Supravalvular Aortic Stenosis
Elastin Arteriopathy

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Supravalvular aortic stenosis is a systemic elastin (ELN) arteriopathy that disproportionately affects the supravalvular aorta. ELN arteriopathy may be present in a nonsyndromic condition or in syndromic conditions such as Williams–Beuren syndrome. The anatomic findings include congenital narrowing of the lumen of the aorta and other arteries, such as branches of pulmonary or coronary arteries. Given the systemic nature of the disease, accurate evaluation is recommended to establish the degree and extent of vascular involvement and to plan appropriate interventions, which are indicated whenever hemodynamically significant stenoses occur. ELN arteriopathy is genetically heterogeneous and occurs as a consequence of haploinsufficiency of the *ELN* gene on chromosome 7q11.23, owing to either microdeletion of the entire chromosomal region or *ELN* point mutations. Interestingly, there is a prevalence of premature termination mutations resulting in null alleles among *ELN* point mutations. The identification of the genetic defect in patients with supravalvular aortic stenosis is essential for a definitive diagnosis, prognosis, and genetic counseling.

Definition, Disease Name, and Synonyms

Supravalvular aortic stenosis (SVAS; OMIM 185500, Figure), described for the first time in 1930 by an Italian pathologist,[1] has an estimated incidence of 1:20 000 live births.[2] SVAS is a generalized disease of the arterial wall caused by the thickening of the media or intima layers, not related to atherosclerosis, which results in narrowing of the lumen of the ascending aorta or other arteries. SVAS usually affects branches of the pulmonary and coronary arteries,[3] whereas cerebral circulation, descending aorta, renal arteries, and other aortic tributaries are commonly spared. SVAS is classically associated with Williams–Beuren syndrome (WBS; OMIM 194050), a complex developmental genomic disorder that presents with neurobehavioral, craniofacial, cardiovascular, and metabolic abnormalities. WBS is caused by microdeletion of ≈1.5 to 1.8 Mb at 7q11.23 region that encompasses 27 genes,[4] including *ELN*. The estimated prevalence of SVAS in WBS patients is ≈69%.[5] Nonsyndromic SVAS was recognized as a separate entity from WBS because these patients present with normal intelligence and lack dysmorphic features.[6,7] In addition, nonsyndromic SVAS was shown to be caused by disruption of the *ELN* gene.[8,9] An intermediate form of ELN arteriopathy associated with abnormal visual spatial constructive cognition results from *ELN* deletion extending to the nearly adjacent *LIMkinase1* gene.[10] ELN arteriopathy is inherited as an autosomal dominant disease,[11] with incomplete penetrance and variable expressivity.[2]

Clinical Presentation, Management, and Prognosis

Patients with ELN arteriopathy usually present a systolic murmur related to the SVAS and become symptomatic symptoms before the age of 20 years. When symptoms develop, they are similar to valvular aortic stenosis (dyspnea, angina, and syncope). Although any artery of the body may be affected in ELN arteriopathy, aortic involvement is most often responsible for the clinical outcome. Aortic stenosis results in increased resistance to blood flow that causes elevated left-heart pressure and cardiac hypertrophy. If left untreated, the lesion may evolve to cardiac failure and death. Severity of SVAS ranges from discrete ring-like thickening of the aortic media at the sinotubular junction to diffuse involvement with variable hypoplasia and thickening of the ascending, transverse arch, and descending aorta.

Great systemic arteries that contain the largest number of ELN fibers in their media are the most affected. *ELN* mutations also result in peripheral pulmonary artery stenosis, such as supravalvular pulmonary stenosis or mesenteric and renal artery stenosis or coronary artery lesions.[12–14] Stenoses affecting different arteries are sometimes observed among different members within the same family, carrying the same *ELN* mutation.[2] Hypertension is often present in this patient group and is typically related to lack of systemic vessel distensibility, but occasionally may be secondary to renal artery stenosis.

Intracranial focal and segmental stenotic artery disease can be responsible for stroke.[15–18] In mixed cohorts of individuals with either ELN arteriopathy or WBS, coronary disease was found in 28% to 45%[19,20] of patients.

Whether patients with ELN arteriopathy are at increased risk of sudden death, as reported in patients with WBS, has

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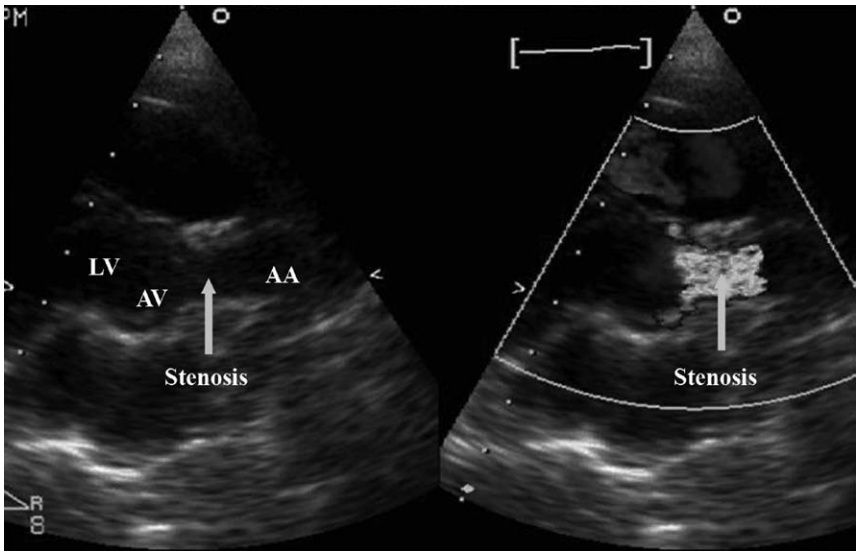

Figure. Echocardiogram of patient with supravalvular aortic stenosis. Parasternal long axis section shows aortic narrowing (indicated by arrows). On the right, the color Doppler image shows blood flow ranging from laminar (dark gray) to turbulent (gray) because of the stenosis. LV indicates left ventricle; AV, aortic valve; and AA, ascending aorta.

not been fully investigated. However, considering that WBS patients who suffered sudden death presented with myocardial ischemia secondary to coronary artery stenosis and severe biventricular outflow tract obstruction,[21] it is very likely that a similar increased risk of sudden death is also present in ELN arteriopathy patients.[22]

Clinical and echocardiographic findings in patients with *ELN* mutations vary widely, even within the same family, and range from calcifications of the ascending aorta in older individuals with minimally increased flow velocity to significant narrowing with impressively increased flow velocity. The phenotype may also include cases with isolated mild pulmonary stenosis.[23] The aortic valve may also be affected in SVAS, causing an additional source of left ventricle outflow tract obstruction. In contrast to pulmonary circulation, arterial stenosis of the systemic circulation may worsen with time; thus, lifelong monitoring of the cardiovascular system is important.

Surgical techniques to repair SVAS based on patch aortoplasty are indicated in severe stenosis with increased pressure gradient. Thirty percent of individuals will ultimately require surgical correction. Surgical treatment of SVAS has a perioperative mortality of 3% to 7%,[24] but diffuse hypoplasia of the aorta, as well as concomitant stenoses, are risk factors for reoperation.

In ELN arteriopathy, myocardial ischemia has been implicated in the majority of cases of sudden death that occurred in conjunction with anesthesia or sedation. This patient group tends to be especially sensitive to falls in blood pressure, perhaps, because of coronary artery narrowing in the location of the coronary arteries below the area of stenosis. Common features in the reported cases are as follows: (1) combined right and left ventricular outflow obstruction, (2) sudden and rapid hemodynamic deterioration associated with hypotension and bradycardia, and (3) lack of response to aggressive resuscitative measures.[25]

Pathogenesis and Differential Diagnosis

The vascular features of SVAS, which are identical in both WBS and in majority of nonsyndromic SVAS, occur as a consequence of reduced ELN protein level.[2,26] *ELN* (ENST00000358929 transcript) is a single-copy gene of 34 exons that encodes for a protein that confers elasticity to various tissues and organs. Pathological hallmark of ELN arteriopathy is the involvement of the media with an increased number of hypertrophic smooth muscle cells, increased collagen content, and reduced elastic tissue in the form of disrupted and disorganized fibers.[3,5] From a dynamic standpoint, the normal biological levels of ELN are responsible for the distensibility of the aorta during systole and its subsequent recoil during diastole. Hydrodynamic energy is stored during systole and released during diastole, a phenomena known as Windkessel effect,[27] whose loss, which normally occurs with aging, produces a wide pulse pressure with elevated systolic and reduced diastolic aortic pressures. Remarkably, a reduction in aortic distensibility impairs the diastolic component of phasic coronary blood flow.

Together with other extracellular proteins, ELN is involved in the assembly and stability of elastic fibers.[28] More than 30 elastic fiber-associated proteins have been identified so far. These proteins include: (1) fibrillins, which are the main structural components of elastic-fiber-associated microfibrils, (2) microfibril-associated glycoprotein 1 and 2, important for structural integrity of microfibrils, (3) latent transforming growth factor-β binding proteins, responsible for tissue targeting of transforming growth factor-β, and (4) several proteoglycans involved in interactions with microfibrils and contributing to their integration in the surrounding extracellular matrix.[29]

ELN is synthesized in fibroblasts, endothelial cells, chondroblasts, or smooth muscle cells and secreted as a soluble, 72 kDa monomer called tropoelastin that alternates hydrophobic and lysine-rich sequences. The hydrophobic domain is responsible for the elastic properties, whereas lysine-rich sequences are needed for lysyl oxidase-mediated covalent cross-linking between monomers, which gives rise to a highly insoluble network of elastic fibers in the extracellular space.[30]

Multiple tropoelastin splice variants have been identified so far, with 6 exons shown to be subjected to alternative splicing, that is, exons 22, 23, 24, 26A, 30, and 32.[31] Many of these isoforms are known to cause variations in the number of hydrophobic and cross-linking domains within a tropoelastin

monomer, thus affecting the functional characteristics of elastic fibers, whose resilience depends upon the overall hydrophobicity and the extent of cross-linking.[32]

The sequence of molecular events that link *ELN* mutations to SVAS is still unknown. ELN haploinsufficiency is the molecular mechanism proposed for the pathogenesis of SVAS because deletion of 1 copy of the *ELN* gene results in ELN arteriopathy in WBS patients. In nonsyndromic SVAS, a large number of premature stop codon mutations in *ELN* leads to insufficient levels of ELN because of mRNA degradation of the mutated allele by nonsense mediated decay.[33,34] A reduction of ELN expression has been also found in skin fibroblasts and aortic smooth muscle cells of affected patients, thus supporting ELN haploinsufficiency as the mechanism involved in the pathogenesis of the vasculopathy.[35,36] Remarkably, ELN expression levels in patients with WBS are ≈15% of controls, despite having 1 intact allele suggesting the presence of post-transcriptional modulation mechanisms.[34] Consistent with this hypothesis is the evidence that the miR-29 family members target the 3′-untranslated region of the human *ELN* mRNA.[37]

Variable expressivity and reduced penetrance, which are observed in both WBS and ELN arteriopathy,[38] are typical features of haploinsufficiency-associated diseases, in which the genetic background is predicted to play a role as a modifier of the phenotype severity.[39]

Nonsyndromic SVAS associated with peripheral pulmonary stenosis has also been reported in other diseases, such as Alagille syndrome 1 (OMIM 118450), Neurofibromatosis type 1 (OMIM 162200), and Noonan syndrome 1 (OMIM 163950). In addition, rare cases of SVAS secondary to aortic hypoplasia and hyperplastic atherosclerotic plaques have been reported in association with homozygous familial hypercholesterolemia (OMIM 143890).[40] SVAS in familial hypercholesterolemia is secondary to foam cells, cholesterol clefts, and fibrocalcific deposits within the aortic root and valve, which is unique to homozygous familial hypercholesterolemia and differentiates these lesions from other forms of aortic stenosis.

SVAS and Cutis Laxa Syndromes

SVAS has also occasionally been found in patients affected by Autosomal Dominant Cutis Laxa (ADCL; OMIM 123700), Autosomal Recessive Cutis Laxa type 1 (ARCL1; OMIM 219100), and Autosomal Recessive Cutis Laxa type 2 (ARCL2; OMIM 219200).

ADCL, which is allelic to ELN arteriopathy, is considered a milder form of cutis laxa with generalized loose skin folds that result in a premature aged appearance, gastrointestinal diverticuli, hernia, and genital prolapse.[41] Occasionally, severe cardiopulmonary complications, such as bronchiectasis, emphysema, pulmonary artery stenosis, and aortic root dilation, which progresses to aortic insufficiency and aneurysms, have been reported.[42–48] Mutations have also been identified in fibulin-5,[53] a member of the extracellular matrix proteins family that is prominently expressed in medial layers of large veins and arteries and plays an important role in the development of normal elastic fibers.

Histopathology in ADCL is characterized by disorganized and often shortened elastic fibers that result in a weakened and less elastic connective tissue.[45,47] In most cases, patients carry mutations at 3′ end of the *ELN* gene, which are all predicted to encode proteins that are extended at their C-terminus region or whose C-termini contain missense mutations. This C-terminus region of tropoelastin has been implicated in microfibril-associated glycoprotein binding[49] and in the interaction with cell-surface glycosaminoglycans,[50] both important for elastic fiber formation.

Recently, electron microscopy examination of skin biopsies of ADCL patients revealed elastic fiber fragmentation and diminished dermal ELN deposition. The expression of mutant ELN in fibroblast cultures resulted in reduced deposition of tropoelastin onto microfibril-containing fibers, and in enhanced tropoelastin coacervation and globule formation, leading to lower amounts of mature, insoluble ELN. Mutation-specific effects also included endoplasmic reticulum stress and increased apoptosis.[45] Mutant tropoelastin showed reduced binding to fibrillin-1 and fibulin-5 and as a result impaired ELN accumulation on microfibrils. Overall, these data suggest that both impaired association of tropoelastin with microfibrils and abnormal aggregation of tropoelastin lead to a reduced integration of the ELN and microfibrils in the elastic fibers of patients with ADCL.[45]

ARCL1 is characterized by peripheral pulmonary artery stenosis and pulmonary emphysema, vascular abnormalities, multiple diverticulae, and umbilical hernia.[51] ARCL1 results from recessive mutations in *fibulin-4* and *5* genes,[52–54] and in the gene encoding latent transforming growth factor β-binding protein 4.[55]

Clinical manifestations in ARCL type 2 include, in addition to excessive congenital skin wrinkling, a general connective tissue weakness and varying degrees of growth and developmental delay, microcephaly, and skeletal abnormalities. ACRL II is caused by mutations of *ATP6V0A2* gene.[56]

Diagnostic Methods

Diagnosis of SVAS is established clinically by (1) systolic ejection murmur in the aortic area that radiates to the carotid arteries often accompanied by a thrill in the suprasternal notch, and (2) echocardiography that documents the SVAS distal to the valvular cusps. Because of the Coanda effect (the tendency of a jet stream to adhere to a wall), the blood pressure in the right arm is often higher than that measured in the left arm.[55] SVAS usually occurs as an hourglass stenosis above the aortic valve but it may also occur as a more diffuse thickening of the wall of the long segment of the aorta.[19] SVAS is easily diagnosed by standard imaging methods, such as Doppler echocardiography, which provides a more accurate definition of the lesions and their severity, and MRI, which gives information on associated vascular anomalies.

The molecular diagnosis of ELN arteriopathy relies on several methods that depend on the type of alteration: fluorescence in situ hybridization to detect *ELN* deletion in WBS, direct sequencing to identify point mutations or small insertion/deletion, Multiplex Ligation Probe Amplification and Real Time quantitative polymerase chain reaction to detect partial or complete *ELN* exon(s) deletions.

Conclusions

ELN arteriopathy results from reduced *ELN* protein level because of either microdeletions or point mutations of the *ELN* gene. The reduction in ELN content of the tunica media of the great arteries leads to a generalized arterial disorder. Although aortic involvement is the predominant manifestation, other arteries are also affected, thus leading to a heterogeneous clinical phenotype. The genetic defects identified in other connective tissue disorders with overlapping clinical presentations have highlighted the complexity of molecular interactions that occur in the tunica media of the great artery and have improved our understanding of the molecular players involved in the structure of the elastic fibers.

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