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Causes and histopathology of ascending aortic disease in children and young adults

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Abstract

Background—Ascending aortic diseases (aneurysms, dissections, and stenosis) and associated aortic valve disease are rare but important causes of morbidity and mortality in children and young adults. Certain genetic causes, such as Marfan syndrome and congenital bicuspid aortic valve disease, are well known. However, other rarer genetic and nongenetic causes of aortic disease exist.

Methods—We performed an extensive literature search to identify known causes of ascending aortic pathology in children and young adults. We catalogued both aortic pathologies and other defining systemic features of these diseases.

Results—We describe 17 predominantly genetic entities that have been associated with thoracic aortic disease in this age group.

Conclusions—While extensive literature on the common causes of ascending aortic disease exists, there is a need for better histologic documentation of aortic pathology in rarer diseases.

Keywords

Aortic aneurysm; Dissection; Genetic

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1. Introduction

Ascending aortic disease can have devastating effects on affected individuals, resulting in severe morbidities including aneurysms, tears, dissections, hemopericardium, supra-valvular stenosis, and aortic valve regurgitation secondary to annular dilatation. While rare, it is an important cause of death in children and young adults. In the adult population, aneurysms have an estimated incidence of 5.9 cases per 100,000 person-years [1]. There are no data on the pediatric population, but aortic disease is expected to be less frequent. At our institution, a major referral center for genetic syndromes associated with aortic aneurysms, ascending aortic specimens from children and young adults represent less than 0.1% of the surgical pathology caseload. In the forensic setting, aortic dissections were found in 5.4% of autopsies performed for sudden cardiac deaths in young individuals [2].

Despite several recent large case studies that have evaluated the histopathology of the ascending aorta, the etiologies of most cases in young adults were unclassified [3,4]. Unlike aortic aneurysms in older adults that are associated with hypertension, smoking, and hypercholesterolemia, aneurysms in young individuals generally occur in the setting of an inherited disorder [5]. Yet, no studies have adequately correlated pathologic and clinical diagnoses in this population. Among genetic disorders, a common final aberration is an up-regulation of tumor growth factor (TGF) β activity in the ascending aorta. These “TGF β -opathies” include Marfan syndrome (MFS), Loeys–Dietz syndrome (LDS), Ehlers–Danlos syndrome type IV (EDS-IV), arterial tortuosity syndrome (ATS), autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive cutis laxa type 1 (ARCL), which are described herein [6–8].

This review provides a description of the entities that can lead to ascending aortic disease in children and young adults to raise awareness on the causes of aortic dissection in this population. We have collected histopathologic descriptions of these entities (Table 1) and have documented known physical findings beyond the ascending aorta to best characterize each disease. As described herein, making a definitive disease diagnosis of an ascending aortic specimen is usually not possible on the basis of histopathology alone. However, histologic features, when correlated with clinical situations, can significantly narrow down the potential causes of the aneurysm/dissection. This can aid clinicians and geneticists in either treatment of the affected individual or counseling of the relatives of the affected individual. Finally, we recommend a handling–dissection strategy for aortic roots as surgical or autopsy tissues, so that maximal information may be gleaned from each case by the examining pathologist.

2. Genetic causes of ascending aortic pathology

2.1. MFS

MFS, first described in 1896, is a genetic disorder caused by mutations in the *fibrillin-1* (*FBNI*) gene (Table 2) [9]. The syndrome’s key phenotypic features are found in the cardiovascular, skeletal, and ocular systems (Table 3).

Cardiovascular disease is, by far, the most common cause of death in patients with MFS. Sixty-one percent of infants and children have a cardiac abnormality, with mitral regurgitation being the most commonly encountered lesion [10]. Aortic root dilatation and ascending aortic aneurysms are cardinal manifestations of the syndrome and predispose these individuals to a potentially fatal aortic dissection. Aortic root dilatation develops early in MFS and is present in 35% of individuals by the age of 5 years and in 68–80% of individuals by the age of 19 years [11].

On gross examination, ascending aortic specimens (when intact) are dilated but generally unremarkable. If seen on autopsy, they often have annuloaortic ectasia in which both the aortic annulus and the ascending aorta are enlarged and display a flask-like shape. The most common histopathologies of the aorta are elastic fiber fragmentation (EFF) and cystic medial degeneration (CMD) with glycosaminoglycan pools (Fig. 1, Table 1). The degree to which these histopathologic findings exist is highly variable, with some individuals (particularly those undergoing prophylactic resection) exhibiting no histologic abnormalities in their aortas.

2.2. LDS

LDS is a recently described disorder of connective tissues that shares some overlapping features with MFS and the vascular type of Ehlers–Danlos syndrome (EDS-IV), although several morphologic differences exist (Table 3). LDS is an autosomal dominant disorder caused by mutations in the *transforming growth factor β receptor 1* (*TGFBR1*) or *transforming growth factor β receptor 2* (*TGFBR2*) gene (Table 2). It has a more aggressive vascular pathology than MFS, with an aortic dissection rate approaching 70% of patients and with a median survival of only 37 years [12].

LDS is clinically classified into types 1 and 2 based on differences in the craniofacial system. LDS type 1 is characterized by craniofacial features including hypertelorism, craniosynostosis, and cleft palate. These individuals more typically have skeletal features that overlap with MFS. LDS type 2 may not present with these features, but can present with cutaneous features that overlap with EDS-IV (Table 3). Aortic aneurysms are common to both types; however, a more severe vascular phenotype is seen in subjects with LDS type 1 compared to those subjects with LDS type 2.

Cardiovascular lesions in LDS include aortic valvular regurgitation and aortic root dilation, aneurysm, and dissection. Aortic aneurysms in LDS subjects tend to be aggressive and to rupture at a smaller diameter than seen in MFS subjects. Thus, prophylactic replacement of the aortic root is recommended for patients with LDS [13].

The pathology of aortas in LDS is generally similar to that seen in MFS. In contrast to CMD, which is usually focally present in MFS, aortas from LDS patients have a more diffuse medial degeneration (DMD) (Table 1) [14]. This degeneration is characterized by fragmentation and/or loss of predominantly intralamellar elastic fibers, as opposed to CMD in which EFF is usually interlamellar (Fig. 1C and D). We have reported a significant correlation between histopathologic severity and echocardiographic Z-scores (age-adjusted measure of aortic diameter) of the aortic root [14].

2.3. ATS

ATS is an autosomal recessive disorder caused by mutations in the *solute carrier family 2 member 10* (*SLC2A10*) gene that encodes for the glucose transporter GLUT10 (Table 2) [7].

Early in their lives, patients usually present with characteristic dysmorphic features: hyperextensible skin and joints (Table 3). Clinically, the disease overlaps with EDS-IV, but these subjects lack the structural collagen defect of EDS-IV [15]. Tortuosity of the aorta and large arteries is invariably present in ATS and often has a striking appearance on radiographic imaging. This is in comparison to tortuous vessels in LDS, where tortuosity is more variable in the presence of—and often confined to—neck or head vasculature. Nineteen to 31% of patients develop aortic aneurysms [16]. Although the exact mechanism is unknown, tortuosity may result in a higher shear stress that might predispose to arterial dissection [17]. Mortality due to stroke and arterial dissection is high in young patients,

although a recent review indicates a less severe cardiovascular prognosis than once believed [16,18].

On gross examination, major vessels, including the aorta, appear thickened, elongated, and tortuous. The stretching and elongation of the great arteries in older persons are due primarily to loss of elasticity. Histopathology of affected vessel walls demonstrates fragmentation of the inner elastic membrane and fragmentation and loss of elastic fibers of the tunica media and external elastic membrane (Table 1). The intima is often markedly thickened due to fibrosis [15].

2.4. Bicuspid aortic valve

Bicuspid aortic valve (BAV) is the most common congenital heart abnormality, affecting up to 2% of the population [19]. Although mutations in *NOTCH1* are associated with a subset of cases of BAV with characteristic aortic calcifications and variable aneurysm formation, the genetic basis of BAV is largely unknown (Table 2) [20]. Patients with BAV have variable expressions of additional cardiovascular pathologies, notably aortic aneurysm. Roughly 50% of young men with BAV have abnormal aortic dimensions consistent with aneurysms [21]. Approximately 5% of patients with BAV will develop an aortic dissection [22]. In contrast to MFS, patients with BAV do not have dilatation of the aortic sinuses [23].

Frequently, a normal media is described in patients with BAV [3]. When histopathologic changes are present, similar to those in MFS, the aortas of patients with BAV have CMD (Table 1) [24]. Patients with BAV have thinner elastic lamellae of the aortic media and greater distances between elastic lamellae than patients with tricuspid aortic valves [25].

2.5. Turner syndrome

Turner syndrome (TS) is a sex aneuploidy syndrome in which a single X chromosome is present (45,XO) (Table 2). The primary manifestations of TS are short stature, webbed neck, and infertility. Cardiovascular diseases are common and include congenital heart defects such as BAVs and a distinctive form of coarctation of the aorta, sometimes referred to as pseudocoarctation [26]. TS individuals have an elongation of the transverse aortic arch, with noticeable kinking in the juxtaductus region of the inferior curvature of the aortic arch [27]. Aortic dilation (or dissection) has been reported in conjunction with other cardiac anomalies (BAVs and coarctation) in ~1.5% of TS subjects [28].

Aortic dilation typically involves the root of the ascending aorta, occasionally extending through the aortic arch to the descending aorta [28]. Aortic dilations and dissections occur in young individuals with TS. In one study, over 65% of subjects with aortic dilation were less than 21 years of age [28]. In a review of aortic dissection cases, over half of patients were less than 30 years of age [29].

On histologic examination, CMD, similar to MFS, has been reported in TS (Table 1) [28].

2.6. EDS-IV

EDS is a rare inherited connective tissue disease with abnormal synthesis of collagens or related enzymes. EDS has been subdivided into six main types, with significant vascular manifestations being encountered in EDS-IV or vascular EDS. EDS-IV results from mutations in the *collagen, type III, α -1 (COL3A)* gene, which encodes for type III *1* collagen present in skin, vessel wall, and hollow organs (Table 2). Clinically, vascular EDS presents with characteristic facial features, thin skin, and rupture of vessels or viscera (Table 3) [30].

Arterial tears of the aorta and its branches are considered hallmarks of this disease. The true incidence of aortic dissection in these patients is not known; however, a review of 112 cases of EDS-IV noted that 10% of patients had an aortic dissection as part of their disease spectra [31]. In general, rupture and dissection outweigh aneurysm. Thoracic aortic aneurysms related to EDS-IV are rarely seen in childhood [32]. Patients have a 25% risk of experiencing a major vascular complication by the age of 20 years, and life expectancy is around 48 years [30]. EDS-IV patients have a low tolerance to surgery owing to the extreme fragility of their vascular wall, making them poor surgical candidates particularly in acute settings, in sharp contrast to patients with other aneurysm syndromes.

Histologic findings may be relatively subtle and nonspecific despite significant transmural tears in the aorta. Microscopic examination reveals minimal medial degeneration of the aortic wall with partial disruption of elastic laminae and intervening organized fibrous tissue (Table 1) [3,30].

EDS-IV is the one aortic disease in which ultrastructural examination by transmission electron microscopy is diagnostically valuable. These aortas have irregularities in the diameter of collagen fibers and an unidentified fibrinogranular substance within the extracellular matrix. However, due to the high number of false negatives, the absence of these features should not exclude the diagnosis of EDS-IV [33].

2.7. Homozygous familial hypercholesterolemia

Homozygous familial hypercholesterolemia (HFH) is an inherited metabolic disorder caused by mutations in the *low-density lipoprotein receptor (LDLR)* gene, leading to hypercholesterolemia and a predisposition to premature cardiovascular disease (Table 2). Children with HFH may have symptoms of coronary artery disease and aortic stenosis [34]. The aortic root is prone to developing atherosclerotic plaque at an early age in these individuals. HFH patients' aortic roots have thicker walls and a reduced cross-sectional area compared to healthy controls [35]. Atheromatous involvement of the aortic root, rarely seen in heterozygotes, is almost always present in homozygotes and leads to aortic hypoplasia, supra-aortic stenosis, and, extremely rarely, to dissection [36]. Aortography shows characteristic aortic root funneling when the proximal ascending aorta is infiltrated by atheroma [37]. Aortic roots have less wall distensibility due to atheromatous plaque lesions [38].

On histologic examination, atheromatous plaques are observed around the supra-aortic ridge, just above the noncoronary cusp and ostia of both coronary arteries. Speckled plaques are spread above the ridge toward the ascending aorta for a few centimeters. The aortic root lesions consist of foam cells, cholesterol clefts, and fibrocalcific deposits (Table 1). The presence of intracellular lipid and cholesterol clefts within cuspal tissues is characteristic [37].

2.8. ADPKD

ADPKD is one of the most common hereditary disorders caused by mutations in the *polycystic kidney disease (PKD) 1* gene (Table 2). Cardiovascular disease is a well-appreciated complication of ADPKD. Left ventricular hypertrophy and valvular incompetence are common features [39]. Saccular (berry) intracranial aneurysms are found in up to half of all patients with ADPKD and are prone to rupture [40]. Ruptured abdominal and/or thoracic aneurysms are also described, but may be the result of significant hypertension in this patient population. Thoracic aortic dissections are extremely rare but potentially fatal complications of this disease [41]. The histopathology of the excised aorta, when present, has been described as showing CMD (Table 1).

2.9. Noonan syndrome

Noonan syndrome (NS) is a relatively common autosomal dominant cardiofacial syndrome. The *protein tyrosine phosphatase, nonreceptor type 11 (PTPN11)* gene has been implicated as causing the majority of NS, although mutations in other genes in the RAS–MAPK pathway have also been described (Table 2) [42]. Cardiac defects occur in over 50% of patients. Cardiac disorders include dysplastic pulmonic valves, hypertrophic cardiomyopathy, and, less commonly, pulmonary artery stenosis, atrial septal defects, or patent ductus arteriosus (Table 3) [43]. The syndrome is associated with aneurysms of the sinuses of Valsalva and rarely with aortic dissection. Medial degeneration has been described in reported cases as a histologic finding suggesting defective connective tissue [44] (Table 1).

2.10. Tetralogy of Fallot (TOF)

TOF is a complex of anatomic abnormalities including pulmonary stenosis, ventricular septal defects, deviation of the aortic origin, and right ventricular hypertrophy. Although it is the most commonly encountered cyanotic congenital heart defect in infancy, insidious development of progressive aortic root dilatation has been seen in adult survivors who have undergone surgical repair [45]. The underlying pathophysiology of ascending aortic dilatation is unknown. In addition to previous long-standing volume overload, intrinsic histologic abnormalities in the aortic root and ascending aortic wall have been observed in various studies (Table 1) [46]. Abnormalities of smooth muscles, elastic fibers, collagen, and ground substance in the tunica media of the ascending aorta were found to be prevalent in these patients, predisposing to aortic dilatation, aneurysm, and/or aortic rupture [47].

2.11. Familial thoracic aortic aneurysm and dissection (FTAAD)

Up to 20% of patients referred for repair of thoracic aneurysm or dissection have familial clustering of the disease. Many of these families do not meet the clinical criteria for any of the abovementioned hereditary disorders. In most of these families, inheritance is autosomal dominant, with decreased penetrance and variable age-related onset of symptoms (Table 2) [48]. A number of different genetic mutations confer a variable constellation of additional phenotypes and can be associated with aortic dissections in mildly aneurysmal aortas (Table 3) [49]. Thus, further characterization and subclassification of this group are warranted.

On gross examination, aneurysms and dissections can occur anywhere along the ascending aorta and are not confined to the annulus. On histologic examination, in aortas from subjects harboring *MYH11* and *ACTA2* mutations, there is focal medial degeneration with disorganization of smooth muscle cells, elastic fiber loss, and increased penetrance of vasa vasorum into the medial layer [50,51].

2.12. Coarctation of the aorta

Coarctation of the aorta occurs in 5–10% of congenital heart disease. It is defined by a narrowing of the aorta just distal to the left subclavian artery or, more rarely, by narrowing proximal to the left subclavian artery. BAVs are frequently seen in conjunction with coarctation [52]. Coarctation has well-described clinical findings, including systolic murmur and high blood pressure in the upper extremities and low blood pressure with near-absent pulses in the lower extremities. While generally detected and treated with surgical repair in infancy, some cases of coarctation remain undiagnosed. Prior to the surgical era, coarctation frequently led to congestive heart failure and aortic dissection. Currently, coarctation is a rare cause of aortic dissection (Table 1) [53].

2.13. Autosomal recessive cutis laxa

ARCL is a rare disorder caused by mutations in the *fibulin 5 (FBLN5)* gene [54]. The disorder is characterized predominantly by loose, sagging skin from an early age (Table 3). These patients can have vascular diseases including fibromuscular dysplasia and pulmonary artery stenosis. Aortic aneurysm is a rarely reported complication. On histologic examination, one case report described degeneration of elastin, while a second case series identified a coarse outline of the elastic lamina in three subjects [55,56].

2.14. Shprintzen–Goldberg syndrome

Shprintzen–Goldberg syndrome (SGS) is a disorder of unknown etiology comprising Marfanoid features, craniosynostosis, and connective tissue abnormalities. Mutations in *FBN1* have been described in this disorder, although at least one mutation was later found to be a polymorphism [57]. Only 23 subjects have been described with SGS through 2005 [58]. Among them, aortic dilation is an appreciated yet uncommon finding. Only a single report of aortic root dissection has been reported in the literature, and the histology of the aorta has not been described [59].

3. Nongenetic causes of ascending aortic disease

3.1. Aortitis

Ascending aortitis is characterized by the presence of inflammation of the adventitia and media, often with giant cells. It includes the diseases Takayasu arteritis (TA), giant cell arteritis (GCA), and isolated aortitis. GCA is generally described in patients older than 50 years of age and will not be described herein. The term “isolated aortitis” is used when patients have no clinical symptoms other than those related to aortic root disease [60].

TA is an inflammatory disease of unknown etiology that predominantly affects the aorta and its main branches [61]. The disease generally presents between the ages of 10 and 30 years, with a female/male ratio of 8.5:1 [62]. Although it is more common in Southeast Asian countries, cases are becoming increasingly recognized worldwide. Overall, the incidence of TA is two to three cases per million people.

On gross examination, the aorta is thick and often rigid secondary to transmural fibrosis. The aortic lumen is narrowed in a “skipped” area fashion and may alternate with aneurysmal dilations. The intima has a cobblestone appearance, with multiple smooth and glistening plaques. Often a thick intima may reveal wrinkling and ridges and may give rise to a “tree bark” appearance, a feature common to many arteritides [63].

On histologic examination, there is an initial inflammatory response in the vasa vasorum, with cellular infiltration mainly by T cells (Table 1). Inflammation extends to the outer layer of the media and adjacent adventitia with a mixture of inflammatory cells, including plasma cells and macrophages [64]. In the media, there is a patchy heavy inflammatory infiltrate with giant cells that causes elastic fiber and smooth muscle cell loss and ultimate replacement by collagen. Endarteritis obliterans or onion-skin-type fibrosis can be present in the vasa vasorum [65]. If there is acute progression with destruction of the media, aneurysms may develop [64]. Aneurysms occur in up to 45% of patients, with the ascending aorta and the aortic arch being the frequent locations [66].

Burke et al. [67] proposed a histologic classification of noninfectious aortitis with two categories: necrotizing and nonnecrotizing. They proposed that the necrotizing form is an autoimmune condition that may be localized (isolated necrotizing aortitis) or may be part of a systemic autoimmune process. Infrequently, it may be a manifestation of TA, suggesting that there are other diseases that cause this histologic appearance.

3.2. Cocaine

Cocaine abuse leads to numerous cardiovascular complications. These include coronary artery vasoconstriction, myocardial infarction, arrhythmia, cardiomyopathy, and aortic dissection. Cocaine abuse causes catecholamine release and stimulation of α and β adrenergic receptors, which can result in vasoconstriction and spasm of any sized artery. Chronic cocaine abuse causes increased diastolic aortic diameter, loss of aortic elasticity, and increased aortic stiffness [68]. These chronic changes, coupled with other risk factors such as untreated hypertension and smoking, likely increase susceptibility to aortic dissections in a small minority of cocaine abusers. In one inner-city population, 37% of aortic dissections were the result of cocaine abuse, predominantly in young male hypertensive smokers [69]. Conversely, cocaine abuse has only been associated with 0.5% of cases in the International Registry of Aortic Dissection, indicating that, with the exception of selected populations, it is a rare cause of dissection [70].

On histologic examination, CMD has been described in a subject with dissection, suggesting the potential for an underlying aortic pathology (Table 1) [71].

3.3. Weightlifting and severe physical exertion

Weightlifting and severe physical exertion have been described as causes of aortic dissections. Recently, 31 patients who developed acute aortic dissection in the context of severe physical exertion were described [72]. Affected subjects ranged in age from 19 to 76 years of age, with a strong male predominance (30:1). Most of these subjects had moderately enlarged aortas (4–5 cm in diameter). Less than 10% of subjects had a family history of aortic disease. The etiology of this dissection appears to be a rapid and dramatic elevation of blood pressure during extreme exertion against a mildly dilated aorta. On histologic examination, CMD was described in a few cases, suggesting the possibility of an underlying condition predisposing to the dissection [71].

3.4. Handling of specimens

For maximization of one's ability to generate a meaningful diagnosis on aortic tissues, certain methods should be used. Ascending aortic specimens will be encountered either as general surgery specimens or on autopsy. Surgical specimens are either obtained from subjects with aortic root dilatation undergoing prophylactic replacement or obtained from subjects with aortic dissection undergoing emergent repair/replacement.

Aortic surgical specimens generally arrive fragmented or complete, in formalin or in saline, depending on the style of a given institution. Aortic tissue should be oriented and measured, and gross photographs should be taken if such facilities exist (Fig. 2). If a complete ring of aorta is available, the diameter should be measured. Tissue should be examined for evidence of dissection or intimal tears. The presence of atherosclerotic plaques, intimal thickening, evidence of prior surgery, and/or thrombus material should be commented upon. If there is significant calcification of the vessel, the use of a decalcifying agent would be appropriate before sectioning. A small piece of aortic media should be placed in glutaraldehyde for ultrastructural examination if EDS-IV is included in the differential diagnosis.

For histology, full-thickness sections should be taken perpendicular to the luminal surface. A minimum of six sections, which can be placed in two cassettes, should be taken [3]. A complete histologic analysis should always include a hematoxylin–eosin slide and an elastic stain (Verhoeff's Van Gieson stain, Movat pentachrome, or a similar stain) to evaluate EFF. A collagen stain (Masson trichrome) and an Alcian blue periodic acid Schiff stain are useful in detecting scarring and accumulation of collagen, proteoglycans, and mucopolysaccharides. Immunohistochemical stains for inflammatory markers (CD68, CD3,

CD20, and CD138) can be obtained, as appropriate, when inflammatory cells are detected by hematoxylin–eosin. The presence of the findings described in Table 1 should be reported for each specimen, as appropriate.

As with any autopsy, careful external examination of the body is essential for delineating genetic causes of ascending aortic dissection. A recent study describes a useful autopsy checklist for evaluation of physical findings in subjects with thoracic aortic aneurysms [73]. Upon removal of the chest plate, careful examination of the chest cavity will determine if there is a hemothorax or a hemopericardium. If blood is found, the amount should be documented, and a careful search of the aorta should be performed *in situ* to identify the source of bleeding. Gross photographs should be taken. The chest block should be removed, with the thoracic aorta left attached to the heart. If the ascending aorta is aneurysmal, its diameter, length, and general shape should be documented. The aorta should then be removed at the level of the aortic valve, and the ascending aorta can be opened longitudinally opposite any gross pathology (tears and dissections). The specimen should then be cut and evaluated for histology as in the protocol for surgical specimens described above.

4. Conclusion

As can be noted from this review, the causes of ascending aortic aneurysm/dissection in children and young adults are varied, with inherited syndromes being the predominant causes of aortic disease in this age group. While no histologic features are sensitive to and specific for a particular etiology, the patterns of findings in a given case in which a particular diagnosis has not been rendered can help the pathologist suggest a direction for genetic follow-up. Despite the thoroughness of our search to identify cases of these entities with described histopathology, for most rare diseases, there are only scattered case reports without formal histologic analysis. Furthermore, the terminology for describing the histology is inconsistent, allowing for a range of interpretations of reported findings. Therefore, it is difficult to make any definitive conclusions about the range of histopathology of the rare causes of aortic aneurysms and dissections. This review therefore identifies gaps in our knowledge of ascending aortic disease and should be a starting point for more thoughtful and in-depth histomorphometric and immunohistochemical analyses of diseases of the ascending aorta.

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Fig. 1. Histology of ascending aortas. (A) Normal ascending aorta showing dense elastic fibers in a young adult (Movat pentachrome, original magnification, $\times 10$). (B) Ascending aorta with CMD and elastic fiber loss, characteristic of many genetic forms of aortic disease (Movat pentachrome, original magnification, $\times 10$). (C) Ascending aorta from a subject with LDS with generalized widening of intralamellar spaces, typical of DMD (hematoxylin–eosin, original magnification, $\times 15$). (D) Ascending aorta with CMD secondary to focal interlamellar degeneration (hematoxylin–eosin, original magnification, $\times 10$).

Fig. 2. Proper ascending aortic evaluation. (A) If intact, the diameter (d) of the aorta should be recorded. (B) Additional measures of size (h =height) and other pertinent findings should be noted. (C) Six sections of the aorta, fitting into two tissue cassettes, should be evaluated for histologic changes.

Table 1
Pathologic changes in the ascending aorta in diseases of children and young adults

Disease	ANEU	DISS	TOR	BAV ^a	CMD	DMD	LMN	EFF	INF	GC	AT&IC	n	References ^b
MFS	+++	++	+/-	+++	+++	+/-	+++	+++	+ ^{c,d}			218	[3,4,24]
LDS	+++	+++	++	++	+/-	+++		+++				17	[6,14]
ATS	+/-	+/-	+++					+++ ^e				6	[15]
BAV	++	++		+++	+++		+++	+++	+ ^f			479	[3,4,24]
TS	+	+		+++	+++							16	[28]
EDS-IV	+/-	+++ ^g		+								5	[3,30]
HFH	- ^h	-		+/- ⁱ					+ ^j	+++		7 ^k	[35,38]
ADPKD	+	++		+								3	[41]
NS	+/-	+		+/-	+					+ ^l		3	[44]
TOF	+	++		++	++	++		++				182	[46,47]
FTAAD	+++	++		+/- ^m	+++			++	+ ^d			24	[50,51]
Coarctation	++	+		+++	++		+	++	+/- ⁿ			4	[53]
ARCL	++	+/-	+			+		++ ^o				4	[55,56]
Aortitis	+	+/-					++		+++	++		46	[3,61]
Cocaine	+	++			++							2	[71]

ANEU, frequency of aneurysm; DISS, frequency of dissection; TOR, tortuosity; BAV, bicuspid aortic valve; CMD, cystic medial degeneration; DMD, diffuse medial degeneration; LMN, laminar medial necrosis; EED, elastic fiber fragmentation; INF, inflammation; GC, giant cell; AT&IC, atherosclerosis and intimal calcification; n, number of subjects studied.

(+/-) Questionable feature; (+) rare feature; (++) feature; (+++) common feature.

^aRelative to background population frequency.

^bA complete list of references is available from the authors upon request.

^cIncreased presence of macrophages in media around the vasa vasorum.

^dIncrease in lymphocytes and macrophages in media and adventitia.

^eElastic lamellae were twice as large as normal/primary fragmentation of IEL.

^fInfiltrating lymphocytes with increased apoptosis in 10 cases of BAV.

^gEasy friability to manipulation.

- h* Stenosis is increased.
- i* Foam cells or collagen rather than mucopolysaccharides.
- j* Extensive infiltrate of macrophage foam cells even into media.
- k* Additional 25 subjects were evaluated by MRI for aortic calcifications.
- l* Giant cell aortitis in one case.
- m* Varies depending on genetic etiology.
- n* Two cases had mycotic aneurysms.
- o* Coarse elastic fibers.

Table 2

Hereditary disorders affecting ascending aortas

Disease	Estimated incidence	Mode of inheritance	Gene
MFS ^a	2–3 in 10,000	Autosomal dominant	<i>FBN1</i> <i>TGFBR2</i> ^b
LDS ^a	Not known	Autosomal dominant	<i>TGFBR1</i> , <i>TGFBR2</i>
ATS ^a	Not known	Autosomal recessive	<i>GLUT10 (SLC2A10)</i>
BAV	1–2 in 100	Unclear	<i>NOTCH1</i> ^c
TS	1 in 2500	Monosomy X	
EDS-IV	1 in 75,000	Autosomal dominant	<i>COL3A1</i>
HFH	1 in 1,000,000	Autosomal dominant	<i>LDLR</i>
ADPKD ^a	1–2 in 1000	Autosomal dominant	<i>PKD1</i> , <i>PKD2</i>
NS	1–2 in 2500	Autosomal dominant	<i>PTPN11</i> <i>SOS1</i> <i>KRAS</i> <i>RAF1</i>
FTAAD	Not known	Autosomal dominant	<i>TAAD1</i> <i>FAA1</i> <i>TGFBR2</i> <i>MYH11</i> <i>ACTA2</i>
ARCL ^a	Extremely rare	Autosomal recessive	<i>FBN4</i>
SGS	Extremely rare	?	<i>FBN1</i> ^d

^aTGFβ-opathy.^bAtypical presentation; controversial.^cEarly calcification; low penetrance of aneurysm.^dRare cause; most mutations unknown.

Table 3

Systemic features of diseases causing aortic aneurysms

System	MFS	LDS	ATS	BAV	TS	EDS-IV	HFH	ADPKD	NS	FTAAD	ARCL
<i>Cutaneous</i>											
Hernias	++	++	++			+				+/- ^a	+/-
Soft, smooth (velvety) skin	+/-	+	++			++			+		
Translucent skin	+/-	+				++					+
Cutis laxa			++								++
Easy bruisability	+/-	+				++			+		
Xanthelasma							++				
Nevi					++				+		
Abnormal scarring	+/-	+				++					
Acrogeria	^b		++			++					
Livedo reticularis	+/-	+/-				+/-				^c	
Short, webbed neck					++				+		
Lymphedema					++				++		
<i>Ocular</i>											
Lens dislocation	++	+/-									
Cataracts	+										
Retinal detachment	+	+/-									
Exotropia		+							+		
Blue/grayish sclerae		++				++					
Downslanting palpebral fissures		+	++						+		
Keratoconus/keratoglobus	++	+	+/-			+					
Corneal arcus and planar							++				
Iris flocculi										^c	
<i>Skeletal</i>											
Arachnodactyly	++	+	+								
Pectus deformities	++	++	+		+				+	+/- ^a	+
Thoracolumbar scoliosis	++	+	+/-		+					+/- ^a	

System	MFS	LDS	ATS	BAV	TS	EDS-IV	HFH	ADPKD	NS	FTAAD	ARCL
Joint laxity/subluxations/dislocations	+	++	++		+	+			+	+/-a	+
Joint contractures		+	+/-								
Pes planus	++	+									
Dolichostenomelia	++	+/-									
Talipes equinovarus		+				+					
Cervical spine instability		+									
Short stature					++				+		
Cubitus valgus					++				+		
Shield chest/wide-spaced nipples					++				+		
Tendon and tuberos xanthomas							++				
<i>Craniofacial</i>											
Dolicocephaly	+	+	++								
Hypertelorism		++	+						++		
Bifid/broad uvula or cleft palate		++									
Craniosynostosis		+									
Malar hypoplasia	++	++	++								
<i>Vascular (not ascending aorta)</i>											
Tortuosity	+/-	++	++								
Aneurysm	+/-	+	+			+		+			
Stenoses			+				+				+
Rupture and dissections	+/-	+	+			++	+	+			
Postsurgical hemorrhage		+				++					
Wound dehiscence						+					
<i>Visceral</i>											
Apical blebs of lungs	+	+									
Emphysema	+										+
Spontaneous pneumothorax/pneumohemothorax	+	+				+					
Kidney/urinary tract malformations			+/-		+			++	+		+/-
Hollow organ rupture/prolapse/perforation		+				++					
Diaphragmatic hernia			+								+
<i>Cardiac</i>											

System	MFS	LDS	ATS	BAV	TS	EDS-IV	HFH	ADPKD	NS	FTAAD	ARCL
Patent ductus arteriosus		+							+	^a	
Mitral valve prolapse	+	+			+	+		+			
Coarctation of the aorta			+/-	+	+						+
BAV		+		++	++						
Aortic stenosis/regurgitation		+/-	+	+	++		+	+			
Pulmonary stenosis			+						+		
Atrial septal defect		+			+						
Ventricular septal defect		+			+						
Dilatation of main pulmonary artery	++	++									
Hypertrophic cardiomyopathy											
<i>Central nervous system</i>											
Chiari malformation		+									
Developmental delay		+/-			+/-						
Hydrocephalus		+/-									
Dural ectasia	++	+				+					
Cerebral aneurysm		+				+					
<i>Gonadal</i>											
Gonadal dysgenesis					++						
Poor breast development					++						

(+/-) Rarely present; (+) present; (++) frequently present.

^a Observed with *MYH11* mutations and variably reported with *TGFBR2* and *ACTA2* mutations.

^b Most severe presentation in childhood.

^c Reported in association with *ACTA2* mutations.