Case Reports

Focal seizures as first presentation of Pepper syndrome in a six-week-old girl

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Introduction

Neuroblastoma, an embryonal cancer of the sympathetic nervous system, accounts for 7% of malignancies in childhood[1,2,3]. It is the 4th common solid tumour among Sri Lankan children[4]. Metastatic neuroblastoma can involve bones, bone marrow, liver, lungs, and brain. Different syndromes associated with neuroblastoma have been described according to the organ involved and/or clinical presentation[1,2]. Pepper syndrome is where neuroblastoma presents with diffuse hepatic metastasis[3].

Staging of neuroblastoma is important for its management and prognosis[5]. The International Neuroblastoma Staging System (INSS) categorizes neuroblastoma with limited metastasis (including isolated liver involvement) in a less than 18-month-old child as stage 4S, which has a good prognosis. Thus, these patients can be observed for possible resolution of lesions without treatment[3]. Failing spontaneous resolution, chemotherapy and/or surgery/radiotherapy are required[5]. Seizures with developmental arrest are described as an uncommon presentation of neuroblastoma[1]. We report an infant who presented with afebrile focal seizures and subsequently was found to have right suprarenal neuroblastoma with multiple liver metastases.

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Case report

A six-week-old girl was admitted to a Base hospital with two episodes of left sided focal afebrile seizures. Mother reported a similar episode at 3 weeks of age. There was neither a history of adverse perinatal events nor a family history of epilepsy. The girl was a second born to healthy parents at a period of gestation of 38 weeks delivered through a normal vaginal delivery with a birth weight of 3.1 kg, length of 50 cm and occipito-frontal circumference of 32 cm. Her developmental milestones were age appropriate.

On examination, she had a weight of 3.7 kg, a temperature of 37^0C, a pulse rate of 132/min and an oxygen saturation of 98% in room air. Blood pressure was normal and the rest of the cardiovascular and respiratory system examinations were unremarkable. Abdominal examination revealed a liver which was just palpable below the costal margin with the upper border at the 4th intercostal space, and the neurological examination did not find any focal neurological signs, neurocutaneous stigmata, blue berry muffin spots or abnormal eye movements.

Full blood count, serum electrolytes, serum calcium, serum magnesium and the venous blood gas were within normal limits (Table 1). The capillary blood sugar was 126 mg/dl. Electroencephalogram (EEG) was normal.

It was decided to start her on anti-epileptic medication with a broad spectrum to control recurrent seizures; she developed another convulsion of similar semiology after admission. Levetiracetam was the drug chosen as raised liver enzymes were noted on routine screening of liver transaminases before commencing antiepileptics.

The baby was referred to a tertiary care centre for further evaluation. Subsequent investigations are summarized in table 2.

Table 1: ***Haematological investigations***

Investigations	Results
Full blood count Haemoglobin White blood cell count Neutrophils Lymphocytes Platelet count	 11.7 g/dL (Normal range 11-17 g/dL) $9.45\times10^3/\mu L$ (Normal range 5-19.5$\times10^3/\mu L$) 11.6 % 81.7 % $442\times10^3/\mu L$ (Normal range 150-450$\times10^3/\mu L$)
Serum sodium	134 mmol/L (Normal range 134-150 mmol/L)
Serum potassium	4.6 mmol/L (Normal range 3.5-5.5 mmol/L)
Serum calcium	2.2 mmol/L (Normal range 1.8-3.0 mmol/L)
Serum magnesium	1.5 mEq/L (Normal range 1.4-1.7 mEq/L)
Liver enzymes Aspartate transaminase Alanine transaminase	 63.4 U/L (Normal range 0-40 U/L) 45 U/L (Normal range 0-35 U/L)

Table 2: ***Summary of additional investigations***

Investigation	Results
Ultrasound scan (USS) of abdomen	• Multiple focal liver lesions seen in both lobes of the liver • No duct dilatations • No para-aortic lymphadenopathy • No detectable masses in supra-renal area or renal medulla
Contrast enhanced computed tomography (CECT) of the abdomen	• Multiple focal lesions of varying sizes were involving both lobes of liver (arrow heads Figure 1); no calcific foci within the lesions • Portal vein and hepatic veins showed normal opacification without filling defects • No obvious para-aortic lymphadenopathy (Figure 1) • A soft tissue density mass lesion in right adrenal gland measuring 13mm (AP) × 9mm (TR) × 15mm (CC) with minimal enhancement (arrow head, Figure 2) • Left adrenal gland was normal (Figure 2)
USS guided Tru-cut needle biopsy of a focal liver lesion	• *Microscopy* – histo-morphologic features are compatible with metastatic deposits of a malignant small, round, blue cell tumour favouring a neuroblastoma • *Immunohistochemistr*y – The tumour cells are positive for Neuron-Specific Enolase (NSE) and negative for WT1, LCA and CD 99 ***Findings are consistent with deposits of a neuroblastoma***
CECT of neck and chest	• Both lung fields normal • No mediastinal or hilar lymphadenopathy • No abnormality detected in the neck region • No bone metastasis
Magnetic resonance imaging of brain	• No structural abnormality and evidence of metastasis
Skeletal survey	• No evidence of metastasis
Electroencephalogram	• Normal
Blood investigations	• Lactate dehydrogenase 290 U/L (normal range 60–170U/L) • Alpha-fetoprotein 150.8 ng/ml (normal range 10–20 ng/ml)
24-hour urine vanillyl mandelic acid excretion	• 1.19 mg/24 hours (normal range 1-11 mg/24 hours)
Bone marrow aspiration and trephine biopsy	• Normal with no evidence of metastasis

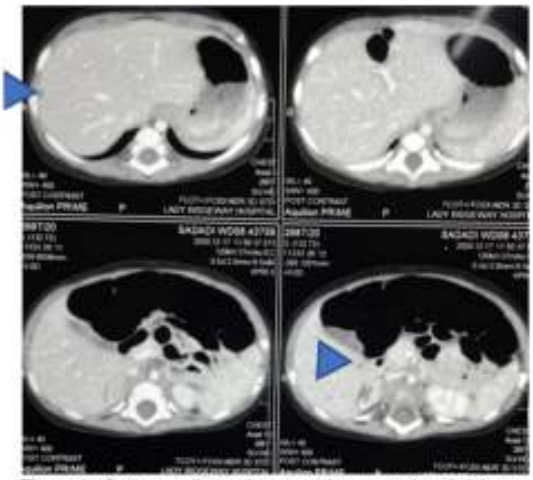

Figure 1: ***Contrast enhanced computed tomography of abdomen***

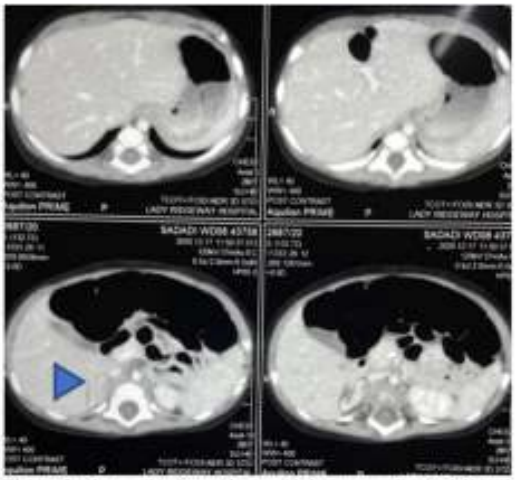

Figure 2: ***Contrast enhanced computed tomography of abdomen***

The investigations confirmed a diagnosis of Stage 4S neuroblastoma. It was decided to observe the child for possible spontaneous resolution of the tumour. An ultrasound scan (USS) of the abdomen eight weeks later showed an increase in size of the adrenal tumour, with the focal liver lesions enlarged as well. There was clinically significant hepatomegaly; in the context of this patient, in comparison to the first encounter, the extension of the liver beyond the costal margin was increased (0.5 cm from the previous span). Thus, she was commenced on chemotherapy based on the Children's Cancer and Leukaemia Group Guidelines with a combination of vincristine, cyclophosphamide, etoposide and doxorubicin given at 3 weekly intervals.

There were treatment delays due to febrile neutropenia and prolonged bone marrow suppression, and the total time taken for delivery of 4 cycles was 14 weeks. However, following 4 cycles of chemotherapy, Magnetic Resonance Imaging (MRI) of the abdomen and pelvis was performed, which showed complete resolution of the tumour in the right adrenal gland and a few small residual hypointense lesions of uncertain significance in the right lobe of the liver suggestive of near complete resolution of liver metastasis.

It was decided to follow up the child closely, clinically and with imaging, without surgical intervention. Though she had poor weight gain initially, her weight had improved subsequently, which was evident at the review on 10 months of age (Figure 3). Development was normal. She did not have further convulsions while being on Levetiracetam for the last eight months.

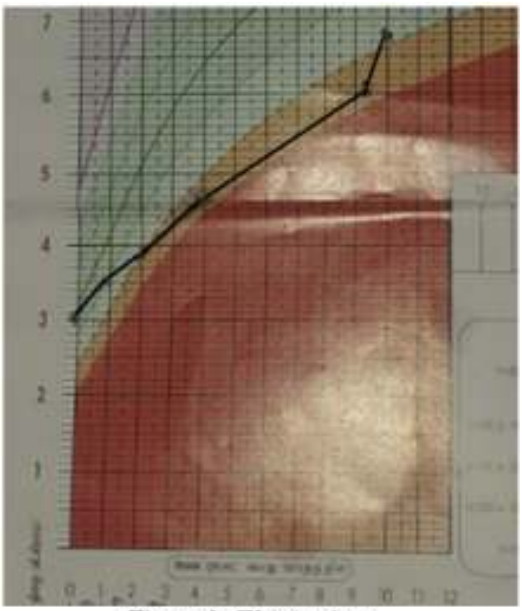

Figure 3: ***Weight chart***

Discussion

Neuroblastoma presenting with epilepsy, in the absence of opsoclonus-myoclonus syndrome is very rare[1,2]. Our case represents a rare presentation of Pepper syndrome with focal seizures in a young infant. Neurotransmitter related mechanism and/or paraneoplastic mechanism are postulated theories for the occurrence of seizures in neuroblastoma[1,2]. White AV, *et al* reported a patient who had raised immunoglobulin in the cerebrospinal fluid (CSF) which may suggest an immunological mechanism[1]. In this child, the negative biochemical results, i.e., the absence of hypoglycaemia, hypocalcaemia, hypomagnesaemia, and hyper or hyponatraemia, the presence of which could give rise to afebrile convulsions, the normal MRI of the brain and the absence of a structural cause for convulsions, might indicate that one of the above-mentioned reasons is

the cause for convulsions. Abnormal electroencephalogram (EEG) has been described[2]. EEG was normal in our child. Martins CL, *et al* reported a 5-month-old infant who presented with seizures and developmental regression and was later found to have pre-sacral pelvic neuroblastoma[2]. We did not observe developmental delay, arrest or regression in this child, and this could be due to early detection and treatment or the onset of disease very early in life before achieving developmental milestones.

Liver involvement in Pepper syndrome could range from asymptomatic liver disease to decompensated liver failure. Jha SK, *et al* described a case of decompensated liver disease due to neuroblastoma in a 3-day-old neonate[3]. In our patient, raised transaminases and multiple focal lesions were present despite the baby being asymptomatic with regard to liver-related clinical features. The elevated liver transaminases normalized after the first cycle of chemotherapy. The suprarenal tumour was not visible on USS but was detected on contrast enhanced computed tomography (CECT). This highlights the importance of CECT or MRI of abdomen in arriving at the underlying diagnosis in patients with focal liver lesions[6]. Vanillyl Mandelic Acid (VMA) can be positive in urine in 90-95% of patients with neuroblastoma. Patients with early disease and localized forms of the disease are more likely to have negative urinary VMA[7]. This child had a normal VMA possibly due to those reasons. Pepper syndrome can be a rare but important cause for young infants presenting with unexplained seizures.

Stage 4S neuroblastoma is the most frequent type of neuroblastoma in infancy[5]. Pritchard J, *et al* described three main disease outcomes of neuroblastoma, namely, progression to a life-threatening condition, maturation to ganglioneuroma or spontaneous regression. Despite the large tumour burden, spontaneous regression is often observed in stage 4S neuroblastoma[8]. The postulated theory is that the mechanism of cell apoptosis matures with age, which will help in spontaneous tumour regression[8]. Thus, the initial plan was conservative management to spare the child chemotherapy-related toxic effects. Our patient's tumour size was doubling within 8 weeks and only came under control with chemotherapy. Schleiermacher G, *et al* retrospectively reviewed 94 infants with stage 4S neuroblastoma of which the first line therapies were liver irradiation and chemotherapy[9]. The clinical response observed in those infants showed that if chemotherapy is to be given, an intensive regimen such as carboplatin-etoposide may be beneficial for a better outcome[9]. Our patient received carboplatin-etoposide based chemotherapy, to which she responded very well.

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