Delving into Management of Marfan Syndrome

Marfan syndrome (MFS) is an autosomal dominant connective tissue disease affecting 1 in 5000 [1, 2]. Caused by mutations in the FBN1 gene that encodes fibrillin-1, the disease exhibits phenotypes varying according to the haplo-insufficient or abnormal fibrillin-1 produced by mutated genes [3, 4]. Fibrillin-1 is a major component of microfibrils which provide structural support for the structural integrity of the connective tissue, while mutations in FBN1 genes may lead to weakened connective tissues, causing various symptoms around the body [5, 6]. Apart from the structural importance, fibrillin-1 is also involved in TGF-β signaling regulation, as an elevated TGF-β level was observed in MFS patients, while TGF-β antagonists in mouse models alleviated the phenotypes. Further research pointed out that it could be Ang-2 in renin–angiotensin system could be upstream of TGF-β that leads to aortic dilation [7, 8].

One of the most visible manifestations of MFS includes abnormally long, slender fingers or toes and other skeletal abnormalities [3], yet the modern clinical phenotypic phenotypes includes aortic root dilation and lens dislocation, with other symptoms such as aortic dissection and curved spines as well as the family history to support the diagnosis [6]. We will continue discussing about the diagnosis in the next section. Then, the major treatment today and possible new directions for treatments will be covered.

Challenges Facing the Genetic Diagnosis

The asymptomatic sudden death and aortic dilation caused by MFS is so disastrous is life-threatening. The early diagnosis is beneficial in management of lethal aortic events, but the popularizing genetic tests have limitations [9]. Despite increasing FBN1 mutations reported to the FBN1 database [3], a report showed that the reliability of the database could be unreliable due to misinterpreted data [10]. The uncertain genotype-phenotype links complicate the prenatal genetic diagnosis and screening [11]. Therefore, phenotypical diagnosis is still a necessary diagnostic method.

Managing the Cardiac Impacts

Aortic dilation and sudden death are the major causes of deaths in MFS patients, a follow-up management of the cardiovascular impacts are requisite for patients [12,

13], especially for pregnant women, for the aortic dissection and hemorrhage under high blood pressure and hormone-stimulated vascular dilation could be lethal and repair surgeries should be carried out prior to conception [14].

Continued administration of β-blockers is recommended for most patients, for it could reduce myocardial contractility and the blood pressure and could promote the elasticity of the aorta [15, 16]. A 10-year clinical trial confirmed the drug effectively retarded aortic dilation [17]. Adverse effects in kids, although contradictory, should be paid more attention to [18]. Inhibitors targeting renin–angiotensin system like Losartan have been also found effective in retarding dilation by regulating TGF-β signaling. Sole administration and co-administration with β-blockers can both retard aortic root dilation, yet further trials should be made to determine the side effects [19].

However, as the dilation worsens, preventive replacement of the affected aortic part with/without valves are recommended to increases their life expectancy, especially for those with a significant dilation rate exceeding 5 mm per year or the aortic over 50mm in diameter. After replacement, continued administration of β-blockers is still required, yet patients should take anticoagulation and antibody drugs to avoid infection and thromboembolic events. [20, 21]

Outlooks of the Treatment

Since the genotype-phenotype associations could be misinterpreted, the diversity of the phenotype makes diagnosis hard; thus, a subdivision of the disease based on several different mutations is recommended. Thus, differential diagnosis can lead to differential treatment and thorough understandings of different pathogenesis.

As to drug development, the complex genotype-phenotype links provide soil for a personalized cell model for drug development using induced pluripotent stem cell (iPSC) [22]. Comparative studies among phenotypes should be done to understand how drugs like β-blockers work differently and how they affects women and children.

Lastly, more affordable bio-friendly material should be introduced, in which personalized cell model can possibly use iPSC to develop material free from immune rejection. Whether the material could possibly provide microfibrils and other factors for wounding healing after implanted into the body is also worth further research.

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