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Co-existence of Neuroblastoma, Congenital Adrenal Hyperplasia and Congenital Heart Disease: A Case Report

Mohammed A[2]*, Fatime UK[1], Farouk ZL[2], Umar IU[2], Shehu UA[2] and Idris MY[3]

[1]Department of Pediatrics, Aminu Kano Teaching Hospital, Kano

[2]Department of Pediatrics, Bayero University, Kano./Aminu Kano Teaching Hospital, Kano

[3]Department of Chemical Pathology, Bayero University, Kano/ Aminu Kano Teaching Hospital, Kano

***Corresponding author:** Dr. Mohammed Abdulsalam, Department of Pediatrics, Bayero University Kano/Aminu Kano Teaching Hospital, Kano, Nigeria, Email: daktamohammed2011@gmail.com

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Abstract

There are various reports on co-existence of neuroblastoma with congenital heart disease, however, the presence of congenital adrenal hyperplasia (CAH) is quite rare especially one presenting with hypertension and hence the need to look out for other anomalies and complications especially adrenocortical defects in patients with neuroblastoma. We report a case of a neonate who presented to our neonatal care unit with respiratory distress. On examination, he had abdominal distension, elevated blood pressure with presence of cardiac murmurs. A provisional diagnosis of Neuroblastoma to rule out congenital adrenal hyperplasia was made. He was admitted into the neonatal care unit and laboratory results showed high levels of urinary catecholamine metabolites homovanillic acid (HVA) and vanillylmandelic acid (VMA) with low cortisol level and high 11-deoxycortisol level. Abdominal ultrasound scan and chest computed tomography showed suprarenal mass and a posterior mediastinal mass respectively. Echocardiogram revealed a small ventricular septal defect (VSD) and a patent ductus arteriosus (PDA). He was reviewed by endocrinologist, cardiologist and oncologist. Blood pressure was controlled with anti-hypertensive with spontaneous closure of both VSD and PDA. Growth has remained steady with no complications on follow up. This is interesting because of the co-existence of neuroblastoma with congenital adrenal hyperplasia and congenital heart disease. We therefore recommend routine blood pressure monitoring in all neonates while patients with neuroblastoma may require further investigations and echocardiogram.

Keywords: Neuroblastoma, Congenital, adrenal hyperplasia, Heart disease, Blood pressure

Abbreviations: CAH: Congenital Adrenal Hyperplasia; HVA: Homovanillic Acid; VMA: Vanillylmandelic Acid; VSD: ventricular septal defect; PDA: Patent Ductus Arteriosus; MIBG: Meta-iodobenzylguanidine.

Introduction

There are various reports on co-existence of neuroblastoma with congenital heart disease however, the presence of congenital adrenal hyperplasia is quite rare especially CAH presenting with hypertension and hence the need to look out for other anomalies and complications especially adrenocortical defects in patients with neuroblastoma [1,2].

Case Report

XY was a two day old male neonate that presented on the second day of life with fast breathing. He was delivered via spontaneous vertex delivery at 38 weeks gestation to non-consanguineous parents following a booked uneventful

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pregnancy. Patient was put breastfeeing within the first hour of life, no history of choking while feeding, no bluish discoloration of lip, tongue, palms or soles of the feet On examination he was in respiratory distress with a respiratory rate of 100 breaths per minute and a peripheral oxygen saturation of 92%. Peripheral pulses were normal with a heart rate of 138 beats per minute, normal heart sounds and a systolic murmur grade 2 in the left upper sternal border, non-radiating. Blood pressure was elevated ranging from 90-110mmHg (right arm) on more than 3 occasions (Stage 2 hypertension). His weight was 3.6kg.

Abdomen was distended with an umbilical hernia, defect measuring 2.5cm reducible, soft with no palpable mass or organ. A provisional diagnosis of neuroblastoma to rule out congenital adrenal hyperplasia with acyanotic congenital heart disease was made. .He was admitted in to our special care baby unit and relevant investigations were carried out as follows Chest X-ray was normal but echocardiogram revealed multiple shunt lesions- atrial septal defect (mm) with a patent ductus arteriosus (mm). Laboratory investigations revealed a highly elevated urinary level of both vanillyl-mandellic acid (VMA) of 31.2umol/l and homo-vanillic acid (HVA) of 56.8umol/l a low serum Cortisol level with an elevated 11-deoxycortisol level for patient's age. Abdominal ultra-sound scan showed a fairly oval hyperechoic mass lesion adjacent to the superior pole of the right adrenal gland measuring 2.49 x 3.16 x 3.78cm in size, no calcifications while computed tomography of the abdomen revealed a huge fairly dome shaped mass in the right posterior mediastinum displacing the ipsilateral diaphragm inferiorly.

He was reviewed subsequently by both paediatric oncologist and endocrinologist. Blood pressure was controlled with nifedipine and propanolol. Steroid treatment with dexamethasone was commenced but discontinued after a month due to worsening of hypertension. Repeat echocardiogram at 6months revealed closure of both ASD and PDA. Repeat abdominopelvic ultrasound at 6months revealed normal study while abdominopelvic MRI showed a well demarcated, pyramidal-shaped, extra-pleural mass in the posterior-inferior aspect of right hemi-thorax measuring 6.5cm x 3.7cm in size suggestive of right-side extra pulmonary lobar sequestration. Repeat urinary VMA and HVA were within normal reference range. He was being followed up at neonatology and endocrinology clinics with regular monitoring of the blood pressure which responded well to nifedipine and dexamethasone. Patient's growth and milestones were also appropriate for age.

Discussion

Neonatal tumours are tumours that occur in the first 28 days of life and are quite rare [2]. Neuroblastoma is the commonest malignancy in the fetal and neonatal period and the second commonest solid tumour of childhood [3-4]. The association of neuroblastoma with congenital heart disease is still not very clear but has being described as multifactorial [5]. The most common site of primary tumour is the adrenal gland followed by retroperitoneal nodes, Para spinal ganglia and posterior mediastinum [3]. Metastasis to other sites is not uncommon especially the liver while other sites commonly involved are, umbilical cord, bones and skin [6]. In this case the primary tumour is in the retroperitoneal region and posterior mediastinum. Commonest presentation is an abdominal mass however can present as respiratory distress when the tumour is located in the chest or with features of paraneoplastic syndrome such as persistent intractable diarrhea, opsoclonus myoclonus syndrome [7]. Severe erythroblastosis, jaundice, hepatosplenomegaly and sepsis may represent distant metastasis [7]. Familial cases occur in 1-2% transmitted in an autosomal dominant fashion with incomplete penetrance via mutation in phox2b and ALK which are involved in the development of the sympathoadrenal lineage and nervous system respectively [3]

Neuroblastoma and Congenital Heart Disease

The co-existence of congenital neuroblastoma with congenital heart disease has been reported by various studies [5,8]. The relation between the two conditions still remains unclear although various theories have being postulated to explain the relation between the two among which are:

1. Abnormal neural crest development: neuroblastomas and other neuroblastic tumours are derived from neural crest cells which also contribute to the development of the outflow tract and conotruncal part of the ventricular septum [5]. Abnormalities with migration or development of neural crest cells has been associated inflow heart lesions (double inlet left ventricle, tricuspid atresia), outflow heart lesions (common arterial trunk, double outlet right ventricle, tetralogy of Fallot, transposition of the great arteries) and aortic arch lesions (interrupted aortic arch, double aortic arch). Neural crest derived congenital heart disease was observed more frequently in patients with congenital neuroblastoma than the normal population [5].
2. The "two-hit" theory of carcinogenesis proposed by Chatten and Voorhess: They proposed that a first prezygotic (germline) mutational event of a tumour suppressor gene may result to the development of a cardiovascular anomaly (teratogenesis) and when a second post zygotic mutational event occurs later due to the loss of the second allele, it results to the development of neuroblastoma (carcinogenesis) [5,8].
3. Hypoxia-induced changes: It has been suggested that

cyanotic cardiovascular lesions which are associated with chronic hypoxia may stimulate the proliferation of neural crest derived primitive adrenal medullary cells of the sympathetic nervous system. This compensatory increase in cellular proliferation may result to a neoplasia [5]. However, the early diagnosis of neuroblastoma in some cases makes this theory unlikely as the solitary cause of neuroblastoma [8].

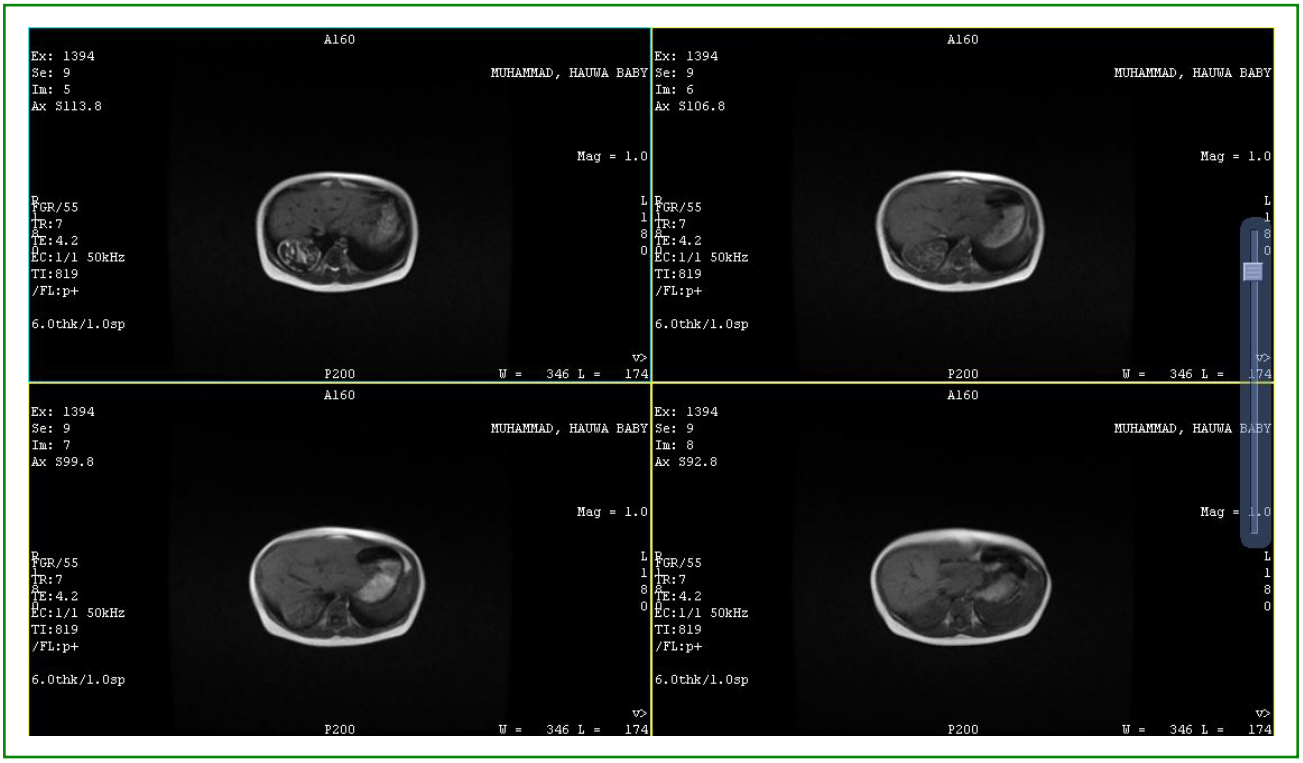
4. Genetic factors: several underlying aetiolgic factors have been suggested in the aetiogenesis of neuroblastoma such as dominant inheritance with variable penetrance. The combination of neuroblastoma with congenital heart disease has been associated with chromosomal abnormalities such as translocation 3; 10, 8p trisomy, 15 or 22q11 deletion or new mutations in genes controlling neural crest development.

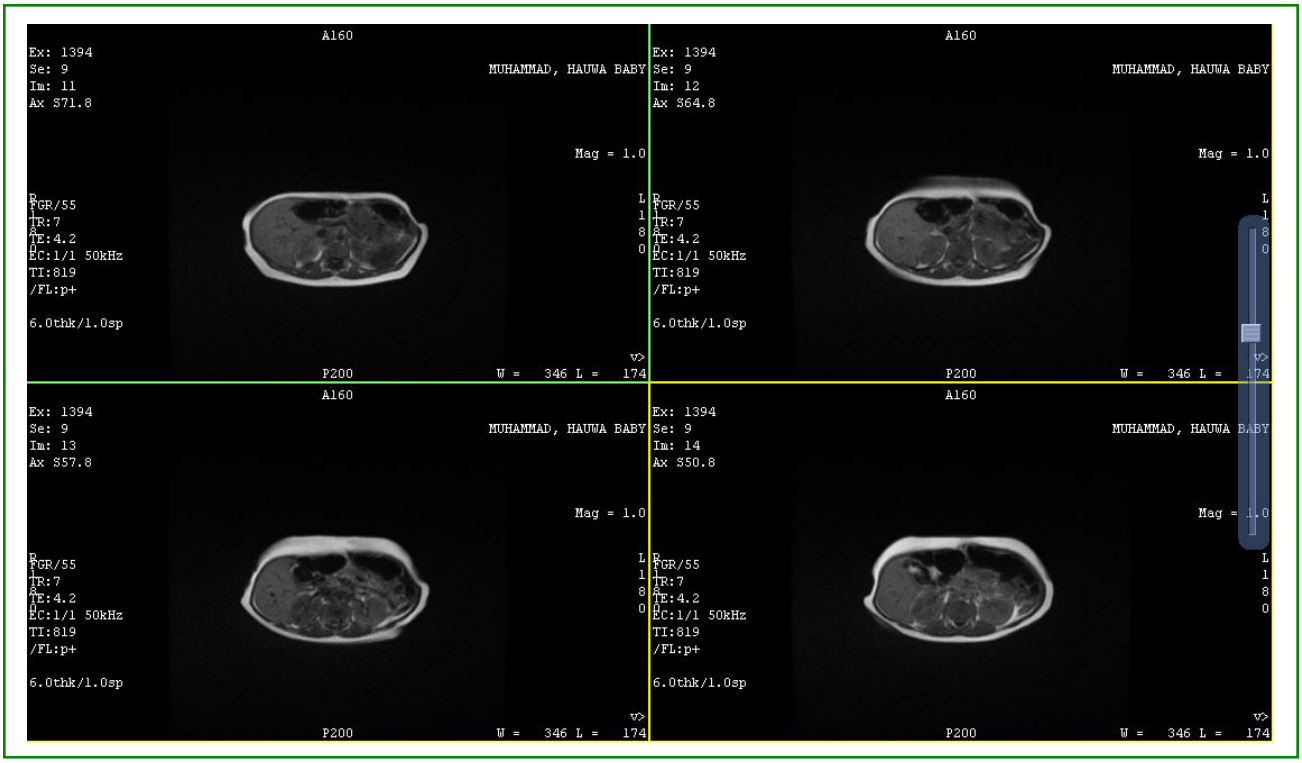
Some studies have however reported that there is no clear evidence of association between the two disease entities and their occurrence may just be a coincidence [9-10].

Neuroblastoma and Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of enzymatic disorders inherited in autosomal recessive disorders resulting from the deficiency of one of the five enzymes required for cortisol production in the adrenal cortex [11]. The commonest type of CAH is the 21-hydroxylase deficiency, accounting for more than 90 percent of cases while deficiency of the enzyme 11-beta-hydroxylase which converts 11-desoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol is the second most common cause accounting for 6-8% of cases of CAH [11,12].

There are two variants of CAH due to 11-beta-hydroxylase deficiency, the classic form (more severe form) and the non-classic form [13] the classic form presents with early development of secondary sexual characteristics while affected females may present with atypical genitalia [13]. About 60% of affected individuals have hypertension which typically develops in the first year of life [13]. Males with the non-classic CAH due to 11-hydroxylase deficiency may be normal except for short stature while females may present with irregular menstruation and hirsutism [13]. Mutations in *CYP11B1* and *CYP11B2* genes were linked to CAH due to 11-hydroxylase deficiency [14]. Other genes identified were the *p.R448H* among Moroccan Jews, *g.4671_4672insC* and *g.2791G>A* among Brazilians and *p.Q356X* and *p.G379V* among in Tunisians and persons of African descent [11]. The genetic analysis of parents of an affected child is also important.





The treatment of CAH involves use of glucocorticoids to suppress the synthesis of ACTH. Anti-hypertensives may be added to the treatment regimen more frequently, with potassium- sparing diuretics [11]. There have been few reports of CAH in patients with neuroblastoma [12]. Four cases have so far been reported in the literature and the occurrence of the two was linked to adrenal defects that may result to development neural crest tumours including neuroblastoma [1,15,16].

Congenital neuroblastomas have a favorable prognosis compared to neuroblastoma occurring after infancy as a large number undergo spontaneous regression [6]. There are no reports of co-existence of congenital heart disease, neuroblastoma and congenital heart disease in one individual. The co-existence of the neuroblastoma, congenital heart disease and CAH in our patient may be due to their common origin from neural crest cells. Few reported cases of neuroblastoma in patients with CAH may be due to the early regression of the tumours A Twenty-one hydroxylase deficiency was reported in the four cases of CAH with neuroblastoma. This the first report of 11-hydroxylase deficiency co-existing with neuroblastoma and congenital heart disease.

Limitation

A biopsy was not done in our patient due to the position of the mass in the thorax and genetic analysis is unavailable in our facility to determine the genetic mutation and also screen the parents. Meta-iodobenzylguanidine (MIBG) scan could have been helpful in the diagnosis of the neuroblastoma however; due to its unavailability in our health facility was not done on this patient.

Conclusion

Neuroblastoma and CAH are uncommon, especially the hypertensive types of CAH. The blood pressure of all neonates should be monitored routinely to avoid missing out such patients while patients diagnosed with neuroblastoma should be subjected to further investigations and echocardiogram.

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