The Multidisciplinary Approach to the Marfan Patient

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Marfan syndrome is a multisystem disorder with manifestations typically involving the cardiovascular, skeletal and ocular systems. It was first described more than 100 years ago by a Parisian professor of pediatrics, Antoine-Bernard Marfan, who reported the association of long slender digits and other skeletal abnormalities in a 5 year old girl, Gabrielle [1].

In the past three decades there has been significant advancement in the diagnosis and treatment of this disorder. Marfan syndrome mortality from aortic complications has decreased (70% in 1972, 48% in 1995) and life expectancy has increased (mean age at death 32 ± 6 years in 1972 compared to 45 ± 17 years in 1998) [2,3]. These significant improvements are a direct result of a better understanding of the pathogenesis of the disease and the implementation of a multidisciplinary approach that generates improved diagnosis, prophylaxis, and timely medical and surgical intervention.

This issue of *IMAJ* includes several papers on the diagnosis and treatment of Marfan syndrome patients [4-8]. Those papers were presented at the first "Marfan syndrome conference" held at the Sheba Medical Center in January 2007 and reflect the multidisciplinary approach implemented in the dedicated Marfan Clinic in the Sheba Medical Center.

Diagnosis and differential diagnosis

One of the most important factors in reducing mortality from the disorder is accurate diagnosis. Miss-diagnosis exposes affected individuals to the complications of the disorder. The incidence of classic Marfan syndrome is about 2–3 per 10,000 individuals. Gray et al. [9] reported the incidence in Scotland as 1 in 9802 live births in 1994. Various factors contribute to an underestimation of the disease prevalence. Firstly, the phenotype becomes more apparent only with increasing age. Secondly, about 25% of cases are sporadic due to *de novo* mutations. A family history of Marfan syndrome is not always present as a risk factor. Thirdly, many of the manifestations are common in the general population and physicians may miss the diagnosis. Finally, although it is known that mutations in the FBN1 gene are the predominant cause of classic Marfan syndrome, there is no rapid and efficient molecular diagnostic test.

To make the diagnosis of Marfan syndrome more consistent and of more prognostic value, the Berlin diagnostic criteria of 1988 [10] were revised and the clinical features were codified as the "Ghent criteria" in 1996 [11]. These criteria placed greater emphasis on the diagnostic use of skeletal findings and accented the requirement that a positive family history of the disorder could only be used as a major criterion for diagnosis of a proband if at least one family member met the diagnostic criteria on the basis of physical manifestations alone. Using these criteria helps identify which patients with a Marfan-like build are at risk of cardiovascular complications that require regular follow-up with prophylactic medical and surgical treatment, and which can be reassured that they are unaffected, thereby avoiding the stigmatization, the financial burden and the lifestyle restrictions that may accompany the diagnosis.

Several disorders are included in the differential diagnosis of Marfan syndrome. On the basis of similar skeletal, cardiac or ophthalmological manifestations, many individuals referred for possible Marfan syndrome are shown to have evidence of a systemic disorder of the connective tissue but do not meet diagnostic criteria for the disorder. This constellation is referred to by the acronym MASS phenotype (**m**itral, **a**ortic, **s**kin, and **s**keletal manifestations). MASS phenotype can segregate in large pedigrees and remain stable over time. Other fibrillinopathies, such as familial mitral valve prolapse syndrome and familial ectopia lentis, also include subclinical manifestations and can be due to mutations in the gene encoding fibrillin-1 [12,13]. Also included in the differential diagnosis of the disorder is homocystinuria. Observation of raised concentrations of plasma homocysteine is an efficient mechanism to distinguish homocystinuria from Marfan syndrome.

Familial thoracic aortic aneurysm syndrome segregates as a dominant trait and can show vascular disease identical to that seen in Marfan syndrome, including aortic root aneurysm and dissection. These individuals generally do not show any of the systemic manifestations of Marfan syndrome. Other families ex-

hibit the association between bicuspid aortic valve and ascending aortic aneurysm, which can also segregate as a dominant trait [14]. Here, maximum dilatation usually occurs further up in the ascending aorta, beyond the sinutubular junction. Once again, affected individuals do not show systemic features of a connective tissue disorder. Although genetic loci have been described for thoracic aortic aneurysm syndrome, no specific genes (or molecular screening tests) have been described so far for these disorders, mandating ongoing follow-up of all at-risk family members. The management principles that have been generated for Marfan syndrome have proven effective for these other forms of familial aortic aneurysm.

Patients with Loeys-Dietz aortic aneurysm syndrome show some systemic features of Marfan syndrome with other features that are unique. They have high frequency of hypertelorism, broad or bifid uvula, arterial tortuosity, and aneurysms with dissection that can occur throughout the arterial tree. The aneurysms may dissect at sizes not associated with risk in Marfan syndrome and frequently lead to death in early childhood. In view of its aggressive behavior, the distinction of Loeys-Dietz syndrome is essential to individualize management.

Management

The diagnosis, follow-up plan and treatment strategy for Marfan syndrome require a multidisciplinary team. The team should include a geneticist, an ophthalmologist, a cardiologist and an orthopedic surgeon.

In order to decrease the chance of aortic dissection or rupture once a clinical diagnosis of Marfan syndrome is established, it is crucial to place the patient on a routine plan of aortic growth monitoring.

Although ectopia lentis is a major criterion in the diagnosis of Marfan syndrome, these patients are also at increased risk of glaucoma, retinal detachment and cataracts. Thus, Marfan patients should undergo comprehensive yearly assessments by an ophthalmologist, ideally with expertise in this disorder.

Severe orthopedic issues will need the involvement of a skilled orthopedist. Bracing is generally inadequate to manage severe and progressive scoliosis, which often requires surgical stabilization. This situation must be monitored closely during growth. Pectus deformity is largely a cosmetic issue but many patients have restrictive lung disease. A recent report of 45 patients who underwent minimally invasive surgical intervention (Nuss procedure) for pectus excavatum described a significant increase in forced vital capacity after surgery, with improvement most prominent in patients older than 11 years [15]. If done too early, however, continued rib growth will lead to recurrent deformity [16].

Treatment to prevent or delay aortic aneurysm

Beta-adrenergic receptor blockade to delay or prevent aortic aneurysm and dissection is currently regarded as the standard of care for patients with the disorder. Although small, most published studies have shown benefit of treatment with beta-blockers in Marfan syndrome, including in children [17,18]. The only randomized trial assessing the effect of beta-blockade was published in 1994 [19]; using propanolol fewer patients reached a primary clinical endpoint of aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure and death. Furthermore, the normalized rate of aortic dilatation was lower in the propranolol group than in the control group. It is important to remember that around 10–20% of patients with Marfan syndrome are intolerant to beta-blockers due to chronic obstructive lung disease, depression and fatigue. For such patients, a trial of verapamil should be instituted based on the study that showed that treatment with verapamil can slow aortic growth rate [18]. It is also important to note that aortic growth is not stopped or reversed but is slowed in response to treatment. Recently an Australian study claimed that a regimen of standard beta-blocker with angiotensin-converting enzyme inhibitors (namely perindopril) reduced aortic stiffness and aortic diameter and attenuated aortic dilatation in patients with Marfan syndrome, possibly through attenuation of transforming growth factor-beta signaling [20]. In the setting of aortic enlargement, even though the patient is under treatment with pharmacological agents, vigilance for further aortic enlargement with at least yearly measures of aortic dimensions is indicated.

The rate of acute aortic dissection is directly proportional to the maximum diameter of the aorta. Elective surgery to repair the aortic root is recommended when the maximum aortic diameter reaches 5 cm. Additional considerations include the rate of aortic growth and family history of aortic dissection less than 5 cm. In those circumstances a 4.5 cm diameter will be an indication for elective surgery. Composite surgical replacement of the aortic root and valve was first reported by Bentall and De Bono in 1968 [21]. Gott and colleagues from the Johns Hopkins Medical Center [22] reported outcomes for 675 patients with the disorder who underwent aortic root replacement surgery at ten experienced surgical centers (seven in North America and three in Europe). Mortality for elective surgery was 1.5% compared with 2.6% for urgent surgery. Mortality was 11.7% among patients who underwent emergency surgery. This study and others emphasize the importance of timely and non-urgent surgery. Due to risks of thromboembolism and the lifetime requirement of warfarin anticoagulation in the setting of a mechanical prosthetic aortic valve, recent surgical efforts, pioneered by David and Feindel [23], attempted to spare the native aortic valve leaflets. To date, no randomized clinical trials of valve replacement versus valve-sparing aortic root surgery have been undertaken, and the very long-term data on the outcomes with valve-sparing surgery are not yet available. Nevertheless, this procedure has shown excellent short and mid-term results and is now the preferred treatment in all eligible patients who present for surgical intervention [24,25]. In this issue, Sheick-Yousif [8] describe our experience using the valve-sparing techniques and composite replacement in patients with the disorder. As demonstrated, in the beginning of the series the "remodeling" technique was used and, as in other reports, it resulted in a relatively high incidence of recurrent aortic regurgitation. The "reimplantation" technique resulted in a more stable repair and may be the treatment of choice. The

valve-sparing approach is especially attractive for young women who anticipate pregnancy.

Other aspects

Sudden death in the setting of unrecognized Marfan syndrome among high profile athletes has helped to emphasize the importance of early recognition and activity limitations for this disorder. Patients should be counseled not to engage in contact sports, competitive athletics or isometric exercise. However, they should be encouraged to remain active with aerobic activities performed in moderation. This will promote physical and psychosocial health in the long term.

The issue of pregnancy in Marfan syndrome draws attention to concerns about the risk of transmission of this disease. Genetic counseling should be undertaken and parents should be informed of the 50% risk of the offspring inheriting a genetic predisposition to the disorder. Earlier experience indicated a high risk of aortic dissection during pregnancy. More recent analyses have indicated that if an aortic root measures less than 4 cm the risk of aortic dissection through pregnancy is low [26]. Improved antenatal care and early surgical intervention have changed the current paradigm. Systemic anticoagulation with warfarin during pregnancy in the setting of a mechanical prosthetic aortic valve is associated with increased risk of fetal demise and embryopathy.

Low molecular weight heparin seems safer than warfarin as it does not cross the placenta, however it can result in heparin-induced thrombocytopenia and might not prevent prosthetic valve thrombosis [27]. Ideally, pregnancy in patients with the disorder should precede significant aortic enlargement or follow an aortic valve-sparing procedure.

Future perspectives

There is new realization that Marfan's syndrome manifests postnatally as acquired tissue pathology to indicate a failed regulatory (as opposed to structural) role of the extracellular matrix. This represents the optimistic view of the healing perspectives of the disorder. Most disease manifestations seem to implicate dysregulation of TGFβ activity and signaling. Data from the mouse models suggest that these phenotypes can be productively modified in the postnatal period through manipulation of TGFβ activity, plausibly including the use of drugs that are in development or in use for other indications (unpublished data). These treatments have the potential to not only slow or prevent progression of aortic root aneurysms, but also to attenuate the multisystem pathogenesis of disease.

Summary

Progress in the past century has led to an improved understanding of the cause, pathophysiology and treatment of Marfan syndrome. The "Ghent criteria" constitute currently the most effective way of diagnosing or excluding Marfan syndrome. This system can also help to identify families with aortic aneurysms who do not have Marfan syndrome, but it should not be used to assess risk in such families.

Despite the morbidity and mortality associated with Marfan syndrome, an appropriate multidisciplinary medical and surgical approach can improve and extend the lives of many patients. As knowledge of the consequences of fibrillin-1 deficiency develops, the treatment will continue to advance, providing improved length and quality of life for Marfan patients.

TGFβ = transforming growth factor-beta

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