Novel diagnostic and therapeutic targets in Marfan syndrome

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Chapter 1

General introduction and outline of thesis
INTRODUCTION

Marfan syndrome (MFS) is a heritable disorder of the connective tissue. It has an incidence of 2-3 in 10,000 and it is inherited in an autosomal-dominant manner[1]. It was described in 19th century when the Parisian professor of pediatrics, Antoine-Barnard Marfan reported typical skeletal abnormalities in a five-year old girl Gabrielle[2]. Nowadays, this syndrome bearing his name interests a broad molecular and clinical scientific public because of its pleiotropic phenotype and dynamic pathogenesis. MFS is caused by mutations in the FBN1 gene which codes for fibrillin-1 protein, an abundant protein of the extracellular matrix[3]. In recent years, a role of fibrillin-1 in the bioavailability of the cytokine Transforming Growth Factor (TGF)-β emerged[4]. Increased TGF-β signaling was found to be associated with aortic root dilatation and most other features in a mouse model of MFS[5–7]. Moreover, aortic root dilatation was ameliorated after administration of neutralizing TGF-β antibodies. This shifted our understanding of the MFS from a structural to a functional disease.

Aortic disease in MFS

Aortic root dilatation is the hallmark of MFS and occurs in about 80-90% of patients[8]. It is progressive and leads to aneurysm formation, dissection or rupture if untreated. It is responsible for the morbidity and mortality in this patient group with most progression between 20 and 40 years of age[9]. Yearly follow-up of the aortic root diameters is therefore necessary. Furthermore, up-to 30% of patients develops a dilatation or dissection of the distal parts of the aorta [10,11]. Current treatment includes beta-blockers in order to reduce the haemodynamic stress on the aortic root and surgical repair when aortic root reach diameters which threaten a dissection[12]. It is important to note that even treated patients continue to have abnormal aortic growth. Together, aortic disease is a major health problem in MFS patient population.
Therapy

The prominent role of TGF-β in the pathogenesis of MFS opened novel possibilities for treatment of these patients. Angiotensine II receptor 1 blocker losartan, a drug widely used for treatment of hypertension, emerged as a novel treatment strategy in MFS patients as it reduced TGF-β signaling in several rat models of kidney failure. In MFS mouse model losartan reduced aortic root dilatation to the level of wild-type mice [5–7]. This effect was confirmed in a small observational study in children with a severe aortic root disease. [13] Furthermore, similar effects were achieved with losartan and mitral valve prolapse, myopathy and lung emphysema in these mice. These findings introduced losartan as a high potential novel therapy in MFS. We and other groups initiated clinical trials investigating effects of losartan on the aortic disease in MFS patients[14].

Clinical variability in MFS patients

As mutated fibrillin-1 protein is present in the extracellular matrix of most organ systems, MFS is a multi-system disorder. Other features in MFS patients are dislocation of the ocular lens (ectopia lentis), skeletal features resulting from overgrowth of long bones, osteopenia, lung emphysema and mild myopathy.

MFS is a clinically variable disorder with weak genotype-phenotype relations[15,16]. Mutations in the middle part of the FBN1 gene cause more severe phenotype. Mutations involving cysteine-residues are more likely to cause dislocation of the ocular lens. Nevertheless, neither the location of the mutation nor the type of aminoacid altered nor even the family presentation are sufficient to predict the phenotype both among as within the affected families. This suggests that other pathways modify the course of the disease.

The objective of this thesis was to investigate a broad wire of clinical and molecular diagnostic and therapeutic targets in MFS patients which could improve our knowledge about the pathogenesis of MFS and offer novel therapeutic strategies. We searched for modifying pathways of MFS clinical features and explored the variability of the molecular response to losartan treatment in MFS patients. In addition, we
investigated ventricular function and aortic volume in MFS patients using cardiac MRI. Finally, we analyzed the impact of MFS on patients’ quality of life and genetic susceptibility to its impairment.

OUTLINE OF THIS THESIS

Work presented in this thesis explores both clinical and molecular aspects of MFS. In Part 1, chapters 2-5, we describe clinical aspects of the disease: the Dutch losartan clinical trial (COMPARE study), repercussions of revised diagnostic criteria in adult MFS patients, cardiac function of MFS patients and aortic volume as a global monitoring method of aortic disease.

Losartan showed very promising effects on the aortic root dilatation in MFS mice. We, therefore, initiated a clinical trial investigating the effects of losartan on the aortic root dilatation and several other cardiovascular end-points. Rationale and design of the COMPARE trial are described in chapter 2.

Ever since it was described, MFS remained a clinical diagnosis. Our knowledge about its molecular basis increased throughout the years and additional related connective tissue disorders emerged, i.e. Loeys-Dietz syndrome. Diagnostic criteria for MFS were revised by Loeys and Dietz whereby aortic root dilatation, defined as a Z-score of the aortic root diameter, was made central. In chapter 3 we applied the revised criteria in an established adult MFS patient group in order to define its repercussions for clinical practice and individual patient.

Several lines of evidence suggested a ventricular dysfunction in MFS patients without valvular disease. In chapter 4 we analyzed biventricular function in a large cohort of MFS patients when compared to healthy volunteers and its’ correlation with the elastic properties of the aorta.

In chapter 5 we investigated aortic volume measured by 3D Magnetic Resonance Angiography (MRA) as method of global aortic expansion surveillance in MFS patients. This method would allow more accurate surveillance of the aortic disease than by using aortic diameters only and can be of particular importance in clinical trials.
In Part 2, chapters 6-10, we investigated molecular aspects of clinical variability in MFS patients. In chapter 6 we investigated global gene expression profiles in skin of MFS patients using microarrays and compared expression profiles between patients with different disease features. Patients with more severe aortic disease had higher expression of inflammatory genes. This was validated by cytokine levels in blood and inflammatory cell profile in the aorta. Similarly, patients with other disease features had pro-inflammatory expression profiles. Inspired by these findings, in chapter 7 we explored the genetic variability (single nucleotide polymorphisms-SNPs) in inflammatory genes which could contribute to the aortic root disease severity, the most important disease characteristic of MFS.

MFS is a clinically variable disorder and it is, therefore, likely that MFS patients might have a variable response to losartan treatment. Molecular response to losartan, measured as circulating TGF-β decrease and gene expression changes, was investigated in chapter 8.

Quality of life is an emerging parameter of patients’ well-being and it is not related to disease severity or therapy. As such, it might have a genetic basis. In chapter 9 we explored the quality of life in MFS patients, measured by means of SF-36 questionnaire. As it was not strongly related with disease severity, we explored its genetic basis using gene expressions and SNPs.

Chapter 10 summarized the findings of this thesis in the light of the aortic disease pathogenesis in MFS. We discuss the contribution of different pathways in the aortic root disease and implications for the further research.
REFERENCES


