ORIGINAL ARTICLE

Congenital heart disease and neuroblastoma: just coincidence?

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The clinical history of a neonate with simple transposition of the great arteries in whom a metastatic neuroblastoma was diagnosed incidentally at autopsy is described, and the literature containing all 66 previously reported cases of neuroblastoma associated with congenital cardiac malformations is reviewed. One third of the described cases were classified as in situ neuroblastoma; neural crest derived cardiac lesions were present in 31%. Several possible aetiological mechanisms are discussed, and we conclude that the association of neuroblastoma with congenital cardiac malformations is multifactorial in origin. The described case represents the first reported example in which catecholamine release may have contributed to the fatal outcome of definitive congenital cardiac surgery.

The association between congenital heart disease and neuroblastoma has been well described, with different theories put forward to explain a possible underlying fetal origin of this relation.^{1–4} However, many of these “congenital” cases have been classified as in situ neuroblastomas, and some authors believe that this represents a different entity to clinically apparent neuroblastoma—possibly not even a malignant disease.¹ We provide further documentation of this relation by reporting a neonate, in whom an adrenal neuroblastoma with hepatic metastases was present in a case of transposition of the great arteries, and possibly contributed to the intraoperative death of the patient.

CASE REPORT

A term female infant was born at home by normal delivery after an uneventful pregnancy to non-consanguineous parents with no relevant family history. Birth weight was 4.12 kg. She was noted to be cyanosed at birth, and a nitrogen wash-out test at the local hospital failed to improve the saturation above 85%. She was commenced on prostaglandin E2 and transferred to a tertiary centre for further investigation and treatment.

On examination she looked well, but centrally cyanosed with a saturation of 60% in air. The skin looked unremarkable; nodular changes were not present. Peripheral pulses and heart sounds were normal with a soft systolic murmur. The patient's heart rate and blood pressure were in the high normal range (heart rate 160–180 beats/min; right arm 87–99/45–68, mean 54–74) and remained so throughout the preoperative period. The electrocardiogram and chest x ray were normal for age. An abdominal ultrasound scan was not performed. Echocardiography revealed usual atrial arrangement with atrioventricular concordance and ventriculoarterial discordance. A 3 mm patent oval foramen was present with an intact ventricular septum and four normal valves. There was a large patent arterial duct with bidirectional flow across it. The coronary arteries appeared normal.

Surgical correction with the arterial switch procedure was undertaken two days later using the Lecompte manoeuvre (bypass time 116 minutes, cross clamp time 53 minutes) and without prior atrial septostomy. Other than a double orifice of the left coronary artery, there were no unusual anatomical features, and following surgical correction the child was

weaned off cardiopulmonary bypass. Although initially ventricular contraction was good, a dark discolouration soon developed over the right ventricle with ST segment elevation in the inferior leads. Cardiopulmonary bypass was reinstituted, cardioplegia readministered, and the left coronary ostium was detached and reanastomosed. Bypass was then discontinued after 94 minutes (cross clamp 42 minutes), using mild inotropic support of adrenaline and noradrenaline at 0.03–0.06 µg/kg/min and enoximone 5 µg/kg/min, to establish an average systolic arterial pressure of 55 mm Hg. After several hours of stability, chest closure was attempted using large stents, but was interrupted by intractable ventricular fibrillation. Bypass was reinstituted but there was no return of cardiac output on subsequently removing her from the circuit. She was certified dead on the operating table.

Postmortem examination revealed repaired transposition of the great arteries with all anastomoses intact, including no evident distortion or kinking of the coronary arteries. There was haemorrhage into the right ventricular myocardium with possible focal subendocardial necrosis, as well as petechial haemorrhages on the face, lungs, bowel, and adrenals; multiple small intravascular thrombi in the lungs and brain and stress changes in the thymus and adrenals. As an incidental finding there was a unilateral adrenal neuroblastoma (diameter 0.7 cm) with multiple hepatic metastases (NSE positive, LCA negative). Cytogenetics revealed a normal female karyotype. There were no other associated anomalies found and a skeletal survey was normal.

DISCUSSION

To our knowledge, this is only the third confirmed case of congenital metastatic stage 4 or 4S neuroblastoma in conjunction with congenital heart disease, and the first case in which the neuroblastoma may have contributed to the fatal outcome.^{5–6} To date 67 cases of neuroblastoma with congenital heart disease have been reported (table 1), the diagnosis being established at postmortem examination in 31 cases.

In situ neuroblastomas

These have been defined as a “group of minute, incidentally encountered tumours” which are “cytologically identical with typical malignant neuroblastoma, but are rendered distinctive by their microscopic size, and by the absence of demonstrable

Table 1 Reported cases of neuroblastoma and in situ neuroblastoma classified by main associated cardiovascular anomaly, including the current case

Neuroblastomas: dominant associated cardiac malformation	Total	In situ	
		No	Yes
Persistent arterial duct	9	5	4
Transposition of the great arteries	8	4	3
Ventricular septal defect	8	3	3
Hypoplastic left heart syndrome/mitral atresia	5	2	3
Tetralogy of Fallot/pulmonary atresia	6	3	2
Aortic stenosis/bicuspid aortic valve	4	1	2
Coarctation of aorta	4	3	1
Anomaly of aortic arch/vascular ring	3	1	2
Pulmonary valvar stenosis	2	2	0
Cor triatriatum	2	0	0
Atrial septal defect	2	0	1
Atrioventricular septal defect	2	1	0
Complex cardiac malformations	5	2	3
Unclassified and others	7	6	1
Total	67	33	25
Total neural crest derived anomalies	21	10	9

metastases".¹ They were found in 25 (37%) of the 67 described cases (table 2), in all of whom the diagnosis was made incidentally at postmortem examination in early infancy. Estimated incidence varies between 1 in 10 and 1 in 500 post-mortem examinations^{1-3,7}—up to 40 times that of clinically apparent neuroblastoma.^{8,9} The clinical significance and natural history of these tumours is poorly understood. They may

represent a non-neoplastic lesion, such as a transient fetal cell rest ("developmental remnant"), which spontaneously regresses, possibly with selective distribution to children dying in infancy because of significant associated congenital malformations.^{1-10,11} It is well established that neuroblastomas and other embryomas often regress, even in the presence of metastases, especially when first clinically apparent in early infancy.³

Neuroblastoma and congenital heart disease

This relation remains unclear. It is supported by several authors, especially with respect to neuroblastoma in situ,^{1,12} but discounted by others.^{5,13} These conflicting data partly relate to differences in study design and observer bias of the involved pathologists, as not every postmortem examination includes a thorough investigation of the adrenal gland.^{6,14} Several theories have been put forward to explain this association and its timing.

A fetal origin of the neuroblastomas was clearly apparent in four cases: three electively terminated fetuses at 18, 20, and 22 weeks gestation in which a ventricular septal defect, hypoplastic left heart syndrome, and complete atrioventricular septal defect were coexisting, respectively, with neuroblastoma; and a case of mitral atresia with double outlet right ventricle, found on antenatal sonography together with a postnatally confirmed neuroblastoma.¹⁵⁻¹⁸ In the UK only 33 neonates were identified with neonatal neuroblastoma between 1986 and 1994, most of whom had stage 4S disease, as in the present case.¹⁹ A fetal origin appears to be almost certain in 21 (32%) of the 67 described cases (including the present case), given that the diagnosis was made within the neonatal

Table 2 Reported cases of neuroblastoma and in situ neuroblastoma associated with congenital heart defects with age of diagnosis

First author	Total	In situ neuroblastoma					
		Yes			No		
		Diagnosis			Diagnosis		
		Total	Fetal	<1 mth*	Total	Fetal	<1 mth*
Beckwith ¹	8	7	—	5	1	—	—
Russell†	1	1	—	1	—	—	—
Bellah ²	3	—	—	—	3	—	1
Miller ³	8	—	—	—	9	—	1
Fischer ⁴	1	—	—	—	1	—	1
Shanklin ⁷	10	7	—	4	3	—	—
Mittelbach‡	1	—	—	—	1	—	—
Evans‡	1	—	—	—	1	—	—
Bulmer‡	1	—	—	—	1	—	—
Chatten ¹⁰	2	1	—	1	1	—	1
Wells ¹¹	1	1	—	1	—	—	—
De la Monte ¹²	7	—	—	—	—	—	—
Berry ¹³	6	4	—	—	2	—	—
Fryns ¹⁵	1	—	1	—	—	—	—
Kapur ¹⁶	1	—	—	—	1	1	—
Herman ¹⁷	1	—	—	—	1	—	1
Qureshi ¹⁸	1	1	1	—	—	—	—
Rosti ²²	1	—	—	—	1	—	—
Patrone ²³	1	—	—	—	1	—	1
McElhinney ²⁴	1	—	—	—	1	—	—
Friedman ²⁵	4	—	—	—	2	—	—
Voisin ²⁸	1	—	—	—	1	—	—
Reisman ³³	1	1	—	—	—	—	—
Barbet ³⁴	1	—	—	—	1	—	—
Medart ³⁵	1	1	—	—	—	—	—
Current case	1	—	—	—	1	—	1
Total	67	24	2	12	33	1	7

*First diagnosed at less than 1 month of age.

†Cited in Beckwith and Perrin.¹

‡Cited in Sy and Edmonson.⁸

period (table 2). The presence of associated non-cardiovascular congenital anomalies in 21 (31%) of the 67 cases may also support a fetal origin, which is consistent with a report by Kobayashi *et al* who identified coexistent congenital malformations in 35% of childhood neuroblastomas.²⁰

Neuroblastomas and other neuroblastic tumours are derived from cells of the neural crest, an early and transient developmental structure. Changes within the "cardiac neural crest" have been implicated in a wide variety of congenital heart lesions, from inflow lesions (tricuspid atresia, double inlet left ventricle) to outflow anomalies (tetralogy of Fallot, transposition of the great arteries, double outlet right ventricle, common arterial trunk) and aortic arch lesions (interrupted aortic arch, double aortic arch), as well as non-cardiovascular anomalies of thymus, thyroid, and parathyroid gland.⁴⁻²¹ Neurocristopathies with maldevelopment and/or abnormal migration of neural crest cells might therefore be an underlying mechanism which could contribute to the coexistence of congenital cardiovascular malformations and neuroblastoma.^{2-3, 22} Of the 65 patients with neuroblastoma and cardiovascular malformations, 21 (31%) had neural crest derived cardiovascular anomalies (table 1), which is more then expected when considering the normal distribution of congenital heart disease.

Another possible explanation for the fetal origin and association of neuroblastoma and cardiovascular malformations was given by Chatten and Voorhess using the "2-hit" theory of carcinogenesis.^{9, 10} They proposed that a first prezygotic mutational event might lead to an expression of a cardiovascular anomaly (teratogenesis) as well as forming the basis for later development of neuroblastoma after a second postzygotic mutational event (carcinogenesis).^{3, 9}

Several underlying genetic factors have been suggested in the aetiology of neuroblastoma, such as dominant inheritance with variable penetrance, while some affected families with neuroblastoma and congenital heart lesions may not be identified because of non-clinical in situ lesions.¹⁰ Other possible mechanisms include the spontaneous mutation of lethal genes or the combined effect of genes controlling the neural crest development.¹⁰ To date, however, the combination with neuroblastoma has only been reported in gene defects which were felt to be incidental, for example, translocation 3;10,¹⁸ 8p trisomy,¹⁵ or 22q11 deletion.²³ Most cases in which cytogenetic investigations were performed revealed a normal karyotype without associated anomalies or microdeletions. Only one familial case has been described with four of five siblings having neuroblastoma, two of whom had congenital heart disease.¹⁰

It has been suggested that cyanotic cardiovascular lesions with chronic hypoxia may create an anoxic stimulus for neural crest derived primitive adrenal medullary cells of the sympathetic nervous system to persist^{7, 10, 12} with a "compensatory increase in cellular proliferation which may become autonomous and thereby give rise to neoplasia".¹² Twenty three of the 67 cases (34%) had cyanotic anomalies. However, the early neonatal diagnosis of neuroblastoma in some cases makes chronic hypoxia as a sole aetiological factor unlikely.^{6, 11, 24}

Neuroblastoma and arrhythmias

An uncommon feature of this case was the sudden development of therapy resistant ventricular fibrillation, particularly given intact coronary anastomoses. Excessive secretion of adrenaline and noradrenaline leading to hypertension, worsening heart failure, and other features of hyper-adrenalism are well described complications of neuroblastomas.²⁵⁻²⁷ In a case of tetralogy of Fallot, catecholamine excess was believed to have contributed to early "decompensation" by infundibular spasm.²⁸ Although tachyarrhythmias are not a common documented feature of this catecholamine excess they may have contributed to the fatal

outcome in the current case. Relevant case reports include: a patient with catecholamine induced cardiomyopathy which resolved on removal of a coexistent neuroblastoma²⁷; a 15 year old patient with recurrent episodes of ventricular tachycardia and fibrillation linked to neuroblastoma mediated catecholamine release²⁹; and fatal supraventricular tachycardias in a child with Costello syndrome and neuroblastoma.³⁰ Although increased urinary catecholamines have been reported to be associated with a poorer prognosis in neuroblastoma, this seems mainly related to the fact that higher levels also correlate with larger tumour mass and advanced tumour stage.^{31, 32} Nevertheless, it remains possible that a sudden surge of catecholamines in the present case may have contributed to the occurrence of severe ventricular fibrillation, although the substrate of transitory myocardial damage caused by the coronary arterial problems, deep hypothermic cardiac arrest, and prolonged cardiopulmonary bypass remain dominant as aetiological factors giving rise to the fatal outcome.

In summary, the coexistence of neuroblastoma and congenital cardiovascular malformations appears to be multifactorial in origin, and further pathological and embryological studies remain necessary to define this relation. Although it is important to be aware of this association, especially when undertaking non-cardiac investigations such as abdominal ultrasound scans, the rarity of this finding mitigates against routine screening of all infants requiring cardiac surgery. Nevertheless, if a postmortem examination is performed for a death in early childhood associated with congenital heart disease, care should be taken to look for microscopic and macroscopic evidence of this rare associated anomaly.

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