A large family with patent ductus arteriosus and unusual face

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Abstract

A large family is described in which patent ductus arteriosus in association with an unusual facial appearance affected nine family members in three generations. The segregation pattern suggests autosomal dominant inheritance with incomplete penetrance with respect to the PDA. The facial features included a broad, high forehead, flat profile, and short nose with a broad, flattened tip.

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Persistent patency of the ductus arteriosus (PDA) affects approximately 1 in 2000 newborn infants and accounts for between 5 and 10% of congenital heart defects in mature infants. As with other congenital heart defects familial instances of PDA are well documented. Rarely, the pattern of inheritance is compatible with a single defective gene causing PDA but most cases are sporadic and the empiric recurrence risk is only 2.5%.¹ In those instances where a single gene has been suspected the inheritance pattern has been interpreted in some families as showing autosomal

dominant²⁻⁴ and in others autosomal recessive inheritance.⁵ In the family described here, PDA in association with an unusual facial appearance affects nine relatives. The segregation pattern is compatible with inheritance as an autosomal dominant trait.

Case report

The proband, V.10, was noted to have a murmur at a few days of age, and had several chest infections during infancy. Initially, a pansystolic murmur was heard and this later became continuous, with collapsing pulses and hepatomegaly. Patent ductus arteriosus was diagnosed and a large, 1 cm ductus was ligated at 9 months of age. Two of the proband's three sibs had also had surgical repair of PDA, and this family history of PDA prompted us to examine the case notes of other family members and to interview and examine as many of the relatives as possible (fig 1).

The oldest sib, V.7, was found to be bradycardic at birth with alternating second and third degree heart block on ECG, but she appeared to thrive initially. A quiet systolic murmur noted at 1 year of age was continuous

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Figure 1 Family pedigree.

by the age of 2, and cardiac catheterisation at 3 years of age confirmed the presence of a PDA which was ligated shortly thereafter. The duct was noted to be large (1 cm) at operation. She remained well until 5½ years of age when her mother complained that she was breathless and blue on exercise; this resolved with the insertion of a DDD pacemaker.

V-8 is asymptomatic and normal on examination: she has never been noted to have a murmur. V-9 had a murmur detected at 14 months of age. She previously suffered from frequent upper respiratory infections. She had full volume pulses with a loud pulmonary component of the second heart sound, a continuous murmur, and mild cardiomegaly. Echocardiograph confirmed the clinical diagnosis of PDA and a large, 1 cm ductus was found at operation two years later.

Their mother, IV-3, was noted to have a murmur at 1 month of age. She had several chest infections during childhood. At 4 years of age she had a collapsing pulse, accentuation of the pulmonary component of the second heart sound with a continuous machinery murmur and systolic thrill, and had a 'larger than average' PDA ligated.

This patient's mother, III-18, has no history of a PDA ligation or murmur and is normal on clinical examination. Her sister (III-24), however, was asymptomatic during childhood but a routine medical check at 17 years of age indicated a murmur. As she did not attend for further investigation, nothing further was done until her pregnancy three years later when clinical examination suggested a PDA.

At the age of 39, she remains asymptomatic but has collapsing pulses, a heaving apex beat which is displaced 2 cm laterally, and a loud, continuous murmur accompanied by a systolic thrill maximal over the pulmonary area. She continues to refuse any further investigation.

Her brother, III-25, was lost to follow up after a murmur had been noted during childhood. At the age of 21 he presented again with a six month history of tiredness and palpitations. A machinery murmur was noted over the left sternal edge and a short, wide PDA with an aneurysmal base on the aorta was found at operation soon after.

This man's daughter, IV-27, had no symptoms at routine examination aged 19 months when the characteristic murmur of a PDA was heard. She remained well and an average sized PDA was ligated at operation at 5 years of age.

She now has two children. V-18 presented at the age of 3 months with vomiting, poor weight gain, and dyspnoea during feeds and was found to have heart failure with a triple rhythm, 4 cm liver, and a loud pansystolic murmur. Echocardiograph showed a PDA. He was treated to good effect with diuretics and operated on two weeks later. V-19 was transferred from the maternity hospital for an echocardiograph at 10 days of age in view of the family history and the presence of a loud, pansystolic murmur. This showed a small, muscular ventricular septal defect. She has remained well and is now normal on examination at 10 months of age.

A second cousin of these children's mother, IV-1, was also found to have a PDA. During a

Figure 2 Family members who have a PDA. (A) and (B) III-24. (C) from left to right, V-8 (unaffected), V-7, V-10, and V-9. (D) IV-27 with V-19 on the left and V-18.

chest infection at 2 months of age a loud, continuous murmur with a thrill over the pulmonary artery was heard. A moderately sized PDA was ligated at 4 years of age.

All of the affected subjects have growth parameters, developmental milestones, and intelligence within the normal ranges. One of them, IV-3, has had her chromosomes checked and these showed a normal female karyotype. However, family members who have the PDA have in common certain facial features including a flat profile, high forehead, and a short nose with a broad, flattened tip (fig 2).

Where relatives with the PDA were not available to be examined in person, photographs were examined to confirm the facial similarity. Similar features are also present in other family members who are normal on clinical examination but who are obligate gene carriers (fig 3).

Discussion

At least nine persons in three generations of this family have had a PDA. The diagnosis has been confirmed at operation in all but one patient, a woman with typical signs who refuses further investigation. Two more relatives are thought by the family to have been affected but we have been unable to trace their

hospital records to confirm this. In this family, the PDA segregates with an unusual facial appearance and is inherited as an autosomal dominant trait.

The syndrome shows incomplete penetrance with regard to the patent ductus as four adults who have the facial features have no clinical signs or history of PDA although they must have transmitted the gene to their affected offspring (II-1, III-1, II-7, III-18). However, spontaneous closure of an asymptomatic duct, which occurs in up to 20% of ducts by the age of 60,⁶ cannot be excluded. The importance of the facial features is recognised by the family themselves who are able to select from the younger relatives those who have not had a PDA but who resemble those who have and so may have an increased chance of having an affected child themselves (IV-8 and IV-29).

In this family, the ducts tended to be short and wide. This feature has been commented on in previous reports of familial PDA, and the presence of such a duct was thought to increase the risk to the offspring of an affected subject in the large study by Zetterqvist.¹ The associated facial appearance has not been noted previously, but it could easily be overlooked. There have been two families reported with an association of PDA and specific facial appearance but these families in addition have learning difficulties, strabismus, ptosis, and patulous lips, and loss of the distal interphalangeal crease in the fingers and toes.^{7,8} Some of the affected members of this family have fifth finger clinodactyly but this is not a consistent finding and is also seen in others without the PDA or facial features.

I suggest that, especially if there is evidence of an unusually short, wide PDA, the facial morphology of the patient and parents be examined closely before estimating the recurrence risk for the cardiac defect.

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Figure 3 Family members with no evidence of PDA but who are obligate gene carriers and share the facial features. (A) and (B) III-18, (C) and (D) II-7.