Marfan syndrome: Getting to the root of the problem

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Summary & Future perspectives
Summary

Marfan syndrome (MFS) is the most common connective tissue disorder, with a prevalence of 1 per 5000 individuals. In 2010, the criteria for assessing the MFS diagnosis were improved. Currently, the diagnosis of MFS is established by the revised Ghent criteria, which includes the family history, an $FBN1$ mutation, aortic dilation (Z-score $\geq 2$), aortic dissection, ectopia lentis and a list of systemic features. Cardiovascular manifestations of the MFS comprise aortic root dilation, with or without aortic valve regurgitation, thickening and prolapse of the mitral valve, and aortic dissection. Chapter 1 introduces this thesis by providing the history of MFS, highlighting the progress in treatment of MFS patients and describing the progress in the diagnosis of MFS including some critical remarks upon the revised Ghent criteria. These criteria are predominantly based on the Caucasian race. Although MFS is equally prevalent all over the world, specific racial diagnostic criteria are lacking. In Chapter 2, we demonstrate that the Ghent criteria do not necessarily apply to Asian MFS populations. The clinical features of the cardiovascular, ocular and skeletal systems differ significantly between the Caucasian and Asian MFS populations. The Asian MFS population in this study as well as previously described Asian MFS populations present with a more severely affected cardiovascular phenotype, including higher rates of aortic dilation and dissection. This may be caused by under diagnosis of MFS due to genetic and racial differences, and due to the use of absolute aortic diameters in Asian populations instead of using the Z-score. Based on chapter 2, we recommend to genetically test young and mildly affected patients in order to diagnose MFS before the onset of (severe) cardiovascular complications.

The median life expectancy among non-treated MFS patients is approximately 32 years. After the introduction of prophylactic aortic root replacements, the median life expectancy has been increased tremendously to 72 years. However, MFS patients experience an increased morbidity, and they still have an increased risk of premature death. Especially aortic dissection impacts the life span negatively. Identification of MFS patients at risk for aortic dissection remains difficult and seems to be dependent on prior aortic root surgery, aortic diameters, aortic distensibility and an aortic dilation rate above 0.5 mm/year. Besides dilating in the width, the aorta also elongates, and subsequently becomes more tortuous during elongation. In chapter 3 we introduce the aortic tortuosity index (ATI) as a novel and straightforward method to measure the tortuosity of the aorta. We demonstrate that the ATI slowly increases over time and that an increased tortuosity of the aorta is associated with increased age, aortic diameter, and the volume expansion rate. Interestingly, MFS patients with a high ATI are at increased risk for aortic dissection. Despite novel imaging markers for the prediction of aortic dissection, we also show that plasma TGF-$\beta$ levels might serve as a prognostic biomarker in MFS. Since 1991, $FBN1$ mutations are strongly related to the MFS phenotype.
fibrillin-1 protein constitutes in the extracellular matrix and has a role in maintaining the structural integrity and cell development in arteries. Furthermore, fibrillin-1 is known to bind to latent TGF-β complexes, and therefore seems to play a role in the TGF-β homeostasis.

In chapter 4 we demonstrate that plasma TGF-β levels are elevated in MFS patients compared to healthy controls, and that elevated plasma TGF-β levels correlate with larger aortic root diameters, faster aortic dilation rates and predict cardiovascular events, including prophylactic aortic root surgery and aortic dissections. However, a drawback for the implementation of plasma TGF-β as a prognostic tool for aortic damage may be the large variability in TGF-β measurements in different laboratories.

Currently, FBN1 mutations are found in approximately 90% of the MFS patients. A mutation in the FBN1 gene may lead to less or less functioning fibrillin-1 protein. These different mutations result in the highly variable phenotypic appearance of MFS patients. In the chapters 5, 6 and 7 we focused on the importance of genetics in MFS. An extensive overview covering all the different FBN1 mutations found in the Universal Mutation Database is given in chapter 5. FBN1 mutations are classified based on their actions on DNA level. We identify some interesting genotype-phenotype correlations, such as an association between cysteine mutations and ectopia lentis, and an increased skeletal and cardiovascular involvement in patients with a whole gene deletion or premature termination codon (PTC) mutation, which are called haploinsufficiency (HI)-FBN1 mutations. In HI-FBN1 mutations only non-mutated fibrillin-1 is produced due to degradation of mutated fibrillin-1 mRNA or due to protein leading to a decreased amount of normal functioning fibrillin-1 protein incorporated in the aortic wall. In dominant negative (DN)-FBN1 mutations, non-mutated as well as mutated fibrillin-1 proteins are incorporated in the extracellular matrix. In chapter 6 we confirm that patients with an HI-FBN1 mutation are at increased risk for prophylactic aortic root surgery, aortic dissection and cardiovascular mortality, compared to patients with a DN-FBN1 mutation. Currently, there is no definite explanation for the more severe vascular phenotype in HI patients. Between families as well as between members of the same family, differences are found in features and their severity, which might be explained by the fact that there is a normal distribution of the amount of fibrillin-1 protein in non-MFS patients as well as in MFS patients with a HI mutation. In MFS patients with a HI-FBN1 mutation, less fibrillin-1 expression lead to a more severely affected phenotype, which suggests that a lack of fibrillin-1 protein is more important than the shape of fibrillin-1 protein. The results of chapter 6 are validated in a different cohort in Spain and described in chapter 7. MFS patients with a HI mutation in Spain are also at increased risk for the combined endpoint cardiovascular death and aortic dissection, as well as for increased aortic dilation rate measured by echocardiography. The results of chapter 6 and 7, in combination with the available evidence so far, imply that patients with a reduced amount of fibrillin-1 protein
have a worse prognosis. Therefore, for optimal assessment of prognosis and treatment of MFS patients, more research upon genetic screening and clinical evaluation is warranted.

Complications later in life may be accelerated by aortic root surgery due to altered hemodynamic factors and wall dynamics, which affect the distal part of the aorta. In order to reduce aortic dilation rate and subsequently delay the prophylactic aortic root surgery, patients are normally pharmacologically treated with β-blockers, which reduce the stress on the aortic wall by decreasing inotropy, reducing chronotropy and lowering the average blood pressure. However, β-blockers are not able to completely prevent aortic dilation, and aortic complications, thus novel treatment strategies are still necessary. In Chapter 8 we show a beneficial effect of losartan treatment on aortic root dilation rate in adults with MFS in a prospective, randomized, controlled trial. Furthermore, losartan is significantly associated with a reduced aortic dilation rate of the aortic arch in the subgroup of patients with a history of aortic root surgery. However, we do find large variability in individual aortic root dilation rates upon losartan treatment.

Chapter 9 could not show the benefits of TGF-β as therapeutic biomarker for effectiveness of losartan on the aortic dilation rate. A variable effect of losartan on plasma TGF-β levels is found; MFS patients who responded with a decrease in plasma TGF-β level during losartan therapy, have higher baseline TGF-β levels and a faster aortic dilation rate during follow-up. Therefore, we hypothesize that TGF-β is rather a readout of the disease state of the aorta than the initiator of aortic dilation in MFS patients.

Chapter 10 shows that losartan significantly reduces the aortic root dilation rate in the MFS patients with a HI- FBN1 mutation, whereas only a modest insignificant reduction is found in those with a DN- FBN1 mutation. A possible explanation may be that the aortic wall of HI patients suffers from hyperextension due to a thinner fibrillin-1 network, causing increased angiotensin II receptor 1 activation and increased local angiotensin II release. However, more translational research is necessary to confirm this hypothesis.

Finally, in Chapter 11 we show increased vascular inflammation in the aortic root of adult MFS mice, which is significantly reduced by a short term treatment with losartan or anti-inflammatory treatment. However, anti-inflammatory agents do not reduce the aortic dilation rate in MFS mice, and possibly lead to an increase in aortic damage.

In the first part of chapter 12, we provide an overview of all finished randomized losartan trials in MFS patients so far. Despite the differences in study design and outcome, we conclude that losartan on top of β-blockers seems to be more effective than a low dose of β-blockers. However, losartan does not seem to be more effective in reducing the aortic dilation rate than a high dose of β-blockers. To conclude, while awaiting the ongoing losartan trials and the final meta-analysis, losartan is well-tolerated and a safe treatment option in MFS patients and can be administered as an alternative treatment when β-blockers are not well tolerated.
**Future perspectives**

In this thesis we have tried to get to the root of the problem of MFS. We obtained more insight in the diagnosis, prognosis and markers of aortic disease, and we obtained more knowledge about the importance of genetics in MFS. Although not in this thesis, we have previously identified the aortic diameter, prior aortic root surgery, aortic distensibility and an aortic dilation rate above 0.5 mm/year, as clinical parameters associated with type B aortic dissection. Now, we have added three novel predictors for aortic complications: the aortic tortuosity index, the biomarker TGF-β, and the HI-FBN1 mutation. A risk model including all predictors for cardiovascular outcome, may help to identify patients at risk for aortic dissection and cardiovascular mortality in MFS. Furthermore, the importance of genetics was shown because losartan significantly reduce the aortic root dilation rate in the MFS patients with a HI-FBN1 mutation, whereas only a modest insignificant reduction is found in those with a DN-FBN1 mutation. This benefit is important, since patients with a HI-mutation are at increased risk for growth of the aorta, aortic dissection and mortality. However, our results are not yet confirmed by the ongoing trials, and the meta-analysis should be awaited. In addition, due to genetic variation the amount of normal fibrillin-1 protein varies, even between unaffected (non-MFS) persons. Thus the type of FBN1 mutation and the related genetic classification (HI/DN), in combination with the amount of produced wild-type/healthy fibrillin-1 protein may impact disease severity. Moreover, there may be other (epi)genetic variations that can modify disease severity on top of the FBN1 mutation, which is a highly interesting field for exploration.

Finally, we obtained more insight in novel pharmacological strategies to prevent aortic complications. We demonstrate that losartan on top of β-blockers is more effective than a low dose of β-blockers, especially in patients with a HI-FBN1 mutation. However, not all the other international research groups could confirm this beneficial effect of losartan. The variability in outcome may be explained by important differences in study design. For example, in the COMPARE trial the MRI was used to measure aortic dilation rate, which is more accurate than echocardiography. Studies with longer duration of follow-up will clarify the effect of losartan on the descending aorta, taking into account clinical events such as aortic dissection and cardiovascular death.

**Reference list**