Left ventricular dysfunction in a mouse model of Marfan Syndrome

L. Campens1, M. Renard1, B. Trachel2, P. Segers2, B. Loeys3, H. Dietz4, A. De Paepe1, J. De Backer1,5

1 Center for Medical Genetics, University Hospital Ghent, Belgium, 2 Institute of Biomedical technology, Ghent University, Belgium, 3 University Hospital Antwerp, Ghent University, Belgium, 4 McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, USA, 5 Department of Cardiology, University Hospital Ghent, Belgium

Background

Marfan syndrome (MFS) is an inherited connective tissue disorder caused by mutations in the Fibrillin1 gene (FBN1) and characterized by manifestations in different organ systems. The clinical diagnosis is based on specific criteria, as formulated in the “Revised Ghent Nosology”(1). According to this new nosology, lens luxation and aortic root dilatation play a cardinal role.

Materials & Methods

Serial cardiovascular studies of aortic dimensions (figure 2), systolic and diastolic function were obtained in 15 MFS and 10 wild-type (WT) mice with a dedicated ultrasound apparatus (Vevo 2100, Visualsonics) equipped with a high-frequency linear array probe (MS 550D, frequency 22-55 MHz).

Results

Investigate the natural evolution of Left Ventricular (LV) dimensions and function as well as aortic diameters in a heterozygous MFS mouse model (fbn1/C1039G/+).

Background

In addition to aortic root dilatation, other established cardiovascular features of MFS include Mitral Valve Prolapse and pulmonary artery dilatation. Less known, although clinically potentially relevant is the existence of cardiomyopathy in MFS. Over recent years, several studies have confirmed the existence of (mild) left and right ventricular dysfunction in MFS patients (2-5). Study of the pathophysiology of aortic dilatation in a MFS mouse model (fbn1/C1039G) elucidated the crucial role of increased TGFβ-signalling. This subsequently led to promising new therapeutic options. Whether cardiomyopathy is recapitulated in this mouse model is not known at present.

Results are summarized in table 1

MFS mice at six and twelve months had significantly larger diameters versus controls at the level of the aortic sinus (figure 3), ascending aorta and transverse aorta. There was a non-significant trend towards larger aortic diameters at 1 and 3 months. Pulmonary artery diameters were not significantly different in MFS mice.

Results

Left ventricular ejection fraction (EF) was lower in MFS mice at all time points and evolved towards significant lower values at one year of age (figure 4). This finding was unrelated to valvular dysfunction.

Conclusions

Here we provide evidence for LV dysfunction, unrelated to valvular dysfunction in a mouse model of MFS. This model recapitulates the findings in humans and may not only enable further studies of the development and treatment strategies of cardiomyopathy in MFS but may ultimately also increase the insight into more common forms of cardiomyopathies.

References


Laurence.campens@ugent.be