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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.

Keywords

ELN; supravalvular aortic stenosis; intracranial aneurysm; sudden death

Introduction

Supravalvular aortic stenosis (SVAS) is a congenital narrowing of the ascending aorta and has an incidence of 1:20000. SVAS often occurs sporadically [1]. A non-syndromic, hereditary form of SVAS has been known since 1964 when *Eisenberg et al* described several cases with

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more than one affected generation [2]. The autosomal dominant condition was later linked to chromosome 7q11.2 and point mutations were found in the elastin gene *(ELN)* in affected families [3]. Thus, the condition can be classified as an autosomal dominant inherited elastin arteriopathy (OMIM 185500). A syndromic form of SVAS includes 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. In this report, we describe a new genotype-phenotype correlation with a case of an intracranial aneurysm (IA).

Patient report

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

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 an 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 disability. 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 reexamined 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 further. During workup for severe headache a year later she was diagnosed with and treated for hypertension. Furthermore, she had a CT scan of the brain performed, showing an old stroke in the right hemisphere, and unrelated to this, a borderline narrowing of maximum 49% of the left internal carotid artery on duplex scanning.

IV-2, the second daughter of III-3, was referred to the paediatric department five hours after birth because of a heart murmur. She was delivered naturally at term. Birth weight was 4428 g and birth length was 54 cm. Echocardiography revealed a patent ductus arteriosus and stenoses of the pulmonary arteries with gradients on echocardiography and subsequent heart catheterization of 50–60 mmHg and prolonged narrowing of the central sections. No other stenoses were discovered, the ductus closed spontaneously, and the patient was referred to surveillance. At age one, she was admitted to the paediatric department because of suspicion of diabetes mellitus type 1 which was confirmed. Development milestones were normal and she experienced no limitations in physical activity.

Additional family history

A detailed family history revealed that III-3's older brother died at two month of age. He was cyanotic at birth, which improved over the first week of life. Cardiac catheterization on day 11 showed pulmonic stenosis with only a narrow passage and an atrial septal defect. He died at two month of age. No autopsy was performed and we do not have further clinical descriptions.

Furthermore, III-3's maternal grandmother had died suddenly at age 38.

Material and methods

The autosomal dominant pattern of inheritance with several generations with stenoses of the great arteries raised suspicion of an *ELN* mutation. DNA from blood samples from III-3 was analysed by direct sequencing. The entire coding region of *ELN* and flanking intronic regions were sequenced. All sequence data were obtained using ABI Big DYE v3.1 terminator kit and 3730xl automated sequencer and the results were analysed using the Sequencher 4.5 software (GeneCodes, Ann Arbor, MI).

Results

A heterozygous frameshift mutation was detected in exon 12: chr7:74,046,732dupC (GRC38/hg19) c.608dupC, (ENST00000358929), p.L204Tfs*58, that has not been described before. The duplication creates a frameshift and induces a premature stop codon. Segregation analysis in the family revealed that the affected family members II-2 and IV-2 also carried the mutation. Samples from III-1 and I-4 were not available for genetic analysis. The mutation was considered pathogenic due to the nature of the mutation (frameshift, premature stop codon) and because the mutation segregates with affected family members. The mutation is not listed in ExAC and the population frequency is unknown.

Discussion

This report demonstrates the broad phenotypic spectrum of autosomal dominant inherited elastin arteriopathy. In this family, both connective tissue lesions such as inguinal hernias and severe arterial conditions are present. Two family members (I-4 and III-1) died suddenly, and although it was not possible to perform mutation analysis in these individuals, we suspect them to have had the *ELN* mutation. The risk of sudden cardiac death in *ELN* related arteriopathy is unknown, but *Metcalfe et al.* reported one case of sudden infant death [1]. We also report the occurrence of subarachnoid haemorrhage caused by an IA (III-3). This is interesting, as *ELN* has been implicated in the genetic risk of IAs by linkage and association studies [4–7], but not in all [8]. To the best of our knowledge, IA in a patient with an *ELN* point mutation has not been reported previously. As *ELN* mutations seems to result in a general arterial disease, IA may be part of the condition, however co-occurrence by chance in the patient cannot be excluded.

The molecular disease mechanisms of *ELN* related SVAS are beginning to emerge. “Premature stop codons in *ELN* may lead to nonsense-mediated mRNA decay, and thereby decreased levels of ELN and thus result in functional haploinsufficiency as it has been described for Williams syndrome.”[9,10]. Reduced elastin availability during vascular maturation results in increased cell proliferation [11], as a result of excessive integrin β3 signaling [12].

Autosomal dominant cutis laxa (OMIM 123700) is commonly caused by pathogenic mutations in *ELN*. This condition is characterized by loose/wrinkled skin, which lacks elastic recoil. Hernias, pulmonary emphysema, pulmonary artery stenoses, and aortic aneurysms have also been described in these patients [13,14]. The molecular mechanism, however, has been suggested to be a mutant protein (tropoelastin) in which the C-terminus is replaced by an extended missense peptide sequence as a result of a frameshift mutation within any of the last 5 exons of *ELN* [15].

Our family demonstrates the great intrafamiliar variability. This illustrates that (suspicion of) the diagnosis is more difficult in less affected individuals/families. We propose that any history of cardiovascular symptoms in family member of a patient with SVAS should lead to consideration of a hereditary form of SVAS. In addition to point mutations and deletions of *ELN*, SVAS has been observed in patients with autosomal recessive cutis laxa type IA,

caused by mutations in the fibulin-5 (*FBLN5*) gene [16]. Furthermore, arterial stenoses are known to be associated with a larger group of disorders, with pulmonary artery stenoses found in Alagille syndrome, and Noonan Syndrome, and renal artery stenoses in Neurofibromatosis type 1 [17], which should also be considered if other symptoms are present.

A syndromic form of SVAS should be considered if the case appears to be *de novo* and if other symptoms e.g. dysmorphic features and developmental delay are present. When diagnosed, autosomal dominant inherited elastin arteriopathy should be regarded as a generalized disease of the arterial wall, which, in principle, could affect any artery in the body. This highlights the need for further clinical investigations, genetic counselling, and surveillance in affected patients and asymptomatic mutation carriers.

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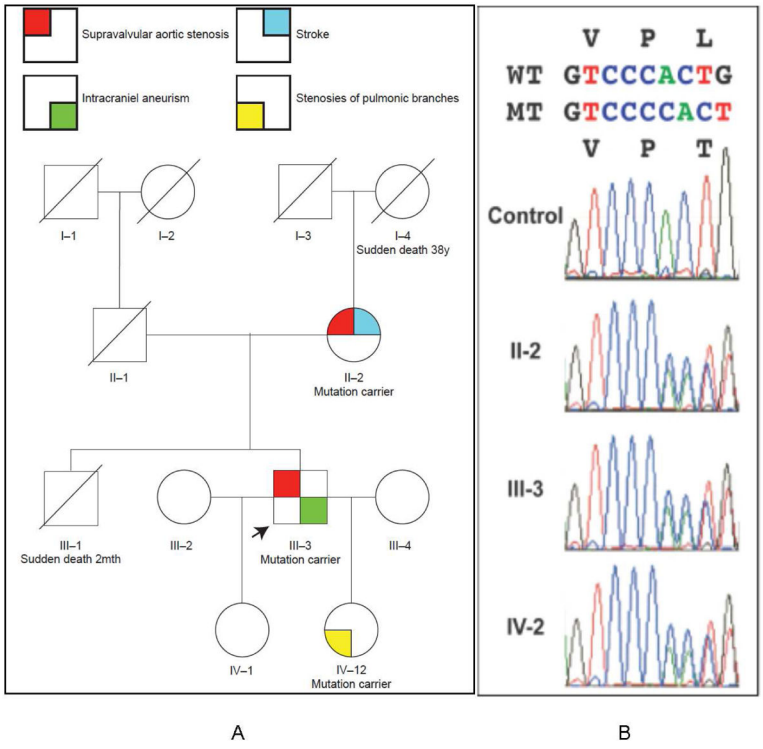

Figure 1. (A) Pedigree of the family; (B) DNA sequence analysis of affected family members

Sequence traces of a control individual and II-2, III-3 and IV-2 are shown stacked. Above the sequence traces the wild-type (WT) protein and DNA sequences are aligned with the mutant (MT) sequences.