Novel ELN mutation in a family with supravalvular aortic stenosis and intracranial aneurysm

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Abstract
Pathogenic germline mutations in ELN can be detected in patients with supravalvular aortic stenosis. The mutation might occur de novo or be inherited following an autosomal dominant pattern of inheritance. In this report we describe a three-generation family suffering from supravalvular aortic stenosis, various other arterial stenoses, sudden death, and intracranial aneurysms. A frameshift mutation in exon 12, not described before, was detected in the affected family members. This report emphasises the importance of family history, genetic counselling, and demonstrates the great variability in the phenotype within a single SVAS family.

1. Introduction

Supravalvular aortic stenosis (SVAS) is a congenital narrowing of the ascending aorta and has an incidence of 1:20,000. SVAS often occur sporadically (Metcalf et al., 2000). A non-syndromic, hereditary form of SVAS has been known since 1964, where Eisenberg et al. described several cases with more than one affected generation (Eisenberg et al., 1964). The autosomal dominant condition was later linked to chromosome 7q11.2 and point mutations were found in the elastin gene (ELN) in affected families (Li et al., 1997). Thus the condition can be classified as autosomal dominant inherited elastin arteriopathy (OMIM 185500). A syndromic form of SVAS include Williams syndrome, which is caused by a microdeletion encompassing ELN, and characterized by dysmorphic features, intellectual disability, and SVAS. Over the years the phenotypic spectrum of ELN related clinical features has been broadened. With this report we contribute to further description of a genotype-phenotype correlation including a case of an intracranial aneurysm (IA).

1.1. Patient report
The proband, a 38-year-old male patient, was referred to genetic counselling because of a family history of congenital heart defect (Fig. 1).

1.2. Medical history
The proband (III-3) was born at term after an uncomplicated pregnancy. Birth length was 50 cm and birth weight was 2750 g. At 13 months he was referred to the paediatric department because of a systolic heart murmur. He was diagnosed with a non-specified congenital heart defect but had normal development. He did not have a syndromic appearance. In his medical records it is stated that at age 2, a cardiac catheterization showed SVAS and a hypoplastic aortic arch, but details from the catheterization are no longer available. During childhood the patient suffered from recurrent pneumonias and an inguinal hernia. At 6 years of age, repeat heart catheterization found the SVAS with a gradient of 190 mmHg and he underwent heart surgery with Dacron patch aortoplasty in the ascending aorta. At this age he experienced limitations in physical activity. Postoperative complications included occlusion of the right femoral artery. The patient had
normal developmental milestones and attended regular school.

At 16 years of age, he underwent heart surgery again because follow-up cardiac investigation had shown a remaining stenosis SVAS of 53 mmHg and a hypoplastic aortic arch, stenosis of the brachiocephalic artery, and stenosis of the left common carotid artery, without reference to gradients in the latter. Minor central pulmonary artery stenoses of 27 mmHg on the left and 10 mmHg on the right side are documented. Heart valves were normal and renal angiography showed a normal variation of the arterial supply with two renal arteries to the right kidney and one to the left. The patient was operated with extension of the previous aortotomy of the ascending aorta with a new Dacron patch extending y-shaped into the right and non coronary sinuses and going up into the proximal brachiocephalic trunk, but omitting surgery on the left common carotid artery.

At age 20, the proband was admitted to hospital because of a sudden pain in the neck, vomiting, and nausea. He was diagnosed with a subarachnoid haemorrhage. Cerebral angiography of the brain showed an aneurysm in the anterior communicating artery. The aneurysm was ligated without complications and the proband had no long-term injuries. At age 27, genetic testing for Williams Syndrome showed normal results. When the patient was 37 year old he was referred to the department of clinical genetics, because his new-born daughter (IV-2) was diagnosed with a congenital heart defect, which raised suspicion of a monogenetic condition. The proband was re-examined by echocardiography, and, subsequently, left heart catheterization, as no signs of remaining pulmonary stenosis were seen on echocardiography, but he had hypertension and suspicion of renewed SVAS. Invasive gradients were only 15 mmHg from the left ventricle to the descending aorta, however, and attends biannual follow-up.

II-2, the mother of the proband (III-3), was diagnosed with congenital heart disease at the age of 10, which was later confirmed to be SVAS. The diagnostic tools used are not described in later records, but from her age at diagnosis, probably by heart catheterization, and in more recent records commenting on echocardiographs, only a minor aortic stenosis of 20 mmHg along with severe hypertrophy owing to severe hypertension, was described. She had normal levels of physical activity and never underwent surgery. She suffered from severe migraine during adulthood. At age 58 she experienced weakness in both the upper and lower extremity on the left side of the body, but was not examined
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