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Case Report

Coexistence of supravalvular aortic stenosis and osteogenesis imperfecta

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CASE REPORT

A 54 year old woman was admitted for cardiac catheterisation. She had been attending the outpatient clinic since 1975, with regular review. She had diagnoses of type I osteogenesis imperfecta, and of supravalvular aortic stenosis. Osteogenesis imperfecta was diagnosed in early life on clinical grounds including the presence of blue sclerae and the occurrence of several bone fractures secondary to minimal trauma. A number of family members have been diagnosed with the same condition (figure 1-family pedigree).

The supravalvular aortic stenosis was not diagnosed until later. She was initially referred to the cardiology clinic for further evaluation following the discovery of a systolic murmur during routine examination at an antenatal clinic. Echocardiography revealed a morphologically normal aortic valve and confirmed the presence of supravalvular aortic stenosis, with an estimated peak systolic gradient of 20 mmHg.

Examination of her family history has also revealed several members with a diagnosis of supravalvular aortic stenosis (Figure). Neither of her parents was known to have had the disease, but her mother had died prematurely at the age of 42 years supposedly due to asthma. There are three family members diagnosed with both osteogenesis imperfecta and supravalvular aortic stenosis. Therefore, some members of this family have either supravalvular aortic stenosis or osteogenesis imperfecta, some have both diseases and some have neither.

Cardiac catheterisation (SVAS) revealed normal coronary arteries and left ventricular function. There was narrowing of the ascending aorta immediately above the aortic valve with poststenotic dilatation of the aorta, giving the typical "hourglass" appearance seen in SVAS. There was a peak-to-peak gradient of 40 mmHg across the lesion on catheter pull-back.

Karyotyping revealed a normal XX pattern with no deletion evident. The mutation causing SVAS in this family has been mapped to the elastin gene on chromosome 7. This family has not yet been investigated with regard to the molecular basis for theirosteogenesis imperfecta.

DISCUSSION

Supravalvular aortic stenosis is defined as an obstructive vascular disease due to severe narrowing of large elastic arteries, particularly the ascending aorta, and including the pulmonary, coronary and carotid arteries. The incidence of the disease is estimated at I in 20,000 births. The large majority of cases are familial, with transmission of the disease in an autosomal dominant manner[1]. The disease is caused by mutation in the elastin gene (ELN), located at chromosome 7q11.23[2]. Supravalvular aortic stenosis is also a common feature of Williams' syndrome, a congenital multisystem disorder caused by contiguous gene deletion that may include the elastin gene[3].

Osteogenesis imperfecta is an inherited connective tissue disorder, characterized by skeletal, ocular, otologic and dental abnormalities with an incidence of around one in 28,500 live

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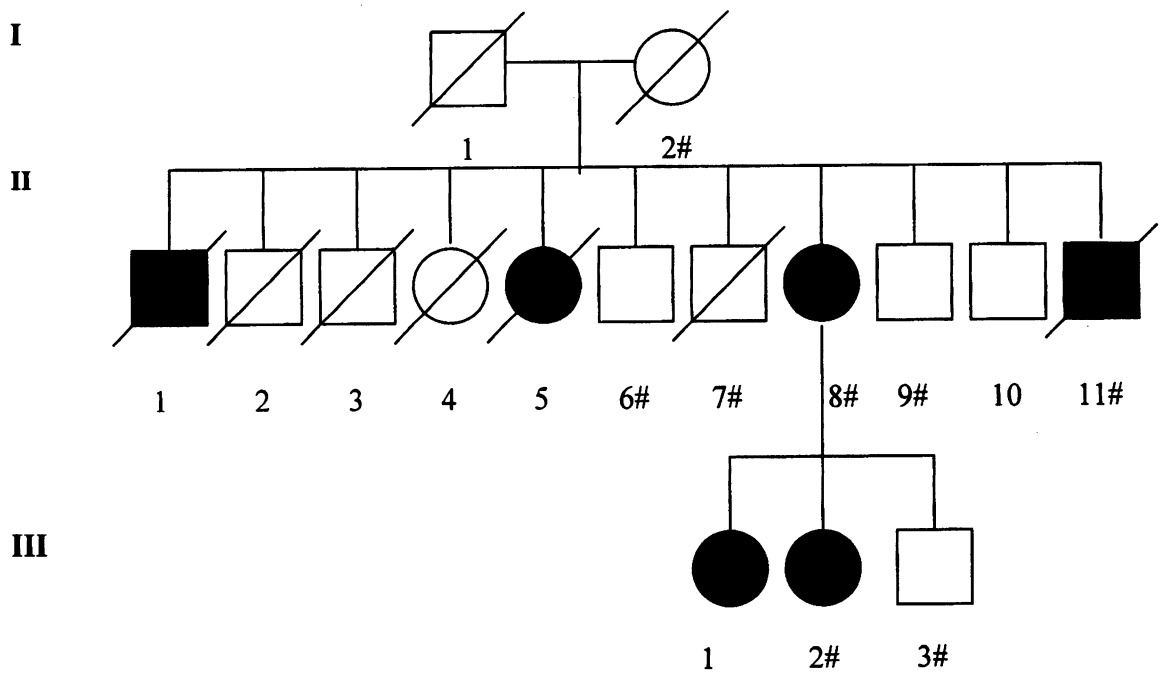
FIGURE

Family Pedigree



■ = Affected SVAS
\# = Affected OI
Individual II8 is the person described in this paper.

births. Sillence *et al* specified four basic types of the disease, based on age-of-onset, severity and mode of transmission[4]. The family described meet the criteria for type I osteogenesis imperfecta. Cardiovascular involvement in osteogenesis imperfecta type I was described in one study and includes mitral valve prolapse in 18% with rare progression to mitral regurgitation, and slight but significant increase in aortic root diameter associated with aortic regurgitation in 1 to 2%[5]. Over 70 mutations have been associated with osteogenesis imperfecta, all affecting type I procollagen synthesis. The osteogenesis imperfecta type I phenotype can be produced by mutation in either the COL1A1 gene on chromosome 17 (17q21.3 1-q22) or the COL1A2 gene on chromosome 7 (7q22.1), and possibly in other genes[6]. The presence or absence of presenile hearing loss was the best predictor of the mutant locus in osteogenesis imperfecta type I families with 13 of the 17 COL1A1 segregants and none of the COL1A2 segregants demonstrating this feature[7].

The estimated incidence of both osteogenesis imperfecta and supravalvular aortic stenosis occurring together by chance in an individual is over one in five hundred million. Although the ELN and COL1A2 genes are both present on chromosome 7, it is highly unlikely that the coexistence in the individuals discussed is due to expression of one genetic defect for a number of reasons. Firstly, the ELN and COL1A2 genes are not closely linked on chromosome 7, and in the knowledge that the individual discussed has a normal karyotype, a large deletion cannot explain coexistence of the diseases. Secondly, the family described have had presenile hearing loss as a feature of osteogenesis imperfecta, which has not been a feature of mutation in the COL1A2 gene; therefore it can be postulated that the mutation in this case is linked to the COL1A1 gene on chromosome 17. Finally, the diseases have not segregated together in this family, so there have been some members with both osteogenesis imperfecta and supravalvular aortic stenosis, some with only one disease and some with neither disorder.

In conclusion, we present a case with coexisting supravalvular aortic stenosis and osteogenesis imperfecta, the first documentation in the literature. Both diseases have a single gene basis, autosomal dominant transmission, altered

production of structural proteins and manifestation in the cardiovascular system. The likelyhood of pure chance association is low.

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