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Original Article

A family with a new *elastin* gene mutation: broad clinical spectrum, including sudden cardiac death

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Abstract Supravalvular aortic stenosis is associated with the Williams–Beuren syndrome, but it also occurs in a non-syndromatic congenital form. An *elastin* gene mutation of chromosome 7q11.23 is responsible in both cases. The vascular features are identical. These patients have a higher risk of sudden death, particularly when undergoing diagnostic or surgical procedures. We report the account of a family with a new mutation in the *elastin* gene. Screening over three generations revealed eight affected individuals. The cardiac and vascular malformations ranged from mild asymptomatic supravalvular aortic stenosis and isolated dysplastic atrioventricular valves to diffuse arterial hypoplasia. Two infants presented arteries affected at multiple locations, including the left coronary artery. Both died of sudden cardiac death and myocardial ischaemia, one while under general anaesthesia for cardiac catheterisation, and the other perioperatively. We discuss the pathophysiological aspects in these patients that deserve consideration before any general anaesthesia is administered.

Keywords: Supravalvular aortic stenosis; general anaesthesia; coronary stenoses

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Supravalvular aortic stenosis is a rare form of left cardiac obstruction. Most of such patients suffer from the Williams–Beuren syndrome. Non-syndromatic, congenital supravalvular aortic stenosis, which lacks the cognitive, behavioural, and phenotypic abnormalities of the Williams–Beuren syndrome, is less common. However, it is known that alterations in the arterial vessels in both illnesses are due to an *elastin* gene mutation.[1–3] This gene is located on chromosome 7q11.23, and it is inherited in an autosomal-dominant trait.[1,4–6] In the Williams–Beuren syndrome, deletion of one complete copy of the *elastin* gene is identified.[7] In non-syndromatic supravalvular aortic stenosis, there are several mechanisms involving the *elastin* gene, such as point mutations,[5,8–12] translocations,[1,13] and gross intragenic deletion.[6,14] The other manifestation of the Williams–Beuren syndrome is encoded by other genes, for example, defects in visuospatial cognition are thought to be caused by the loss of one allele of LIM domain kinase 1.[15,16] The vascular features are manifold. Aortic narrowing is often described as an hourglass deformity with discrete constriction, but it can also occur as diffuse arterial hypoplasia. It is characteristically associated with peripheral pulmonary artery stenosis, such as supravalvular pulmonary stenosis. Biventricular hypertrophy resulting from increased resistance is followed by a progressive clinical course, worsening in patients with coronary artery involvement. There are several reports of sudden cardiac death[17–19] and it is generally acknowledged that these patients are at higher risk when undergoing diagnostic or surgical procedures.[20] In our institution, two patients not known to be related suffered

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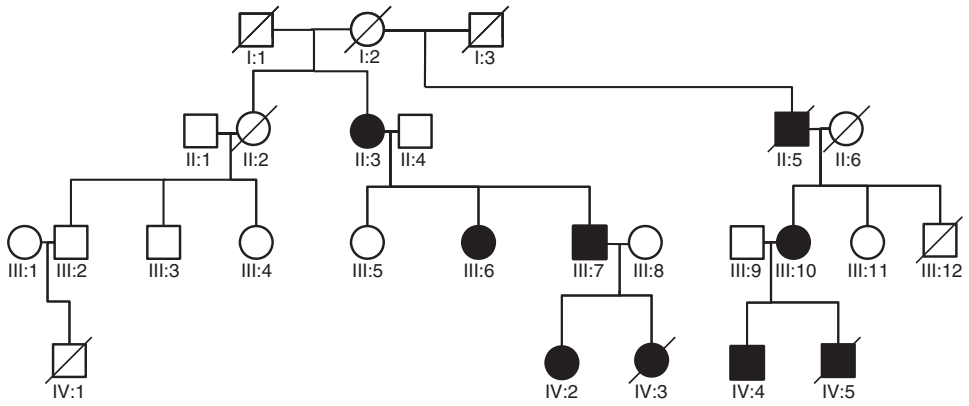

Figure 1.
Pedigree of a family with elastin *gene mutation. Eight individuals are affected and present with different phenotypic expression.*

cardiac arrest, requiring resuscitation while under general anaesthesia for catheterisation. One died during catheterisation, the other shortly after surgical repair. We screened the family and identified eight patients with a new point mutation in the *elastin* gene. We describe the various vascular disorders in this family, as well as the deceased infants' clinical course.

Materials and methods

We investigated three generations of a family of Caucasian origin. Direct sequencing analysis of genomic amplifiers was used to screen the 33 *elastin* gene exons for mutation. Polymerase chain reaction fragments were automatically analysed (ABI 3730, Applied Biosystems, Foster City, California, United States of America). All sequences were evaluated using the Sequence Pilot Software (JSI Medical Systems) and matched with the reference sequences (NT_007758, NM_000501). The cardiac and vascular malformations in these patients were determined by echocardiogram, and angiographically in two patients. One patient was autopsied; thus we had access to macroscopic and histological aspects regarding anatomical vascular abnormalities.

Results

Elastin *gene mutation*

We identified a single base-pair mutation in the *elastin* gene, a deletion of cytosine at position 757 in exon 15. This mutation is predicted to cause a glutamine-to-arginine replacement at position 253 and a frame shift with a premature stop-codon (the mutant allele encodes a 68 amino-acid long-missense peptide sequence). This sequence change has been previously described but given the nature of the mutation and its segregation within the family, it is almost certainly pathogenic.

Cardiovascular features

Eight individuals in this family over three generations are affected by diverse phenotypic expressions (see Fig 1). Two family members have isolated supravalvular aortic stenosis. III:10 has a very mild form, III:6 underwent surgical repair at the age of 11 years. III:7 is the only individual with isolated peripheral pulmonary stenosis, diagnosed at the age of 8 years due to a systolic murmur. He has remained asymptomatic so far. Individuals II:5 and IV:4 have isolated dysplastic aortic valves with mild stenosis. IV:2 suffers from isolated pulmonary valve stenosis.

IV:5 was a 9-month-old boy who died during cardiac catheterisation in 1997. At the age of 7 months he underwent cardiac surgery with patch augmentation of the aortic and pulmonary stenosis and excision of the fibrous tissue, narrowing the left coronary artery ostium. He was discharged home, and presented 5 weeks after surgery in our clinic with increasing hyperventilation, sweating, and exhaustion. Electrocardiography revealed ST-segment depression, and echocardiography showed poor ventricular function. Angiography was therefore performed and showed severe stenosis of the left coronary artery. The child unfortunately died during catheterisation of left ventricular failure due to coronary stenosis. Autopsy revealed all the great arterial vessels to be thick-walled, including the coronary artery. Histological investigation revealed the three layers of the arteries to be hypertrophic with reduced *elastin* content in the media, smooth muscle proliferation, and fibrosis. Textural changes in the *elastin* and collagen fibres also affected the pulmonary valve.

IV:3 was a 5-month-old girl with an initial diagnosis of supravalvular aortic stenosis, supravalvular pulmonary stenosis, aortic coarctation, and biventricular hypertrophy. By the age of 3 months she presented with recurrent, rapidly recompensating syncopes. Her relationship to IV:5 was not known at that time. During the induction of anaesthesia for

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diagnostic catheterisation, she suddenly developed cardiac decompensation. After successful resuscitation and haemodynamic stabilisation, we performed angiography with contrast injection into the left ventricle, additionally revealing a hypoplastic left coronary artery and hypoplastic abdominal aorta. After numerous life-threatening syncopes, we carried out surgical reconstruction of the aortic arch. Cardiopulmonary bypass weaning failed, and a pulsatile left ventricular assistance device (MEDOS Medizintechnik AG, Stollenberg, Germany) was implanted. Nevertheless, the infant died several hours later of biventricular heart failure. An autopsy was not performed.

Discussion

Elastin *gene and morphological features*

Elastin is an essential component of the great arteries. Several *elastin* gene mutations have been reported.[1,5,6,8–14] We have detected a new single base-pair mutation in the *elastin* gene. The molecular sequence conducting from loss-of-function mutation to supravalvular aortic stenosis has been investigated in humanised *elastin* mice.[21] This study illustrates that reconstituting functional elastic fibres corrects the existing cardiovascular changes in *elastin* haploinsufficient mice. The deletion on the *elastin* gene leads to reduced *elastin* content in the medial layer of the arteries, which may be followed by recurrent injury and fibrosis. Microscopically, the involved vessels reveal disorganised, fragmented elastic fibres of reduced quantity, hypertrophied smooth muscle cells, and excessive collagen.[18,22] The postmortem examination of one deceased infant with multi-focal arterial obstruction revealed the same histopathological disarrangements in all the affected arteries. The pulmonary valve is also included here in these histological changes, not yet having caused any clinical valve dysfunction. There are few reports of the semilunar valves having been affected in this disease. One report describes the aortic valve leaflets to be partially adherent to the stenosing supravalvular ridge in more than half of the patients.[23] Echocardiographically, three of our family members (II:5, IV:5, and IV:2) only have dysplastic semilunar valves with mild stenosis, with no evidence of stenotic vessels.

In our family, the vasculopathies thereby range from localised stenosis of the ascending aorta to diffuse obstruction affecting the entire aorta, including the origin of the head and neck vessels;[24] the pulmonary arteries are also commonly affected.[25] Disease severity varies and does not depend on *elastin* gene mutation. The cardiopathic variability within one family is as great as that among individuals with different *elastin* gene mutations.[10] As in our family, the clinical spectrum varies from asymptomatic carriers to individuals who die in infancy from severe cardiac disease.[5]

Sudden cardiac death

Disease severity, especially clinical progress, may be strongly affected by coronary artery involvement. Significant coronary artery involvement in patients with supravalvular aortic stenosis has been described.[26] Coronary artery stenosis occurs as focal or diffuse narrowing of the vessel itself, or it can be due to obstruction by redundant dysplastic aortic valve leaflets.[23,27] In our family with supravalvular aortic stenosis, infants IV:5 and IV:3 presented narrowing of the left coronary artery. The increased risk for sudden cardiac death may be accompanied by coronary stenosis. Bird et al.[17] reported three cases of Williams–Beuren syndrome patients with sudden cardiac death and a displacement of the coronary ostia superior to a position just below the sinotubular ridge with subsequent obstruction. Even without haemodynamically significant supravalvular aortic stenosis, cases of coronary stenosis have been reported.[17,18,22,28–31] The diastolic component of phasic coronary blood flow also depends on aortic distensibility, referred to as the "Windkessel effect". Reduced elastic fibres and increased fibrosis lead to aortic stiffening, which in turn raises systolic and reduces diastolic pressure[32] (thus lowering coronary blood flow).

Biventricular obstruction also leads to ventricular pressure overload, and secondarily to myocardial hypertrophy with a prolonged ejection and high-pressure isovolumic contraction phase. Subendocardial ischaemia can easily develop in such patients. In particular, the administration of anaesthesia in conjunction with a sudden drop in the afterload may well alter this delicate balance between myocardial oxygen supply and demand.

Several series and case reports have described sudden death in association with the administration of sedative or anaesthetic drugs for cardiac catheterisation or surgical, cardiac or non-cardiac, procedures.[17,33–35] Sudden cardiac death correlated with the presence of coronary artery obstruction in most of the affected patients.

Any application of general anaesthesia should undergo careful scrutiny and only be performed by well-experienced anaesthesiologists anticipating such problems. Alternatives for invasive diagnosis should be carefully considered. For example, cardiac magnetic resonance imaging appears to be an increasingly promising non-invasive imaging modality capable of delineating blood flow obstruction.[36]

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