricular arrhythmia. Premature ventricular contractions may be a risk factor for sudden cardiac death, as well as impaired left ventricular function. However, the prediction of sudden cardiac death by *FBN1* mutation or other conditions is currently not possible, due to the high amount of different impacts influencing each patient's clinical status. The long-term study of Yetman et al. mentioned above, aimed to assess outcomes in a series of young MFS patients during a follow-up of 24 years (Yetman, Bornemeier and Mccrindle, 2003). They followed 75 patients diagnosed with MFS and cardiovascular involvement, all of which were on medical therapy. During that study none of their patients died from aortic dissection, whereas 4% died from arrhythmias. In 21% of the study population ventricular arrhythmias were present and associated with increased left ventricular size, mitral valve prolapse and abnormalities of repolarization. Sudden cardiac death

appeared to be more common in patients with left ventricular dilatation and may be prevented by proper management and monitoring. *Figure 11* shows the cardiac characteristics of the study population by Yetman et al. (Yetman, Bornemeier and Mccrindle, 2003).

Characteristic	Prevalence
Aortic root dilation	63 (90%)
Mitral valve prolapse	34 (49%)
Mitral insufficiency	15 (21%)
Mild	13
Moderate	2
Severe	0
Left ventricular dilation	34 (68%)
Aortic insufficiency	6 (8%)
Mild	4
Moderate	2
Severe	0
Left ventricular systolic dysfunction	8 (11%)
QTc prolongation	11 (16%)
QTu prolongation	37 (60%)
Ventricular ectopy	13/62 (21%)
Ventricular tachycardia	4/62 (6%)

Figure 11: Cardiac characteristics of total study population by Yetman et al.

In the study of Savolainen et al. the prevalence of cardiac disrhythmias and abnormalities of conduction and repolarisation in the MFS was evaluated (Savolainen *et al.*, 1997). They recorded 24 hours ambulatory electrocardiograms in 45 adult MFS patients and healthy and reported no difference in heart rates between those two groups. Patients with MFS were found more often to show ventricular premature beats, as well as prolonged PQ and QT intervals at heart rates of 60, 80 and 100 beats. Also ST segment depression was seen more often in the MFS group. In patients with MFS the findings of the electrocardiography did not show an association with aortic root diameters, wall thickness or systolic function, nor did they correlate with the presence of mitral or tricuspid valve prolapse. They concluded that patients with MFS have a higher risk of cardiac arrhythmias and like-wise prolonged atrio-ventricular conduction time and disturbed depolarization (Savolainen *et al.*, 1997).

3.7. Other conditions

Apart from the major conditions described above, also larger and smaller arteries and veins can be affected in MFS (Hetzer, Gehle and Ennker, 1995). A patient with MFS carries also a noteworthy risk of developing infectious endocarditis, applied in particular to the aortic and mitral valves, where the basic defect leading to valve regurgitation may also produce secondary changes playing a role as a nidus for infections. Furthermore, additional degenerative changes such as chordal rupture and annular calcifications can be enhanced by affected aortic and mitral valves. In a publication of Karunanandaa et al. a unique case of a neonate born with hypoplastic left heart syndrome complicated by MFS was reported (Karunanandaa *et al.*, 2019). They highlighted how connective tissue orders may affect the clinical course in neonates.

3.8. Prevention and treatment

The life expectancy of patients with MFS is depending on the severity of the condition, though with proper clinical management and due to progression of medical and surgical therapy, it can be compared to that of the general population.

β-blockers or angiotensin receptor blockers reduce hemodynamic stress on the aortic wall and are routinely prescribed for preventing primary manifestations of MFS (Pepe *et al.*, 2016). The management of MFS should be done by a cardiologist or clinical geneticist familiar with its use. The therapy is usually initiated by the time of diagnosis, independently of age or status of clinical condition.

Patients diagnosed with MFS should be accurately informed about risk factors that accelerate expansion of the aortic wall and cause severe cardiovascular complications, such as smoking, contact sports like rugby or excessive consume of caffeine (Isekame *et al.*, 2016). Smokers are known to have a higher aortic dilatation expansion rate and higher occurrence of dissection than non-smokers, hence it is highly suggested that patients with MFS avoid consuming cigarettes. Other circumstances that should be

avoided are activities that cause joint injury or pain, agents stimulating the cardiovascular system such as decongestants, agents that cause vasoconstriction, LASIK eye surgery or activities such as scuba diving or playing a brass instrument (Pepe *et al.*, 2016).

Furthermore regularly examinations should be performed, including ophthalmologic examinations, orthopaedic and cardiac. Echocardiography for monitoring the status of the ascending aorta should be done yearly, if aortic dimension is relatively small and the rate of dilatation is slow, or more frequent, if the aortic root diameter exceeds 4.5cm in adults and/or the rate of dilatation exceeds 0.5cm per year. Even more frequent cardiac evaluations can be indicated with severe or progressive valve or ventricular dysfunction or with documented or suspected arrhythmia. In addition annually surveillance of the entire aorta with computed tomography or magnetic resonance angiography should be done as soon one gets die diagnosis of MFS, but especially those with a history of aortic root replacement or dissection (Pepe *et al.*, 2016).

3.8.1. Medical treatment

As mentioned above, β-blockers or angiotensin receptor blockers are generally prescribed in the clinical management of MFS.

β-blockers are currently the standard of care as they are known to reduce the progression of aortic root dilatation (Isekame *et al.*, 2016). Hypertensive patients are linked to higher frequency of aortic dissection and rupture, hence antihypertensive medications such as β-blockers are used to minimalize the risk of such adverse aortic events. Another effect of β-blockers is the inhibition of adrenergic β-activation that occurs when adrenaline is released into the blood from sympathetic nerves and the adrenal gland. Furthermore, a therapy with β-blockers decreases heart rate, cardiac contraction, aortic stiffness and myocardial oxygen consumption. Subsequently blood pressure can be reduced which leads, in combination with the effects mentioned above, to a reduced progression of aortic root size. In general it is recommended to initiate the treatment with β-blockers in early stages, because the aorta dilates most between the ages 6-14 years and a therapy is more effective in patients with less

severe aortic dilatation. Possible side effects include bronchospasm, hypotension and bradycardia, which should be monitored while managing MFS with β-blockers. In patients with diabetes β-blockers may mask the symptoms of hypoglycaemia, tremor and hunger because of the effect on the glucose and lipid metabolism. In children sleep disturbances are also common side effects (Isekame *et al.*, 2016).

TGFβ is produced when angiotensin II combines with angiotensin II type 1 receptor. As already mentioned in chapter 2, increased activation and signalling of TGFβ causes aneurysm formation and dissections due to extracellular matrix degradation, and consequent apoptosis and inflammation. Thus, it is reasonable inhibiting the pathways of TGFβ production by angiotensin receptor blockers. So far, there is a number of publications that reported positive impact and results in the treatment of MFS with TGFβ antibodies. According to a study in the Netherlands, Losartan, an angiotensin type 1 receptor antagonist, reduced aortic root dilatation rate in adults with MFS, irrespective of age, sex, blood pressure, aortic root size, presence of *FBN1* mutation and concomitant β-blocker use. However, trials are still ongoing to evaluate the effect of angiotensin receptor blockers in managing MFS (Isekame *et al.*, 2016).

The Pediatric Heart Network conducted a randomized trial comparing the influence of β-blockers and angiotensin receptor blockers on aortic stiffness and aortic growth rate in children and young adults with MFS (Tierney *et al.*, 2019). The primary outcome during a follow-up of three years was a faster growth rate of aortic root enlargement in combination with a higher baseline of aortic-root stiffness. Unlike angiotensin receptor blockers, β-blockers seemed to reduce aortic stiffness, whereas the growth of the aortic root did not show any difference between the treatments of both. Furthermore, diastolic blood pressure was slightly lower in patients treated with β-blockers. They concluded that patients with a higher rate of aortic stiffness may be at higher risk for progressive root enlargement and advise clinical outcomes, and should be closer monitored and treated more aggressive.

4. MFS and pregnancy

4.1. Physiological changes in pregnancy

During a pregnancy physiological changes within a woman's body are occurring in order to nourish the developing foetus and to prepare the woman for labour and delivery. These changes begin after conception and affect every organ system in the body, including the haematological, cardiac, water metabolism, respiratory system and others (Soma-Pillay *et al.*, 2016). Haematological changes include increases in plasma volume proportional to the birthweight of the baby, a decrease in haemoglobin concentration, haematocrit, and red blood cell count due to expansion in plasma volume, and a progressive decrease of platelet count. Furthermore, a pregnancy causes an increased requirement for iron, for haemoglobin synthesis as well as for the foetus and the production of certain enzymes. Also the requirements in folate and vitamin B_{12} are increasing. Changes of the haematology during pregnancy result in a physiological hypercoagulable state, hence certain clotting factors are increased and pregnant as well as postpartum women are at increased risk for thrombosis. Changes in the body water metabolism during pregnancy lead to sodium and water retention in the kidneys and create a characteristic hypervolaemic and hypoosmular state. During a normal pregnancy a significant increase in oxygen demand is significant in relation to respiratory changes that causes a maternal hyperventilation. Breathlessness is a common but physiological feature during pregnancy. Other physiological changes occurring in a pregnancy include the renal vasculature, anatomy and function, glucose, lipid, protein and calcium metabolism, skeletal and bone density changes as well as endocrine changes (Soma-pillay *et al.*, 2016).

In women, experiencing an uncomplicated pregnancy and delivery, these changes usually resolve after pregnancy. Some of these changes influence normal biochemical values while others may mimic symptoms of medical disease.

4.1.1. Pregnancy induced cardiac changes

Pregnancy is the cause of multiple changes within the circulatory system such as the increase in blood volume, cardiac output and left ventricular dimensions, heart rate, all of whom require an aortic wall remodelling (Poniedzialek-Czajkowska *et al.*, 2019).

Changes in the cardiovascular system in pregnancy are profound and begin early in pregnancy (Soma-Pillay *et al.*, 2016), to comply with the increased metabolic demands of the mother and foetus (Regitz-Zagrosek *et al.*, 2018). The plasma volume and cardiac output can reach a maximum of 40–50% above baseline at 32 weeks of gestation, while 75% of this increase is occurring at the end of the first trimester. The increase in cardiac output is achieved by an increase in stroke volume, due to the early increase in ventricular wall muscle mass and end-diastolic volume (Soma-Pillay *et al.*, 2016), in the first-half of a pregnancy and a subsequently gradual increase in heart rate (Regitz-Zagrosek *et al.*, 2018). The heart is physiologically dilated and myocardial contractility is increased (Soma-Pillay *et al.*, 2016). Although the amount of blood pumped by the left ventricle declines towards the late term, the increase in maternal heart rate (10–20 bpm) is maintained, thus preserving the increased cardiac output. In the first and second trimesters the blood pressure decreases but increases to non-pregnant levels in the third trimester (Soma-Pillay *et al.*, 2016).

The aortic compliance and diameter increase throughout pregnancy. Structural remodelling of the aortic wall within the tunica media and intima is induced by estrogen and progesterone as well as by circulating angiogenic factors (Poniedzialek-Czajkowska *et al.*, 2019). The latter are suggested as relevant to the aortic degeneration including hyperplasia of aortic smooth muscle, the decrease in the amount of acid mucopolysaccharides, and the disintegration of elastic fibres. These hormonal induced changes may result in damaging the vascular wall and being relevant for the risk of aortic dissection during pregnancy.

The preconception counselling is vital for patients with aortopathies to assess the risk of aortic dissection. Young women with the family history of aortic dissection or diagnosed connective tissue disorders and congenital aortic abnormality should be examined and counselled properly prior conception. Although patients with connective tissue disorders are the most frequent risk factors for aortic dissection during

pregnancy, such events should be taken into consideration while diagnosing chest pain in pregnant woman in general (Poniedzialek-czajkowska *et al.*, 2019).

4.2. Pregnancy and MFS

MFS, one of the most common connective tissue orders influencing the structure of vascular walls itself, is a high risk factor for pregnant women developing cardiac dysfunction and aortic dissection throughout a pregnancy (Poniedzialek-czajkowska *et al.*, 2019).

There is a wide panorama of problems in pregnancy with MFS which can be deleterious, including the high percentage of yet undiagnosed MFS patients as well as the lethal risk of more than 50%. The diagnosis of MFS has often not been confirmed and is only done in emergency situations or by chance. In that case, women with prior cardiovascular diseases, family history or other known criteria described in the Ghent nosology should undergo genetic testing before considering a pregnancy (Poniedzialek-czajkowska *et al.*, 2019).

4.2.1. Cardiovascular risk of pregnancy in MFS

Knowing that pregnancy itself shows to have cardiac implications, especially during the third trimester, pregnant patients with MFS offer a challenge for physicians because of the required cardiovascular adaption to the pregnant state (Kim, Wolfe and Cynthia, 2017). Poniedzialek-Czajkowska at al. presented guidelines while managing pregnancy in patients with vascular diseases and that those should be assigned to the group of highest risk of aortic dissection during pregnancy and the post-partum period (Poniedzialek-Czajkowska *et al.*, 2019).

4.2.2. Risk for the mother

The most serious risk of pregnant patients with MFS is aortic dissection, which increases during pregnancy and the post-partum period. Maternal cardiovascular changes such as rise in blood volume, heart rate and stroke volume, and hormonally-mediated histologic changes within in the diseased aortic wall, are significantly increasing the risk (Goland and Elkayam, 2017).

Kim et al. published a review about cardiovascular outcomes of pregnancy in MFS patients with the aim to establish a concrete consensus on the management of dealing with this unique patient population (Kim, Wolfe and Cynthia, 2017). They investigated 852 women with MFS and 1112 pregnancies with an aortic dissection rate of 7.9% and a mortality rate of 1.2%. Patients with an aortic diameter higher than 40mm showed a higher prevalence for aortic dissection. The foetal outcome included a mortality rate of 5.6% and frequent caesarean deliveries due to cardiac emergencies. Considering the results of their study, patients with dilated aortic root of more than 40mm should be carefully counselled and advised to ideally await pregnancy until a prophylactic aortic surgery was performed. However, each patients risk for cardiac events should be assessed individually due to the high variability of phenotypic expression in MFS.

Based on recent studies, MFS is still the most frequent cause of pregnancy related acute dissections. The complications mainly occur in the second and third trimester, but also during labour and after delivery, including dissections and in few cases maternal death (Goland and Elkayam, 2017).

4.2.3. Long-term outcome after pregnancy

Information about the expected morbidity and mortality risk after pregnancy should be provided to every woman with MFS considering pregnancy. Major complications after pregnancy can include cardiac arrhythmias, dissections or rupture of residual aorta, heart failure due to mitral valve disease, endocarditis, and intercerebral or spinal haemorrhage (Goland and Elkayam, 2015). Based on a study by Roman et al. 10.6%

of pregnant women with MFS developed an aortic complication during pregnancy and three months postpartum, including aortic dissection and aortic growth (Roman *et al.*, 2016). Cauldwell et al. reported a significant but small increase in aortic root size during follow-up (Cauldwell *et al.*, 2019). Renard et al. showed that aortic root enlargement was seen after delivery, however there was only data available at a single point after delivery (Renard *et al.*, 2017).

The likelihood of complications depends on the severity of every individual patient, although the risk is definitely higher in patients with prior acute dissections and aortic or mitral valve surgery.

4.2.4. Risk for the foetus and obstetric complications

Next to the risk of 50% of inheriting MFS to the foetus as it was described in chapter 2.1, the development of aortic dissection in the mother carries substantial risk to the foetus (Goland and Elkayam, 2017). A publication by Lind and Wallenburg who also included infants with perinatal diagnosis, reported 69% of infants of mothers with MFS were found to be affected by the genetic disease (Goland and Elkayam, 2015). Aortic surgery during pregnancy can be lethal for the foetus und should therefore be prevented. Obstetric risks such as foetal loss and stillbirth have been described, as well as premature delivery due to premature rupture of membranes, intrauterine growth restriction and gestational age. Cauldwell et al. reported that babies of women taking β-blockers were on average 316g lighter than the average of the general population (Cauldwell *et al.*, 2019). They also reported high caesarean rates particularly in women with aortic root dilatation. Out of 218 livebirths among women with MFS, three stillbirths and two neonatal deaths were reported. Available literature regarding foetal risks in pregnancy with MFS is rather poor and generally excluded in studies regarding MFS and pregnancy.

4.2.5. Prenatal and perinatal diagnosis of MFS

Although ultrasound study of the foetal heart and skeletal measurements can raise suspicion of an involvement of MFS, it is not possible to definitely diagnose the foetus (Roman *et al.*, 2016). Prenatal genetic testing is available during pregnancy to diagnose whether the foetus is affected or not. For that, molecular testing can be used, including chorionic villus sampling or amniocentesis in affected families (Goland and Elkayam, 2020). Chorionic villus sampling is performed between 10 and 12 weeks of gestation and done either transabdominally or transcervically (Child, Aragon-Martin and Sage, 2016). The chorionic villi are used for DNA extraction and molecular analysis, and the results are usually available within five days. Chorionic villus sampling carries an overall risk of 1-2% of miscarriage, hence proper counselling with an obstetric specialist and genetic counsellor is of high importance. Amniocentesis is usually carried out later in pregnancy, between 14 and 20 weeks of gestation. It includes a removal of amniotic fluid and subsequent isolation of foetal cells and genetic testing. The miscarriage risk of amniocentesis is 0.5-1%, hence slightly lower than the risk of chorionic villus sampling. Proper support concerning whether to terminate the pregnancy or proceed, preparation for special needs and medication should be provided.

Non-invasive genetic testing such as measurement of cell free foetal DNA can only be used for diagnosing aneuploidy screening is currently not available for routinely screening mutations in *FBN1.* However, as soon as the family mutation is known an individualized test could be developed. The work-up time of such tests is usually up to eight weeks and should therefore be done prior to pregnancy (Child, Aragon-Martin and Sage, 2016).

Early onset MFS is the most severe form of MFS and is associated with a high mortality rate within the first two years of life (Veiga-Fernández *et al.*, 2019). Veiga-Fernández et al. presented a literature review based on published articles about early onsets of MFS, with pre- or postnatal suspicion or diagnosis. In 34.54% of 55 investigated cases MFS was prenatally diagnosed, with the most frequent findings of cardiomegaly, dilatation of the great vessels and mitral or tricuspid valve regurgitation. The mortality rate during the first 15 months of life was 73.68%. In those cases diagnosed

postnatally, arachnodactyly was found to be present in addition to the features mentioned before. The mortality rate of the latter was 61.11%. Genetic confirmation was performed in 67.27% of the cases. They suggest periodic ultrasound examinations and that prenatal invasive diagnosis should be offered to a patient, once early onset of MFS is suspected. Though, prenatal testing of MFS is challenging it is of upmost importance, considering that the management and adequate genetic counselling of early onset MFS should be performed by a multidisciplinary team of experts. Next to the retrospective study, Veiga-Fernández et al. presented a case of a prenatally diagnosed MFS in a dichorionic diamniotic twin pregnancy, where suspicion was raised at 35 weeks of pregnancy. Ultrasound and magnetic resonance imaging findings revealed right diaphragmatic eventration, elongation of humerus and femur and subluxation of the lens. The affected baby died three months after birth (Veiga-Fernández *et al.*, 2019).

4.2.6. Preconception counselling

According to available published reports, preconception counselling in women with known MFS is often not done properly, which can lead to patients being surprised with unexpected complications and unconsidered consequences. Based on the study of Cauldwell et al. only 50% of pregnant women had evidence of proper preconception counselling (Cauldwell *et al.*, 2019).

Ideally the management of pregnancy in women with diagnosed MFS starts prior to conception. The maternal and foetal risk should be estimated and discussed properly within a multidisciplinary group of cardiologists, obstetricians and genetic specialists (Goland and Elkayam, 2017). The proper counselling of affected women is a crucial criteria during the whole process of medical care before, during and after pregnancy. Women have to be informed about potential pregnancy-related complications, as well as the possibility of foetal risks, including prenatal testing and echocardiography during pregnancy. Within a proper preconception counselling the patient as well as the partner and family should be accurately provided with individualised, and contemporary data regarding their risks during and after pregnancy. Thoroughly evaluations for all

cardiovascular abnormalities are vital, especially of the distal aorta in patients with known dilated proximal aorta conditions. For a precise assessment of the aortic size either computed tomography or magnetic resonance imaging can be used. Those investigations are necessary for estimating the risk of aortic dissection and other complications(Goland and Elkayam, 2017).

Next to the individual risk a woman with MFS carries, the common risks of pregnancies in the healthy population should be discussed, indicating that an event-free pregnancy cannot be guaranteed to any patient considering pregnancy and that complications can occur in any stage of gestation as well as afterwards. Due to the current knowledge though, it is recommended to consider pregnancy at younger age, to lower the risk of cardiac complications and aortic dissection.

4.2.7. Surgical treatment in pregnancy

The European Society of Cardiology guidelines on management of cardiovascular disease during pregnancy recommend that women with MFS and indications for elective surgery should undergo aortic root replacement prior to pregnancy to lower the risk of aortic dissection during gestation (Goland and Elkayam, 2017). American guidelines as well as Canadian recommend to avoid pregnancy at all or attempt aortic root replacement. Those guidelines underline that aortic root dilatation and dissection cannot be ruled out in any case of pregnancy, no matter if a patient carries a genetic syndrome, connective tissue disorder or none of them.

Cardiac surgery during pregnancy is associated with increased risks for the mother and high risks for the foetus. A recent publication reported maternal mortality in 8.7% and an extremely high rate of intrauterine death (10 out of 12) during urgent open heart surgeries in pregnant women. Other studies reported less maternal mortality but foetal deaths during surgery (Goland and Elkayam, 2017).

Considering previous publications surgery during pregnancy should be avoided, unless in cases of emergencies and acute dissections. Therefore, if necessary and possible prophylactic surgery prior to pregnancy should be preferred and performed.

4.2.8. Medical therapy

The therapy with β-blockers can slow the growth of the aortic root and reduce the risk of aortic dissection significantly in non-pregnant patients (Goland and Elkayam, 2017). The use of drugs during pregnancy is a highly discussed and critical issue, due to the lack of clinical studies and knowledge. However, the prophylactic use of β-blockers before and during pregnancy makes good clinical sense, considering overall favourable results of previous publications. Known side effects of β-blockers used during pregnancy include fetal growth retardation, bradycardia, hypoglycemia, hyperbilirubinemia, and apnoea at birth in the newborn. Therefore affected women should be informed about those side-effects prior to the start of therapy. During pregnancy the use of selective β_1 receptor blockers should be preferred, as nonselective β blockers may facilitate uterine activity. The dosage should be adapted individually to reach an adequate heart rate, considering increased heart rates during pregnancy. Hence, higher dosage of β-blockers in pregnant than in non-pregnant patients should be prescribed.

Rybczynsky et al. evaluated the relation between cardiovascular manifestations and sleep apnea due to the lack of available literature and knowledge (Rybczynski *et al.*, 2010). Previous studies had documented a connection between sleep apnea and cardiovascular diseases such as arrhythmias, heart failure or aortic dissection. Rybzynsky et al. investigated whether sleep apnea is more frequent in adults with MFS and second, whether sleep apnea relates to cardiovascular morbidity. Their study population consisted out of 33 men and 35 women with MFS and an average age of 41 years. They documented that about 1/3 of adults with MFS exhibited sleep apnea in comparison to 12% of the general population. Sleep apnea is therefore more frequent in MFS but not is predicted by classic risk factors. Furthermore sleep apnea may relate to cardiovascular diseases, but further investigations in larger study populations concerning that correlation is needed.

4.2.9. Labour and delivery

Although vaginal delivery in patients with MFS with no significant cardiovascular involvement and normal aortic root diameter is considered safe, the stress of labour should be maximally reduced. Epidural anaesthesia and β-blockers can be used to minimize pain and hemodynamic fluctuation during labour and delivery. The planning and choice of an appropriate anaesthesia prior to delivery is important, considering the presence of lumbosacral dural ectasia in 70% of patients with MFS (Goland and Elkayam, 2017).

Patients with progressed aortic root dilatation have a high risk of aortic dissection during delivery. In case of progressive root dilatation during pregnancy aortic repair with foetus in-utero or termination of pregnancy should be seriously considered. If aortic repair surgery is indicated, it should be performed few days after delivery. However, surgical treatment and delivery should be undertaken in a hospital with a neonatal intensive care facility. Cauldwell et al. reported that pregnant patients with an aortic root diameter of more than 40mm prior to pregnancy have the prevalence for an elective caesarean section of 70.6% (Cauldwell *et al.*, 2019). In comparison, patients with a diameter less then 40mm the rate was 26%. They also reported a postpartum blood loss of more than 500ml in vaginal births in 21.8%.

Due to the higher risk of dissection postpartum, a weekly or monthly clinical follow-up at least 4-6 months after delivery is suggested.

4.3. In-vitro fertilization and MFS

MFS does not cause infertility in either men or women. For some couples termination of an affected pregnancy is not an option, therefore an alternative prenatal diagnosis such as preimplantation genetic testing can be considered (Child, Aragon-Martin and Sage, 2016). In-vitro fertilisation (IVF) in combination with controlled ovarian stimulation and preimplantation genetic diagnosis increases the chance of conceiving a healthy child and should be considered a valuable option for patients with MFS.

During the process of IVF a blood sample is taken from the affected parent and another relative that acts as reference. If the embryo is found to carry the pathogenic mutation of the prospective parent, it will not be used for transfer. Due to the absence of infertility issues in MFS patients, the success rates of IVF's are slightly higher than in general.

Vlahos et al. reported a case of a 32-year old woman, who had a family case of MFS and considered a pregnancy (Vlahos *et al.*, 2013). The patient was clinically asymptomatic and detailed physical examinations by internists, cardiologists, and ophthalmologists did not reveal any signs of MFS. Due to genetic testing it was confirmed that the woman was carrier of the same heterozygous nonsense *FBN1* mutation as her affected family member. Further investigations did not show any abnormalities within the cardiovascular system and aortic root. Anyway, the patient was advised to undergo IVF and properly informed about the risks of ovarian stimulation, IVF and pregnancy with MFS. 3 out of 9 embryos were tested to be carrier of the known mutations and after further testing apparently only one embryo was healthy and could be used for transferring. The patient had a positive pregnancy test two weeks after implantation. During the pregnancy she had frequent visits with the obstetrician and cardiologist, with no noticeable complications or changes within the cardiovascular system. She eventually delivered vaginally a healthy premature male infant weighting 2440 grams and had an uncomplicated postpartum course. Also later follow-ups in the mother as well as in the child didn't show any conspicuous features.

As already mentioned in prior chapters, a thorough clinical examination is essential in order to estimate the maternal and foetal risk during pregnancy. The primary focus of this assessment should be put on the evaluation of the patient's ability to tolerate the hemodynamic changes that are likely to occur during a pregnancy. Severe expression of the syndrome can occur in an offspring of a mother with a relatively mild symptomatology. Therefore, the significance of preimplantation genetic diagnosis for those patients desiring to conceive cannot be overemphasized.

5. Discussion

In the last 50 years the knowledge about MFS has increased tremendously due to research and rapid medical development. The life expectancy of patients affected with the syndrome is nowadays almost comparable to that of the general population. However, proper clinical management and counselling of MFS patients is crucial. Due to the progress of diagnostic methods, including molecular genetic testing, a diagnosis of MFS can be done much more precise than few years ago. The gathered knowledge of clinical features and genetic variants of the disease in combination with nowadays available screening methods enables experts to make a prediction about a patient's etiopathology. Considering new possibilities of genetic testing such as next generation sequencing, one can suppose that in addition to previous detected pathogenic mutations causing MFS many more are to be found. Previous literature discussed a number of correlations between certain genetic variants and clinical manifestations, such as the study by Franken et al. who presented evidence that patients with a haploinsufficient mutation have a greater aortic risk as compared with dominant negative mutation carriers (Franken *et al.*, 2017). However, a certain prediction is still not possible to be made due to various contradictions. In many cases molecular genetic testing provides the possibility of an early diagnosis of MFS, prior to the onset of phenotypic features. Subsequently a prophylactic therapy can be initiated in the diagnosed patient. Nevertheless, because of the high phenotypic variability of the syndrome the diagnosis of MFS is still confronting experts with difficulties. Considering the many differential diagnoses that show overlapping features of MFS a misdiagnosis is still not unlikely to happen. A diagnosis as well as misdiagnosis of MFS can cause a number of physical and psychological consequences. Next to financial burden, frequent medical treatment and exercise restriction the social stigmatization can disrupt the ability of individuals with genetic conditions to successfully adapt to their situation (Peters *et al.*, 2005). Peters et al. published a survey concerning the perceptions of stigma of 174 adults with MFS. 32% of the interviewed patients reported feeling discriminated against or socially devalued because of having a genetic disease. Conditions such as depressive symptoms and low self-esteem had significant negative consequences on one's life and perceptions of workplace discrimination. Clinicians and genetic professionals may therefore assist patients with MFS by providing them

opportunities to explore their experiences with stigmatization and encouraging coping strategies aimed to improve the quality of the patient's life.

As in many departments of clinical management, compliance in the treatment of MFS is of high importance. A patient showing no phenotypic features yet may not be excited about starting a medical therapy and frequent clinical monitoring. The management of children and young adults may become challenging for physicians or health professionals in regard of compliance, as the refusal of a prophylactic therapy may be lethal in patients with aortic dilatation or other severe cardiac manifestations. Therefore a patient should be properly provided with information about possible risks as well as with individualized predictions about his or her etiopathology.

In general MFS shows skeletal and visual features that do not comply with that of the general population. In the study of Peters et al. approximately 30% of the respondents endorsed using withdrawal as a coping style and 44% of respondents reported a significant level of depression (Peters *et al.*, 2005). Of note, nearly 47% reported that talking with others with MFS is extremely important and helps dealing with issues of daily life. Considering those statements, patients with MFS may consider frequent visits with a psychologist or supporting groups for MFS or other genetic diseases.

Pregnancy in MFS patients offers a challenge for gynecologists as well as genetic experts. The physical changes caused by pregnancy can lead to severe complications during pregnancy and postpartum. Women with MFS considering a pregnancy are at high risk for cardiac complications and should therefore be provided with proper counselling and management prior to conception. Based on the study of Cauldwell et al., who reported that only 50% of pregnant women had proper preconception counselling, it is obvious that there is still a lack of awareness regarding the importance of communication with the patient. Beside the affected women, the husband or partner, as well as close family members should be included in the process of counselling. A partner may be euphoric about getting a child, but may not be aware of the severity and risks a woman is taking within the process of a pregnancy. The literature about in vitro fertilization in women with MFS is rather poor, however it has been reported that IVF increases the chance of women with MFS giving birth to a healthy child. The lack of reports regarding IVF and MFS might be a matter of expense, considering that IVF is still high priced and usually not paid by health insurance.

The correction of genetic mutations, especially those based on CRISRP/CAS9, has revolutionized the genomic research and have been successfully applied in genomic manipulation (Zeng *et al.*, 2018). Zeng et al. reported a successful correction of a MFS mutation in *FBN1* in heterozygous human embryos, with an efficiency of 89%. Recent successes in precise genome editing trials suggest a potential approach for curing genetic diseases in the future. However, genome editing in human embryos is causing huge concerns considering ethical issues and uncertainties regarding efficiency and off-target effects (Zeng *et al.*, 2018).

Although there is plenty of available literature regarding MFS, there is still not a concrete guideline how to diagnose and manage MFS. Further research will be needed regarding genetic testing, pathogenic mutations and their correlation with clinical manifestations, individualized prediction of etiopathology, sufficient clinical education and management and proper preconception counselling of women with MFS considering pregnancy. Generally, the combination of compliance, prevention and personal development of patients with MFS should be argument enough for an extensive steering in the management of MFS. Beside the common monitoring and frequent medical observations, the prevention of psychologic diseases should be focused on and a patient should be supported individually to his deficiencies, whether with discussions in groups or in personal with health professionals.

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