

# Anomalous right pulmonary artery origins in association with the fetal valproate syndrome

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## Abstract

**Two cases are reported of fetal valproate syndrome in association with anomalous right pulmonary artery origin. Both diagnoses were confirmed following cardiac catheterisation as echocardiography alone was inadequate to define the anatomy. Anomalous right pulmonary artery origin is extremely rare making a chance association with fetal valproate syndrome very unlikely. We recommend that anomalous pulmonary artery origin is borne in mind in patients with valproate syndrome undergoing cardiac assessment, particularly as this may be a difficult diagnosis to make on echocardiography.**

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The incidence of both major and minor congenital abnormalities is increased among infants of mothers with epilepsy compared with the general population.<sup>1</sup> This could be the result of maternal seizures leading to periods of hypoxia during pregnancy, intrinsic maternal factors leading to an inherited predisposition to malformations, and teratogenic effects of anticonvulsants.<sup>2</sup> It is now recognised that there is a specific fetal syndrome associated with maternal valproate use, comprising typical dysmorphic features and often involving major organ system anomalies.<sup>2-8</sup>

We describe two infants born to mothers who were treated with sodium valproate monotherapy throughout pregnancy. They had typical features of fetal valproate syndrome and both had rare abnormalities of pulmonary artery origin.

## Case reports

### CASE 1

A male infant presented at the age of 1 week with dusky spells and poor feeding. He was also noted to have a cardiac murmur. He was born to a family in which epilepsy was very predominant; his mother, her father, and two cousins were affected. His mother was treated with sodium valproate throughout pregnancy at a dose of 1.4 g daily. The birth had been uneventful; he was born by normal vaginal delivery at term with a birth weight of 3340 g.

He had dysmorphic features typical of fetal valproate syndrome. These consisted of a high, prominent forehead with midline bossing, upturned nose, low set ears with a straight upper helical border, large eyes, large, wide fontanelles, and small feet with prominent balls and heels. Subsequent investigations included

chest radiography showing a right oligoemic lung, electrocardiography indicating right ventricular hypertrophy and right axis deviation, and echocardiography showing situs solitus, right ventricular hypertrophy, and that the origin of the right pulmonary artery could not be defined. Cardiac catheterisation showed that the right pulmonary artery was disconnected from the main pulmonary artery and was fed by small collateral vessels from the descending aorta. The left pulmonary artery was anatomically normal but had suprasystemic pressure within it. There was also a large patent ductus arteriosus. Karyotype was normal 46,XY.

At the age of 2½ months he underwent reconstructive surgery to reconnect the right pulmonary artery to the main pulmonary artery and to ligate the PDA. Following the operation, clinical improvement was seen and radiologically there was reperfusion of the right lung. Echocardiography confirmed resolution of the pulmonary hypertension. He unfortunately died two months later of unrelated causes.

### CASE 2

A male infant was born at 38 weeks' gestation to a mother taking 1 g sodium valproate daily throughout pregnancy. The birth was normal and birth weight was 2700 g. He presented at the age of 20 days with poor feeding and associated breathlessness. He had a cluster of dysmorphic features, including flat nasal bridge, short nose and anteverted nares, long, shallow philtrum, antimongoloid slant to the palpebral fissures, and downturned angles of the mouth, which confirmed fetal valproate syndrome. He also had bilateral talipes equinovarus, microcephaly, dysplastic proximal phalanges of the index fingers, and unusual bilateral iris defects. Cardiovascular examination showed a systolic murmur and he was clinically in cardiac failure. Chest radiography showed pulmonary plethora, more pronounced on the right. ECG showed inferior QRS complex abnormalities and biventricular voltage increase. Echocardiography showed moderately severe tricuspid regurgitation indicating high pulmonary pressure, the left pulmonary artery arising normally from the main pulmonary artery but the right pulmonary artery arising directly from the aorta (hemitruncus). The pulmonary valve itself appeared dysplastic and stenosed; there was gross right ventricular hypertrophy. These findings were confirmed at cardiac catheterisation (fig 1). This infant also had a normal 46,XY karyotype.

Initially control of heart failure was achieved through diuretics and then at the age of 2 months he underwent surgery to relieve the

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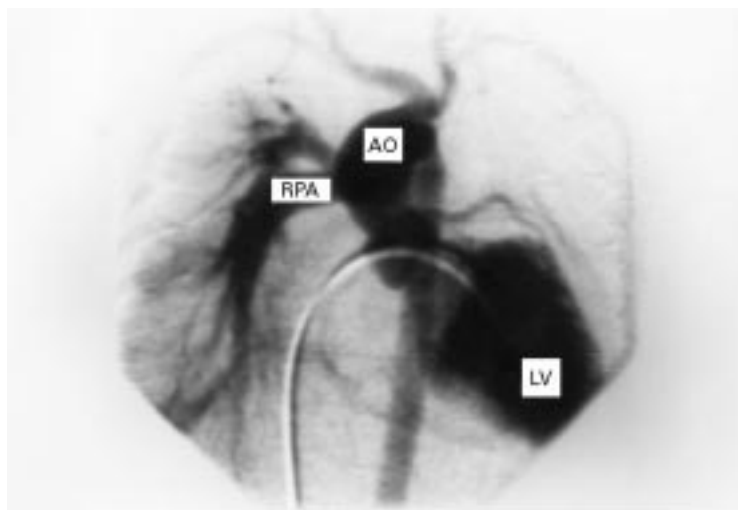


Figure 1 Cineangiogram showing left ventricular injection in case 2. The right pulmonary artery is clearly seen arising from the ascending aorta (hemitruncus). RPA=right pulmonary artery. AO=aorta. LV=left ventricle.

right ventricular outflow tract obstruction and reconstruct a normal origin of the right pulmonary artery. The operation was successful, thus re-establishing blood flow from the main pulmonary artery to the right lung.

This patient died aged 2 years 4 months from complications arising from severe restenosis of his right pulmonary artery and resulting congestive cardiac failure.

### Discussion

Fetal valproate syndrome is characterised by typical facial features including a tall, narrow forehead, epicanthic folds, infraorbital groove, medial deficiency of the eyebrows, flat nasal bridge, broad nasal root, anteverted nares, shallow philtrum, long upper lip with thin vermilion border, thick lower lip, and small downturned mouth,<sup>2</sup> and major anomalies are not uncommonly associated. The most frequently found major malformations are neural tube defects, congenital heart disease, oral clefts, genital abnormalities, and limb abnormalities; to date most attention has been focused on neural tube defects.

Cardiovascular anomalies have been reported in a significant proportion of cases of fetal valproate syndrome; the incidence overall seems to be about four times that expected in the general population. Fetal valproate syndrome has not been associated with any specific heart defect or group of defects, and reports to date have documented ventricular septal defects, patent ductus arteriosus, coarctation of the aorta, left hypoplastic heart, pulmonary valve stenosis, dysrhythmias, and ECG abnormalities.

The pulmonary artery defects reported here are extremely rare and the finding of two cases

of fetal valproate syndrome with such defects implies that a chance association is extremely unlikely. It can be very difficult to make the diagnosis of such defects on echocardiography alone.<sup>9</sup> We recommend that the possibility of abnormal pulmonary artery origin should be borne in mind when babies with the fetal valproate syndrome undergo cardiac assessment. Perhaps also a detailed fetal echocardiogram should be offered to women on valproate therapy who are pregnant, as there is a definite increased risk of cardiac defects, including complex ones as described in this report. This may allow earlier diagnosis and therefore pre-empt the deleterious effect of the abnormality in postnatal life.

The finding of specific cardiac defects in association with fetal valproate syndrome also suggests it has defined effects on the developing embryo. Both pulmonary and aortic outflow tracts are formed from the primitive branchial arches and are largely derived from migrated neural crest cells. Recent studies have shown that ablation of the migratory neural crest can produce specific cardiac defects in chick embryos,<sup>10</sup> comparable to the defects described in this report. The branchial arch syndromes, such as DiGeorge and Goldenhar syndromes, are all associated with similar cardiac defects involving the outflow tracts. Perhaps these conditions and fetal valproate syndrome share a common mechanism of disordered neural crest migration, though they may vary in their aetiologies.<sup>11</sup> Future research may give further understanding of this disease process and the way in which valproate affects the fetus in other systems.

- 1 Dieterich E, Steveling A, Lukas A, *et al.* Congenital anomalies in children of epileptic mothers and fathers. *Neuropediatrics* 1980;11:274-83.
- 2 Clayton-Smith J, Donnai D. Fetal valproate syndrome. *J Med Genet* 1995;32:724-7.
- 3 Jager-Roman E, Deichl A, Jakob S, *et al.* Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. *J Pediatr* 1986;108:997-1004.
- 4 DiLiberti JH, Farndon D, Dennis NR, *et al.* The fetal valproate syndrome. *Am J Med Genet* 1984;19:473-81.
- 5 Ardinger HH, Atkin JF, Blackston D, *et al.* Verification of the fetal valproate syndrome phenotype. *Am J Med Genet* 1988;29:171-85.
- 6 Martínez-Frias ML. Clinical manifestation of prenatal exposure to valproic acid using case reports and epidemiologic information. *Am J Med Genet* 1990;37:277-82.
- 7 Dravet C, Julian C, Legras C, *et al.* Epilepsy, antiepileptic drugs, and malformations in children of women with epilepsy: a French prospective cohort study. *Neurology* 1992;42(suppl 5):75-82.
- 8 Thisted E, Ebbeson F. Malformations, withdrawal manifestations, and hypoglycaemia after exposure to valproate in utero. *Arch Dis Child* 1993;69:288-91.
- 9 Kim TK, Choe YH, Kim HS, *et al.* Anomalous origin of the right pulmonary artery from the ascending aorta: diagnosis by magnetic resonance imaging. *Cardiovasc Intervent Radiol* 1995;18:118-21.
- 10 Kirby ML, Gale TF, Stewart DE, *et al.* Neural crest cells contribute to normal aorticopulmonary septation. *Science* 1983;220:1059-61.
- 11 Clark EB. Cardiac embryology. Its relevance to congenital heart disease. *Am J Dis Child* 1986;140:41-4.