

HERITABLE AORTIC DISEASE

Definitions and Classification

A genetic predisposition to thoracic aortic aneurysm has been established.¹ It involves mutations in genes encoding various components of the transforming growth factor beta (TGF- β) signaling cascade (*FBN1*, *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, *SMAD2*, *SMAD3* and *SKI*), the so-called TGF- β vasculopathies, and in genes encode components of the smooth muscle contractile apparatus (*ACTA2*, *MYH11*, *MYLK*, and *PRKG1*), the smooth muscle contraction vasculopathies, and the proinflammatory protein S100A12, predispose to aortic aneurysms and dissections.¹⁻⁴

Heritable aortic disease may be syndromic or nonsyndromic due to mutations that can be identified or not identified. Congenital conditions may also occur (Table 1). Heritable aortic disease refers to thoracic aortic disease caused by a highly penetrant rare variant (or mutation) in a single gene. A diagnosis is based on ≥ 2 members of a family with disease, the identification of a pathogenic variant in the gene known to cause thoracic aortic disease in a family member, or clinical diagnosis of syndrome that confers risk (eg, Marfan syndrome) in a family member⁵.

Syndromic disease typically has systemic features with multiorgan phenotype, positive family history of aortic aneurysm or dissection, and is often caused by mutations involving extracellular matrix proteins or involved in transforming growth factor- β pathway. Nonsyndromic disease is mainly caused by genes that encode components of the smooth muscle contractile apparatus (*ACTA2*, *MYH11*, *MYLK*, and *PRKG1*) and *LOX*, and confer a highly penetrant risk for disease that is inherited in an autosomal dominant manner.⁵

General recommendations for management and **genetic testing** are provided in Table 2 and Figure 1.

SYNDROMIC HERITABLE AORTIC DISEASE

MARFAN SYNDROME

Definition

Marfan syndrome is multisystem disease characterized by long bone overgrowth and other skeletal abnormalities, dislocation of the ocular lens, decreased skeletal muscle mass, pneumothorax, mitral valve prolapse, and dilatation of the aortic root.

Aetiology

Marfan syndrome is an autosomal dominant condition with high penetrance but variable expression, and represents one of the more common, potentially lethal Mendelian conditions with an estimated prevalence of 1/5000 individuals.⁵ The most common mutations (>800) that cause classic Marfan syndrome are in the gene FBN1 that encodes the extracellular matrix protein, fibrillin-1.¹ In some families or among sporadic patients in which some of the features of Marfan syndrome occur, but usually without ectopia lentis and thus overlapping with the Loeys-Dietz syndrome, have mutations in the gene TGFBR2 that encodes receptors for the cytokine transforming growth factor- β (TGF- β) (Table 1). Children of an affected parent have a 50% chance to develop the syndrome while one third of cases represent de novo mutations. Approximately 25% of patients do not have a family history and represent new cases due to sporadic mutations for the condition.

Pathophysiology

Perturbation of fibrillin-1 results in degeneration of the medial layer with disarray throughout the extracellular matrix, progressive fragmentation, and loss of elastic lamellae, and excess activation of the cytokine transforming growth factor- β (TGF- β), a potent stimulator of inflammation and fibrosis. Ongoing destruction of the elastic and collagen lamellae and medial degeneration result in progressive dilatation of proximal aortic segments, as well as a predisposition to aortic dissection from the loss of elasticity and appropriate medial layer support. Superimposed on underlying Marfan syndrome tissue abnormalities are the normal hemodynamic stressors on the proximal aorta throughout the cardiac cycle.⁶ Recurrent dissection is strongly associated with Marfan syndrome.⁷

Presentation and Physical Findings

Chest pain in a person with tall, asthenic habitus, anterior chest deformity, or a family history of aortic dissection or sudden death should always raise the suspicion of aortic dissection.

Patients with Marfan syndrome are predisposed to thoracic aortic aneurysm or type A or B dissection, and every patients with the syndrome has evidence of aortic involvement at some point during their life. Cardiovascular, ocular and skeletal features are presented in Table 1. Mitral valve prolapse, MR and AR may also be seen. The ECG may show ST-segment abnormalities, prolonged QT and AV conduction disturbances.

Diagnosis

Major criteria for the diagnosis include aortic dilatation, family history, ectopic (dislocated) lens that differentiates Marfan from Loeys-Dietz syndrome, identification of FBN1 mutation, and the presence of systemic features such as wrist and thumb signs, pectus carinatum, and hindfoot deformity, pneumothorax and dural ectasia. The revised Ghent criteria are presented in Table 3.⁸ They might have lower sensitivity even in patients with aortic root > 40 mm Hg, due to the use of the Z-score (aortic size ratio based on gender- and body size-related norms in order to take into account that the diameter of the aorta is directly proportional to body size throughout normal growth) that seems to underestimate aortic root dilatation.⁹ Disorders that are often clinically difficult to distinguish from Marfan syndrome, such as familial ectopia lentis, MASS phenotype (myopia, mitral valve prolapse, aortic root dilatation, striae, skeletal findings), and familial aortic aneurysm, may also be associated with mutations in FBN1. Thus, for the patient being evaluated for the first time, who has some but not enough features for a clinical diagnosis and no or an uncertain family history, molecular analysis is of minimal help. DNA analysis is indicated when a pathological mutation is known in a family, and relatives at risk can be screened for this mutation. Recommendations for diagnostic imaging are presented in Table 4 and Figure 2.

Risk stratification

Aortic size >5 cm, Z-score>3, proximal aortic ratio >1.3 (ie > 30% enlargement of the aortic root above the mean for that patient's age and body surface area), rapid increase in aortic size (>0.5cm/year), and family history are ominous prognostic factors.⁶ Higher aortic stiffness, which can be assessed segmentally using CMR, is associated with higher rates of surgical aortic replacement and aortic root dilation.¹⁰ Identification of a FBN1 mutation in general denotes increased risk.¹¹ Marfan syndrome patients with an haploinsufficient (HI) mutation are at increased risk for cardiovascular death and aortic dissection compared with patients with a dominant-negative (DN) mutation.¹² Apart from aortic rupture patients with Marfan can die from severe MR or ventricular arrhythmias that may be seen in 20% of patients conferring a long-term risk of arrhythmic sudden death of 4%.¹³

Therapy

Beta blockers (aiming at a resting heart rate < 60 bpm) should be given to all patients and may reduce mortality (Table 5).¹⁴ In a recent study in children and young adults with Marfan's syndrome, losartan and atenolol in relatively high doses had a similar effect on the rate of aortic-root dilatation between the two treatment groups over a 3-year period.¹⁵

Angiotensin receptor blockes should also be used in combination with beta blockers, and delay aortic arch dilatation, pre- or post-operatively.¹⁶⁻¹⁸ In the Marfan Sartan RCT, losartan did not limit aortic dilatation during a 3-year period in patients >10 years old,¹⁹ and its superiority compared to beta blockers is not established.²⁰ However, losartan in addition to beta blockade improved outcome after a follow-up period of 8 years (albeit not at 3 years) in the COMPARE RCT,²¹ whereas, in the AIMS trial, irbesartan was associated with a reduction in the rate of aortic dilatation in children and young adults with Marfan syndrome and could reduce the incidence of aortic complications.²² Effects of therapy should be monitored regularly (Table 3). Isometric static exercise, competitive contact sports involving bodily collisions, and marked changes in ambient air pressure (as in scuba diving or sudden changes in altitude in non-pressurized aircraft that may cause pneumothorax) are avoided. Aerobic exercise allowing a heart rate <100 bpm (110 for children) is permitted under beta blockade (see also www.marfan.org).

Surgery

Surgery with a valve conduit is recommended in patients with aortic root diameter > 5 cm, or 4.5 cm in the presence of a family history, rapid diameter change (>0.5cm/y), and significant AR (Table 6). Risk of sudden death or aortic dissection remains low in patients with Marfan syndrome and aortic diameter between 45 and 49 mm.²³ Mortality with elective surgery is 1.5% and 11.7% with emergency root replacement. Aortic valve sparing operations such as the David technique with preservation of the native valve is rather preferable to composite mechanical valve conduits (Bentall), but requires extended experience and patients with totally normal native valves.^{24 25} Emergency surgery for Type A dissection in Marfan should be aimed at replacing the entire aortic arch rather than the hemi-arch. Aortic root replacement or repair is recommended since supracoronary ascending replacement is associated with a high need (>40%) for root re-intervention.²⁶ Type A dissection should be operated whereas medical therapy is preferable in type B dissection, unless if the aortic diameter exceeds 5-6 cm. Stents are not recommended. Elective root replacement by a prosthesis may constitute a risk factor for downstream, type B aortic dissection (because of the loss of the elastic properties of the root or clamp injuries of the aorta) but in clinical practice this appears to be outweighed by the risk of type A dissection if timely proximal repair is not performed.²⁷ Patients with prior prophylactic aortic surgery are at substantial risk for type B aortic

dissection, even when the descending aorta is only slightly dilated.¹⁷ Personalized external aortic root support by a polymer mesh sleeve may also be useful for prevention of aortic root dilatation in Marfan patients.²⁸

Recommendations for pregnancy are provided in Table 7 and for participation in Sports in Table 8.

OTHER HERITABLE AUNDROMES AND GENETIC DEFECTS

Loeys-Dietz syndrome

Loeys-Dietz syndrome is characterized by the triad of arterial tortuosity and aneurysms; orbital hypertelorism (widely-spaced eyes); and bifid uvula or cleft palate. It results from mutations in TGF- β receptors 1 or 2, and diagnosis is confirmed by genotyping. Mean age of death is usually 26 years due to aortic dissection.²⁹ Recommendations for diagnosis and management are provided in Tables 9 and 10 and Figure 3.

Ehlers-Danlos syndrome

The vascular form of Ehlers-Danlos syndrome is characterized by easy bruising; thin skin with visible veins; characteristic facial features; and rupture of arteries, the uterus, or intestines. Diagnosis requires genetic testing to identify a defect in the COL3A1 gene, encoding type III collagen. Median survival is 48 years.²⁹ A pathogenic variant of COL3A1 may be associated with a salutary response to celiprolol, a β_1 -adrenoceptor antagonist with a β_2 -adrenoceptor agonist action.^{30, 31} The addition of irbesartan, a long-acting angiotensin II receptor blocker, has reduced the incidence of new symptomatic and asymptomatic arterial events by 50% over a 2-year period, with no side effects other than hypotension.³²

Recommendations are provided in Table 11.

Turner syndrome

Turner syndrome (short stature and ovarian failure due to absence of one X chromosome) is associated with bicuspid aortic valve and coarctation (see Chapter 7). More rare conditions are the arterial tortuosity syndrome, the aneurysms-osteoarthritic syndrome, and non-syndromic familial thoracic aortic aneurysms and dissections due to mutations in various genes.¹⁷

In addition to these, other genetic syndromes such as **autosomal dominant polycystic kidney disease**, and **Noonan syndrome** are also associated with aortic dissections. No much data exist, but management in general is similar to this with Marfan's syndrome.

NONSyndROMIC HERITABLE AORTIC DISEASE

Nonsyndromic heritable aortic disease (approximately 11-19% of patients referred for aortic surgery) are due to mutations that can be identified or not identified. Recommendations for surgery are provided in Tables 12-14.

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