Case Report

Congenital Neuroblastoma and Congenital Heart Disease

Therese MW Ibrahim1*, Gusztav Belteki1, Martin Richardson2, Wilf Kelsall1

1Neonatal Intensive Care Unit, Cambridge University Hospitals NHS Foundation Trust, United Kingdom  
2Peterborough University Hospital, Peterborough, United Kingdom

Abstract

Introduction: The association of neuroblastoma and congenital heart disease might have clinical consequences and cardiac screening might be required for all patients diagnosed with neuroblastoma for further management.

Presentation of case: We report a case of a neonate, who presented to the paediatrics assessment unit with severe abdominal distension, on examination massive hepatomegaly and splenomegaly were noted and a heart murmur was detected. He was admitted to the paediatric department and the laboratory results showed high levels of urinary catecholamines and their metabolites including homovanillic acid (HVA) and vanillylmandelic acid (VMA). The radiology services were involved and he diagnosed with metastatic adrenal neuroblastoma stage 4S. An echocardiography (ECHO) was performed and showed valvular pulmonary stenosis. He was referred to the oncology department, and made a good recovery following an intensive course of chemotherapy.

Conclusion: This case is of particular interest because of the co-existence of congenital neuroblastoma and congenital heart disease is rare, our case provides further evidence for this association and to review the literature concerning this unusual but clinically significant relationship which might require further investigations and echocardiography might be required for all patients with congenital neuroblastoma.

Keywords: Congenital neuroblastoma; Cathecholamines; congenital heart disease; echocardiography; valvular pulmonary stenosis

Peer Reviewer: Soyeun Park, PhD, College of Pharmacy, Keimyung University, Republic of Korea; Hosni Khairy Salem, MD, Department of Urology, Cairo University, Egypt

Received: November 11, 2013; Accepted: February 3, 2014; Published: February 13, 2014

Competing Interests: The authors have declared that no competing interests exist.

Consent: We confirm that the patient has given their informed consent for the case report to be published.

Copyright: 2013 Ibrahim TMW et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

*Correspondence to: Therese MW Ibrahim, Neonatal Intensive Care Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 0QQ, United Kingdom  
Email: theresmarywilliam@yahoo.com
Introduction

The association of neuroblastoma and congenital heart disease might have clinical consequences and cardiac screening might be required for all patients diagnosed with neuroblastoma for further management [1, 2].

Case presentation

A three-week-old male infant presented with abdominal distension and a history of failure to thrive. He was born at 38 weeks gestation to non-consanguineous parents, following an uneventful pregnancy. On examination, his head circumference, weight and length were in the 0.4th percentile. Both heart rate and blood pressure were in the high normal range. His peripheral pulses were normal and his heart sounds were normal with a soft systolic ejection murmur on the left upper sternal edge, radiating to his back. He was noted to have marked abdominal distension and abdominal palpation indicated massive hepatomegaly and splenomegaly. There was no evidence of skin lesions. Other systems were normal.

Investigations

A diagnosis of adrenal neuroblastoma, stage 4S, was made based on the following investigations: The laboratory results showed high levels of urinary catecholamines and their metabolites including homovanillic acid (HVA) and vanillylmandelic acid (VMA). Abdominal ultrasound (US) showed hepatomegaly with echogenic areas (Fig. 1) and a left suprarenal mass of 1.6 cm diameter. Computed tomography (CT) of the abdomen revealed hepatosplenomegaly and evidence of soft tissue encasing the coeliac axis and superior mesenteric artery (Fig. 2). CT of the head was normal. The meta-iodobenzylguanidine (MIBG) scan showed a focal increase in tracer activity uptake in the left adrenal gland, consistent with the site of tumour mass; uptake elsewhere was within physiological limits. Liver biopsy showed marked parenchymal destruction with nodules of necrotic hepatocytes; there was biliary reaction with neo-ductular proliferation and cholestasis. There was no evidence of N-myc amplification. Bone marrow trephine biopsy showed no evidence of metastatic neuroblastoma within the bone marrow.

At 3 months of age he was referred to a paediatrician with expertise in cardiology. Echocardiography showed moderate valvular pulmonary stenosis with a maximum velocity of 3.5m/s. There was no evidence of right ventricular hypertrophy and right heart dilatation.

Treatment

The child was referred to the oncology department in the tertiary centre and commenced an intensive course of chemotherapy. He responded well and made a good recovery following a long stay in the paediatric intensive care unit. Subsequent abdominal US showed that the left adrenal mass had disappeared. His liver had decreased in size, though a heterogenous echotexture persisted. Subsequent Echocardiography scans over the first year of life have remained unchanged. He remains under regular review as balloon dilatation of the pulmonary valve might be required in the future.
Discussion

The association of neuroblastoma with congenital cardiac malformations is rare and to date, 67 cases of neuroblastoma associated with congenital heart disease have been reported [3]. The exact nature of this association is still uncertain.

Neonatal tumours are rare and comprise 2% of all paediatric malignant tumours. The neonatal malignancies include neuroblastoma (47%), retinoblastoma (17%), soft tissue sarcoma (12%), central nervous system tumours (9%) and leukaemia (8%). Neuroblastoma is the most common type of neonatal tumour.

Neonatal neuroblastoma originates from neural crest cells of the adrenal medulla and can metastasize in utero. The majority of congenital neuroblastoma (34%) had metastatic disease (stage 4S) [4], it comprises as a small primary tumour and metastatic disease confined to the liver, skin, and bone marrow. The most common site of distant metastases is the foetal liver; other sites include the placenta, the retroperitoneal nodes, bone, skin, and the umbilical cord. Pulmonary and brain metastases are uncommon. Overall 3-year survival of stage 4S disease is between 71% and 86%, with significant decrements if any negative biological marker (no MYCN amplification) [5].

Developmental abnormalities of the cardiac neural crest have been implicated in a subset of congenital heart defects. A wide variety of congenital heart lesions have been associated with congenital neuroblastoma, from outflow anomalies (tetralogy of Fallot, transposition of the great arteries, double outlet right ventricle, common arterial trunk) to inflow lesions (tricuspid atresia, double inlet left ventricle) and aortic arch lesions (interrupted aortic arch, double aortic arch) [1, 2].

The association of neuroblastoma with congenital cardiac malformations has been described and is multifactorial in origin. Different theories have been put forward to explain this relationship: 1) Abnormal neural crest development affecting both the cardiac and sympathetic nervous systems 2) hypoxia-induced changes; 3) the ‘2-hit’ theory of carcinogenesis; and 4) the role of genetic factors.

1) Abnormal neural crest developmental affecting both systems

Abnormal development or migration of neural crest cells has been explained as a mechanism that could contribute to the coexistence of congenital cardiovascular malformations and neuroblastoma [6, 7, 1].

Neuroblastomas are derived from cells of the
neural crest. Neural crest cells play an important role in the septation of the outflow tract of the heart and in the formation of the conotruncal part of the ventricular septum. Changes within the cardiac neural crest have been implicated in a wide variety of congenital heart lesions, from inflow lesions to outflow anomalies and aortic arch lesions. Neural crest-derived congenital heart disease has been reported to be more frequent in neuroblastoma patients [2, 3].

2) Hypoxia-induced changes:
Twenty three of the 67 cases (34%) had cyanotic cardiac anomalies. It has been suggested that cyanotic cardiovascular lesions and the resultant chronic hypoxia may stimulate the neural crest derived primitive adrenal medullary cells of the sympathetic nervous system to proliferate. This compensatory increase in cellular proliferation may eventually give rise to neoplasia [8].

3) The ‘two-hit’ theory of carcinogenesis:
It has been proposed that a germ-line (pre-zygotic) mutational event of a tumour suppressor gene might lead to a congenital cardiac malformation (teratogenesis). Loss of the second allele by a post-zygotic mutation may then result in formation of the neuroblastoma (carcinogenesis) [9].

4) Genetics factors
The combination of congenital heart disease and neuroblastoma has been reported in some chromosomal anomalies, for example, translocation 3;10, 8p trisomy, or 22q11 deletion [10,11]. Several underlying genetic factors have been suggested in the aetiology of neuroblastoma, such as dominant inheritance with variable penetrance. Some cases may be related to the new mutations of major susceptibility genes controlling the neural crest development in the affected individual.

**Conclusion**

1. The exact nature of this association is still uncertain and further pathological and embryological studies remain necessary to define this relation. This association might have clinical consequences.

2. If neuroblastoma patients have a higher risk of congenital heart disease (CHD), cardiac screening might be indicated for all neuroblastoma patients. Early detection of CHD could be important for the patient, in terms of choice of anti-cancer treatment and possible need for treatment of the CHD [3].

3. Nevertheless, cardiac patients with cardiomyopathy and recurrent episodes of ventricular tachycardia and fibrillation had been linked to neuroblastoma mediated catecholamine release, and resolved on removal of a coexistent neuroblastoma [12, 13], therefore; urine catecholamines screening might be useful in cardiac patients.

**Acknowledgment**

We are gratefully acknowledging the parents of this child for their consent and allowing us to share his case.

**References**


5. John M. Maris, MD, The Children's Hospital of Philadelphia, Division of Oncology, ARC 902A, 324 South 34th St, Philadelphia, PA 19104-4318