Supravalvular aortic stenosis

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Abstract
Keywords
Excluded diseases
Diagnostic criteria/definiton
Differential diagnosis
Frequency
Clinical description
Management including treatment
Etiology
Diagnostic methods
Genetic counseling
Antenatal diagnosis
Unresolved questions
References

Abstract
*SupraValvar Aortic Stenosis (SVAS) is a rare condition characterized by narrowing of the aorta close to its origin. Other vessels might also be narrowed (branch pulmonary arteries, coronary arteries). This narrowing of the aorta or pulmonary branches induces a heart murmur and might result in ventricular hypertrophy. SVAS is either isolated or part of Williams-Beuren syndrome (peculiar face, mild mental retardation, hypercalcemia). Isolated SVAS is caused by a mutation in the elastin gene (*ELN*) which is located on chromosome 7q11.23. In nearly all cases,* ELN *mutations disrupt the elastin protein synthesis resulting in a deficit of production. This condition is transmitted as an autosomal dominant trait with incomplete penetrance and the expressivity of the disease varies widely within families. However, the progressive nature of the disease makes the identification of mutation carriers important for future preventive treatments. In any case, it is important to follow-up patients to monitor the evolution of the stenosis which can be removed by surgery.*

Keywords
Elastin, supravalvular aortic stenosis, peripheral pulmonary artery stenosis, *ELN*

Excluded diseases

Supravalvular aortic stenosis (SVAS) should be differentiated from:

- valvular and subvalvular aortic stenosis which occur at the aortic valve or below the aortic valve, respectively.
- aortic coarctation which is a narrowing of the aortic diameter or even an occlusion situated at the junction between the horizontal and descending segments of the aorta, right at the level where the ductus arteriosus is connected to the aorta.
- interruption of the aortic arch: continuity between the ascending and descending aorta is missing. The interruption of the aorta occurs downstream of the left subclavian artery (type A), or between this artery and the common carotid artery (type B) or between the left common artery and the innominate artery (type C). In addition, the ascending aorta has usually an uniformly narrowed diameter (it is hypoplastic).
- hypoplastic left heart syndrome (HLHS) with a small aortic orifice and/or a small left

ventricle that may be associated with a small ascending aorta.
- Williams-Beuren syndrome (WBS) since SVAS is one of the major manifestations in this syndrome. WBS, in addition to SVAS, includes "elfin-like" facial features, a particular behaviour and hypercalcemia. WBS is due to a large genomic deletion on chromosome 7q11.23 that encompasses the elastin gene and other genes. Because of this large deletion on one of the two chromosomes 7, patients have only one gene copy in this deleted area resulting in presumably decreased level of gene transcription. This decreased gene transcription is thought to be responsible for the syndrome, a phenomenon called "haploinsufficiency". The cardiovascular phenotype of WBS and the SVAS phenotype are related to the haploinsufficiency of the elastin gene. As a consequence, no difference between the cardiovascular phenotype of WBS and SVAS phenotype has been shown so far.

Diagnostic criteria/definiton

SVAS was first described in 1842 (Chevers 1842). It is a narrowing of the ascending aorta that can occur as a discreet hourglass deformity or as a diffuse hypoplasia originating at the superior margin of the sinuses of Valsalva just above the level of the coronary arteries (Vaideeswar *et al.* 1996; Stamm *et al.* 2001).
Several other arteries might be narrowed, peripheral pulmonary arteries in particular (peripheral pulmonary artery stenosis) in 83% of cases, but also coronary, renal, carotid, innominate, mesenteric arteries.
Occasionally, moderate thickening of the aortic cusps, pulmonary cusps or/and mitral valves resulting in stenosis or insufficiency is observed.
Rarely, SVAS patients present with aortic coarctation in addition or a cardiac malformation such as tetralogy of Fallot or ventricular septal defect (Eronen *et al.* 2002).

Differential diagnosis

A hourglass narrowing of the ascending aorta lumen is specific to SVAS. Nevertheless, hypoplastic ascending aorta of SVAS might mistaken for hypoplastic left heart syndrome but in SVAS the aortic orifice has a normal diameter and the left ventricle is not small. The occurrence of isolated peripheral pulmonary stenosis should prompt for a search of the artery anomalies (SVAS) and extra-cardiac signs (that may lead to diagnosis of WBS).
In any case, the diagnosis of SVAS should prompt for a search for other signs of WBS.

Frequency

No reliable statistical data about SVAS are available. An incidence of 1/20,000 to 1/50,000 is reported for WBS (Duba *et al.* 2002) and SVAS is much rarer than WBS.
The disease is either sporadic or familial. It is then transmitted as an autosomal dominant trait with incomplete penetrance and variable expressivity.

Clinical description

The age at presentation is lower in familial SVAS than in Williams-Beuren syndrome. In most cases, diagnosis is established in the first year of life.
Patients may have no symptom and go and see a physician because of a murmur or have symptoms such as:
- dyspnea (the most common symptom)
- chest pain due to aortic stenosis with coronary abnormalities resulting in myocardial ischemia and ventricular hypertrophy.
- myocardial infarction, stroke or even sudden death occurring during exercise. They are complications of severe coronary or cerebral arteries lesions (Kitchiner e*t al.* 1996).

At examination, SVAS is responsible for a systolic murmur and thrill with a maximum at the first right intercostal space. The irradiation is predominant in the right carotid artery. By contrast, in valvular aortic stenosis, no ejection sound can be heard. The peripheral pulmonary artery stenosis may produce a continuous murmur. The tendency of the jet stream to adhere to a vessel wall (Coanda effect) results in a selective streaming of blood into the innominate artery with a disparity of pulse and blood pressure between the arms. As a consequence, blood pressure in the right arm may exceed the pressure in the left one by 20 mm Hg or more. Femoral pulse is decreased if aortic coarctation is associated.
In severe forms, newborns present with symptoms of left cardiac failure.
Deficient elastin may also account for hoarse voice, hernias, lax skin, the impression of premature ageing, stiffness of joints, and may even be the origin of vascular hypertension.
Electrocardiogram may indicate signs of left ventricular hypertrophy. Abnormal repolarisation is the consequence of left ventricular hypertrophy and/or coronary lesions.
Echocardiogram with doppler is the key diagnostic tool. The narrowed ascending aorta is visualized from the suprasternal, subcostal and long-axis parasternal view. The type of stenosis is revealed as well as the trans-stenotic gradient (supra-sternal window). An obstruction is

significant if mean gradient is above 50 mm Hg. Pulmonary branch stenosis is commonly associated with SVAS but decreases throughout follow-up. In addition, associated lesions are observed:

- Aortic valve: due to pre-stenotic elevated lesions there is a premature degeneration of the leaflets caused by a mismatch between the free edge of the leaflets and the corresponding part of the sinotubular region. As a consequence, 50% of patients have aortic valve anomalies.
- Coronary artery obstruction is assessed by colour and pulsed doppler.
- Left ventricular function and hypertrophy secondary to ischemia and obstruction, respectively.
- Cardiac malformations such as interventricular or interatrial shunts.

Angiography by retrograde femoral arterial catheterization and angio-NMR (nuclear magnetic resonance) allow the assessment of the entire aorta and coronary circulation. Coronary arteries anomalies are diverse: obstruction by a near-circumferential thickening of the left main ostium, fusion of an aortic valve leaflet to the supravalvular ridge, diffuse narrowing of the main coronary artery, distortions, dilatations with premature arteriosclerosis due to elevated pre-stenosis pressure.

Management including treatment

The evolution of artery narrowing and its consequences need to be monitored. An electrocardiographic and echographic control is recommended every 3 months during the first year of life, and every 6 to 12 months thereafter depending on the severity of the narrowing.

In clinical studies, it has been shown that PPAS tends to improve with time and SVAS to progress (Kim *et al.* 1999, Eronen *et al.* 2002). Indeed, mild narrowing of the aorta with pressure gradient of less than 20 mm Hg in infancy generally remained unchanged during the first two decades of life whereas gradients above 20 mm Hg tended to increase (Zalzstein *et al.* 1991; Wessel *et al.* 1994). Surgical relief of the narrowing has good long-term results but aortic hypoplasia and associated coarctation impairs the prognosis of operated SVAS because restenosis may occur.

Arterial hypertension tends to develop over time (Morris *et al.* 88; Eronen *et al.* 2002).

Sudden death may occur in WBS presumably due to myocardial infarction by narrowing of coronary arteries (Bird *et al.* 1996) as well as cerebral stroke (Kaplan *et al.* 1995). Coronary lesions are probably milder in SVAS since only myocardial ischemia was reported (van Son *et al.* 1994), and sudden death due to coronary obstruction is exceptional (Nakanishi *et al.* 1996).

Surgical repair is indicated for significant aortic stenosis on EchoDoppler evaluation (left ventricle hypertrophy and aortic mean gradient higher than 50 mmHg) (Stamm *et al.* 99).

It is necessary to use a cardiopulmonary bypass in all cases and deep hypothermic circulatory arrest is used when the reconstruction extends into the aortic arch or aortic vessels are involved.

Surgical repair with patch aortoplasty is performed for localized forms but diffuse forms require patch aortoplasty and extended endarterectomy.

Coronary associated lesions assessed by coronary angiography and intraoperative examination lead to modified surgical techniques:

- patch aortoplasty encompassing the left main coronary ostium and supravalvular aortoplasty (obstruction from near-circumferential thickening of the left main ostium),
- excision of the fused leaflet from the aortic wall and patch aortoplasty (restricted coronary flow due to fusion of an aortic valve leaflet to the supravalvular ridge),
- bypass grafting and aortoplasty (diffuse narrowing of the left main coronary artery).

Associated lesions are repaired if indicated by doppler measurements and/or angiography:

- pulmonary artery plasty is performed in pulmonary trunk and/ or branches stenosis,
- aortic coarctation is repaired with modified Crafoord operation.

Etiology

SVAS is due to mutation in the elastin gene (*ELN*) on chromosome 7q11.23. The causative role of this gene was demonstrated in several studies of families with chromosomal translocations or deletions (Curran *et al.* 1993; Ewart *et al.* 1994; Olson *et al.* 1995). Other studies demonstrated that point mutation in the elastin gene results also in SVAS (Li DY *et al.* 1997; Tassabehji *et al.* 1997). Most mutations are truncating mutations (leading to truncated protein by aberrant splicing or frameshift). Missense mutations are rarely shown (about 10% of cases) (Metcaffe *et al.* 2000). Except for these later ones, the defect in elastin is thus probably quantitative (insufficient level of elastin is produced). The elastin gene is composed of 34 exons, spans about 45 kb of genomic sequence and produces a transcript of about 3.5 kb comprising 2.2 kb of coding sequences. The

elastin polypeptide is soluble and excreted by fibroblasts, endothelial cells, chrondroblasts and vascular smooth muscle cells (SMC). Elastin molecules are aligned on a scaffolding of microfibrils composed of fibrillin. The copper-dependent lysyl oxydase enzyme stabilized the alignment by creating covalent links. Elastin and fibrillin are the major components of elastic fibres that form concentric lamellae in blood vessels. It has been demonstrated that a decreased production of elastin results in decreased deposit of insoluble elastin in elastic fibbers. This low level of elastin deposition coincides with an increase in proliferation of SMC which could be reversed in vitro by addition of exogenous insoluble elastin (Urban *et al.* 2002). In this study, the drop in elastin deposition was more important in WBS patients than in SVAS patients suggesting that genes removed in the WBS deletion might play a regulatory role in elastin deposition.

Diagnostic methods

SVAS and other cardiovascular anomalies are diagnosed by imaging methods that are prompted by the discovery of a systolic heart murmur. Echocardiography of the heart reveals the topography of the narrowing, its type and severity and associated anomalies.

Angiography and catheterization may be used. Angiography of the coronary arteries reveals dilated and tortuous arteries which may present with focal narrowing of the lumen in particular at its origin.

The molecular diagnosis of SVAS relies on standard caryotype to detect chromosomal translocation, FISH (Fluorescence *In Situ* Hybridization) to detect *ELN* deletion and mutation screening to detect point mutation. The most frequent type of elastin gene defect in SVAS is point mutation. Consequently, normal caryotype and normal FISH do not eliminate a defect in the elastin gene.

Genetic counseling

A precise prediction of the severity associated to a particular elastin mutation is hampered by two phenomena:

1) there is a large variety of mutations with nearly each SVAS family having its own private mutation except for 4 mutations that have been observed in several unrelated families (Y150X (exon 9); K176X (exon 10); Q442X (exon 21); 1501 +11-12insC) (Metcalfe *et al.* 2000).

2) severity of disease varies widely within families ranging from no anomalies to severe forms or WBS. This is particularly true for SVAS family which are secondary to chromosomal translocation (Morris *et al.* 1993; Curran et al. 1993; Duba *et al.* 2002).

This is not a problem in genetic counseling because the disease is not so severe and, when severe, it is amenable to surgical treatment with good prognosis. It is though worth identifying the gene defect and carriers within a family because of the progressive nature of the disease.

Antenatal diagnosis

Antenatal diagnosis can be carried out after amniocentesis if the gene defect has already been characterized. Nevertheless, it is irrelevant since SVAS is not a severe disease and thus there is no indication for termination of pregnancy.

SVAS is exceptionally detected by prenatal echography. Because of the progressive nature of the disease, most cases are diagnosed during the first year of life.

Unresolved questions

- Why do elastin mutations result only in cardiovascular anomalies when elastic fibres are scattered in the whole organism in particular in the lungs, skin, ligaments and cartilage? It is not clear what part of the spectrum of anomalies observed in WBS is related to *ELN* deficiency.
- What are the factors that modulate the severity of the disease within family members carrying the same mutation?
- Would a deposition of insoluble elastin in the artery wall be a cure to this disease?

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