MARFAN SYNDROME AND ITS THERAPEUTIC APPROACHES

Introduction

Isaiah Austin was only days away from realizing his dream of playing pro basketball at the 2014 NBA draft when has was diagnosed with Marfan syndrome (MFS). Austin stands 2.13 meters, has unusually long arms and a detached retina. He indeed fits some features of MFS: disproportionately long limbs, legs and fingers; slender and tall build; flexible joints, crowded teeth; curved spine; funnel chest and pigeon breast. MFS is an autosomal dominant disorder of connective tissue affecting 2 to 3 in 10000 individuals (Judge and Dietz, 2005). Mutations in FBN1 gene on chromosome 15 lead to insufficient formation of fibrillin-1 microfibrils, which disrupt structural stability of elastin in the vascular extracellular matrix and enhance the release of transforming growth factor-β (TGF-β) (Franken et al., 2015). Initial diagnosis of MFS is based on patient's physical appearance and family history, then further confirmed by assessing the eye lens, aortic size, spinal curves or undergoing genetic testing. As approximately 80% of MFS patients will develop aortic aneurysm, dissection or rupture, cardiovascular complications remain the leading cause of death in MFS patients (Wagner et al., 2019). The accumulation of reactive oxygen species and increased matrix metalloproteinase activity in the aortic wall due to excessive TGF-β signaling contribute to the vascular pathogenesis. Both will degrade the elastin and form aortic aneurysm (Wagner et al., 2019). This essay will outline currently available therapeutic approaches and potential future treatment strategies.

Currently Available Therapeutic Approaches

MFS patients now have a near-normal life expectancy, thanks to currently available symptom-based treatments, such as antihypertensive drugs and surgical repair of aortic root, retinal detachment, cataract, severe scoliosis, breastbone deformity and collapsed lung. In the past, untreated MFS patients only lived for a mean of 32 years (Murdoch et al., 1972). Two major antihypertensive drugs used to retard aortic root growth are β-blockers (BB) and angiotensin II type 1 receptor (AT1) blockers. Shores et al. (1994) published the first convincing evidence of β-blockers efficacy: MFS patients who were treated with propranolol and monitored for an average of 10.7 years showed a significant reduction in aortic root growth. BB prevents the binding of stress hormones noradrenaline and adrenaline to β-adrenoceptors on sino-atrial node (the pacemaker of the heart), resulting in a negative inotropic and chronotropic effect. Although recommended as a first-

line treatment for MFS, β-blockers are unsuitable for patients with bradycardia or bronchospasm (Teixido-Tura et al., 2018). One alternative is losartan, an AT1 blocker that is known to downregulate TGF- β signaling. The superiority between β-blockers and AT1 blockers remains to be clarified. Brooke et al. (2008) found that angiotensin II receptor blockers significantly slowed the growth rate of aortic aneurysm in a small cohort of MFS patients. However, a recent study suggested that losartan produced non-significant benefit over β-blockers (Kang et al., 2019). Besides producing similar outcomes, their market prices per tablet on drug.com are also comparable, US $1.06 for losartan 25 mg and US $1.08 for propranolol 20 mg.

Once MFS patient's aorta reaches >= 50 mm in diameter or starts expanding rapidly, surgery is recommended. Prophylactic surgery has been reported to remain the only approach that results in life expectancy prolongation (Wagner et al., 2019). Three forms are available: total root replacement (TRR), valve sparing root replacement (VSRR) and personalized external aortic root support (PEARS) (Treasure et al., 2014). While both TRR and VSRR use a Dacron graft to replace the diseased aortic root, VSRR preserves the patient's own valve, different from TRR which replaces it with a mechanical one. PEARS is an alternative to replacement as it prevents further growth in aneurysm by wrapping the aorta with a polymer mesh sleeve 3D printed to the patient's aortic dimensions. PEARS is especially recommended for patients with genetically determined aortic aneurysm before the valve fails or the aortic size mandates replacement surgery.

Potential Future Treatment Strategies

Sellers et al. (2017) argued that focusing on antihypertensive drugs might be of low therapeutic value in preventing MFS aortic complications, compared to focusing on increased protective endothelial function. They concluded that endothelial nitric oxide release and blockade of angiotensin II stimulated ROS production mediated losartan's anti-aortic root remodeling activities in several MFS clinical trials. Thus, the author suggests future research on endothelial function-optimized approaches for MFS patients. The author also predicts the availability of gene therapy for MFS patients in 10-15 years, as this technique has been used for other genetic diseases. Gene therapy using adeno-associated virus could be an option for MFS patients for its lack of pathogenicity, low host immune response, long-term expression and ability to transfect both dividing and non-dividing cells (Luo et al., 2015). However, considering today's overly expensive gene therapies, such as $ 2.1 million ZOLGENSMA, will MFS patients be able to afford it?

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