

Persistent cerebellar ataxia with cerebellar cognitive affective syndrome due to acute phenytoin intoxication: A case report

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Abstract

Phenytoin is one of the commonly used antiepileptic drugs. The common dose dependent and reversible neurological side effects of phenytoin are nystagmus, diplopia, dysarthria, ataxia, incoordination, chorioathetosis, orofacial dyskinesias and drowsiness. Persistent cerebellar dysfunction with cerebellar atrophy is a well known complication of long term phenytoin use. There are several mechanisms proposed including hypoxia due to frequent seizures or toxic effects of phenytoin on cerebellar Purkinje cells. However, irreversible cerebellar dysfunction following acute phenytoin intoxication is rare. We report a 20 year old female who presented with nystagmus, dysarthria, limb and truncal ataxia with orofacial dyskinesias and chorea. She also had cognitive and affective symptoms in the form of reduced attention, slow responses, lalling speech, blunting of affect, inappropriate laughter, reduced self care and executive dysfunction. The symptoms started 2 weeks following the initiation of phenytoin 300mg/day, given prophylactically following left basal ganglia bleed. Her serum phenytoin was in toxic range, hence phenytoin was stopped. Her PET scan revealed bilateral cerebellar hypometabolism. At 6 months follow up, she had persistent ataxia with cognitive and affective dysfunction and follow up MRI showed diffuse cerebellar atrophy. The clinical and radiological findings suggest that acute phenytoin intoxication is responsible for persistent ataxia and cerebellar cognitive affective syndrome.

INTRODUCTION

Phenytoin (PHT) is one of the commonly used antiepileptic drugs. It is known to have neurological, hematological, metabolic and endocrinal side effects. The common neurological side effects of PHT include nystagmus, diplopia, ataxia, incoordination, chorioathetosis, orofacial dyskinesias and drowsiness.¹⁻⁴ At higher levels ophthalmoplegia and encephalopathy may be seen.⁵ The symptoms are dose dependent and are usually reversible but persistent effect on CNS, most commonly as cerebellar dysfunction may be seen with prolonged use.^{6,7}

Irreversible cerebellar dysfunction is a well known complication of chronic PHT toxicity⁸⁻¹¹, but is rarely seen following acute intoxication.¹²⁻¹⁵ We report a 20 year old female patient who developed persistent ataxia with cerebellar cognitive affective syndrome following acute PHT intoxication.

CASE REPORT

A 20 year old right handed female with a history of right hemiplegia due to left basal ganglia bleed 8 weeks back; referred to us with tremulousness in left upper limb, slurring of speech, blurring of vision, excessive sleep and imbalance while sitting and standing since last 6 weeks. Her weight was less than 40 kg and she was on PHT 300 mg/day for seizure prophylaxis, however there was no history of any seizures. She was on PHT for 2 weeks prior to the onset of neurological symptoms and for a total of 8 weeks before presentation. There was no history of hypertension, at the time of stroke her BP was 130/80 mm of Hg and at the time of presentation to us BP was 110/70 mm of Hg. She denied any history of illicit / recreational drug use.

At the time of presentation her general physical examination was normal. On neurological examination she was conscious, oriented but excessively sleepy. She had differential

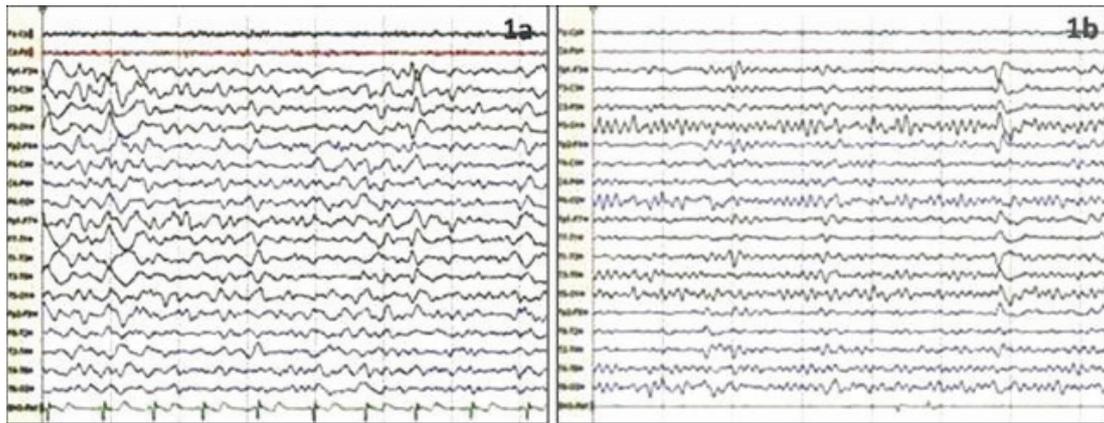


Figure 1. EEG on admission (a) was showing diffuse slowing of background activity. Repeat EEG (b) was normal.

right hemiparesis with right facial palsy. Her cerebellar examination revealed scanning speech, bilateral horizontal gaze evoked nystagmus, titubation, severe generalized hypotonia with severe limb, truncal and gait ataxia. She also had extrapyramidal features including orofacial dyskinesia, chin tremor, and choriform movement of the tongue and left hand. Considering a possibility of PHT toxicity we did her serum PHT level, which was found to be markedly elevated at 55 microgram/ml (therapeutic range 10-20 microgram/ml). Her electroencephalogram (EEG) showed diffuse slowing of background activity without any epileptiform discharges. (Figure 1a) As the patient did not have any seizures, PHT was rapidly tapered off. Her repeat EEG performed a week later showed normal background activity (Figure 1b).

After stopping PHT she was more awake and alert. On detailed higher mental function evaluation she had cognitive and affective changes in the form of reduced attention span, slow to respond, lalling speech, childish behaviour, blunting of affect with inappropriate laughter, reduced self care, executive dysfunction as lack of planning and initiation, deficient abstract thinking and working memory.

A diagnosis of acute cerebellar dysfunction with orofacial dyskinesia and chorea with cerebellar cognitive affective syndrome due to acute PHT intoxication in a case of right hemiparesis due to left gangliocapsular bleed was made.

Her non-contrast CT brain (done at the time of ictus) showed acute bleed in left gangliocapsular area with mass effect. (Figure 2) We investigated for the cause of her intracranial bleed. Her routine

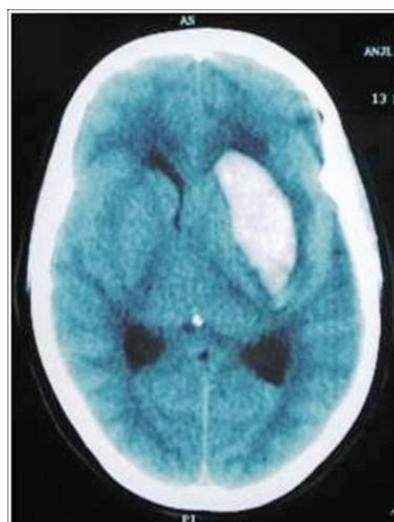


Figure 2. Non contrast CT brain showing acute bleed in left gangliocapsular area with mass effect.

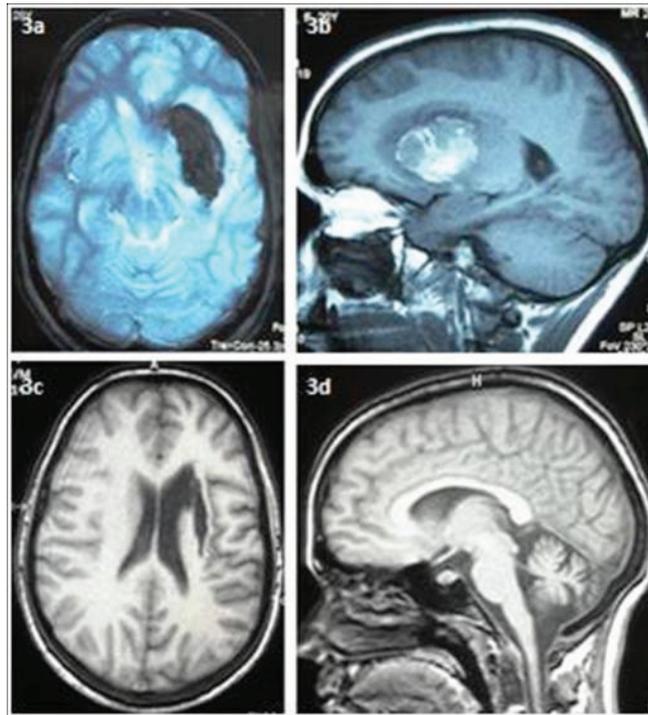


Figure 3. (a), (b). MRI brain (GRE and T1W) showing subacute bleed in left gangliocapsular area, with normal appearing cerebellar hemispheres. (c), (d). Repeat MRI brain (T1W) revealed resolving bleed in left gangliocapsular area with diffuse cerebellar atrophy.

investigations including complete blood count, renal and liver function tests, blood sugar, serum electrolytes, x-ray chest, ultrasound abdomen, carotid doppler and 2d-Echo all were normal. Her HIV ELISA was negative, vasculitic profile (ANA, ANCA, RA factor) and thyroid functions were normal. MR imaging brain with intracranial MR angiography (done eight weeks after the ictus) revealed subacute bleed in left gangliocapsular area with resolving mass effect, with normal cerebellum and normal intra cranial vasculature. (Figure 3a,b and 4)

During 4 weeks of hospital stay she had near complete improvement in her right sided weakness and dyskinesia but her ataxia and cognitive dysfunction were persistent. Her Positron Emission Tomography (PET) scan of the brain showed reduced metabolism in left basal ganglia, left fronto-parietal cortex and bilateral (right>left) cerebellar hemispheres. (Figure 5a,b)

At her last follow up 6 months after discharge she did not show any significant clinical improvement with persistent ataxia, cognitive and affective dysfunction. Repeat MR imaging brain at 6 months follow up revealed resolved bleed in left lentiform nucleus with bilateral cerebellar atrophy. (Figure 3c,d)

DISCUSSION

The temporal relationship between the initiation of the PHT prophylactically and the occurrence of orofacial dyskinesias, chorea, ataxia, cognitive and affective symptoms in our patient led us to attribute the clinical picture to acute PHT intoxication. In our patient seizures, hypoxia, intercurrent infection, or other metabolic causes were not contributory. The common dose dependent neurological side effects of PHT are nystagmus, dysarthria, diplopia, ataxia, incoordination, chorioathetosis, orofacial dyskinesias and drowsiness.¹⁻⁴ At higher levels (>40 µgm/ml) ophthalmoplegia and encephalopathy (lethargy, delirium, psychosis, stupor or coma) may be seen.⁵ However, there are considerable variations among patients in the serum PHT concentration at which a symptom appears.¹⁶ The symptoms are usually reversible but persistent effect on CNS, most commonly as cerebellar dysfunction may be seen with prolonged use.^{6,7} Atrophy of cerebellar vermis and hemispheres with loss of cerebellar Purkinje cells after long term use of PHT has been reported.⁸⁻¹¹ There are several mechanisms proposed including hypoxia due to frequent seizures or toxic effects of PHT



Figure 4. Normal intracranial MR Angiogram

on cerebellar Purkinje cells.¹⁷ There is no well established correlation between serum PHT level and development of cerebellar atrophy, as it has also been reported with long term use of nontoxic levels of PHT.¹⁸ Irreversible cerebellar atrophy after acute intoxication is very unusual, very few case reports have suggested such a sequelae.¹²⁻¹⁵ The mechanism of cerebellar atrophy following acute PHT intoxication is not clear.

Clinically, our patient had severe, irreversible, symmetric pancerebellar involvement attributable to acute PHT intoxication (55 microgram/ml). In addition to motor cerebellar dysfunction our patient had cognitive and affective symptoms in the form of poor attention, lalling speech, childish behaviour, blunting of affect with inappropriate

laughter, reduced self care executive dysfunction as lack of planning and initiation, deficient abstract thinking and working memory. Similar symptoms because of cerebellar dysfunction have been well recognized and labelled as “cerebellar cognitive affective syndrome”.^{19,20} The mechanism proposed are involvement of pathways linking cerebellum with prefrontal, posterior parietal, superior temporal, parahippocampal and limbic cortex.

Her PET scan of the brain showed reduced metabolism in left basal ganglia, left fronto-parietal cortex and bilateral (right>left) cerebellar hemispheres. The frontoparietal cortical hypometabolism ipsilateral to basal ganglia bleed and contralateral cerebellar hypometabolism may be explained by the phenomenon of diaschisis, but

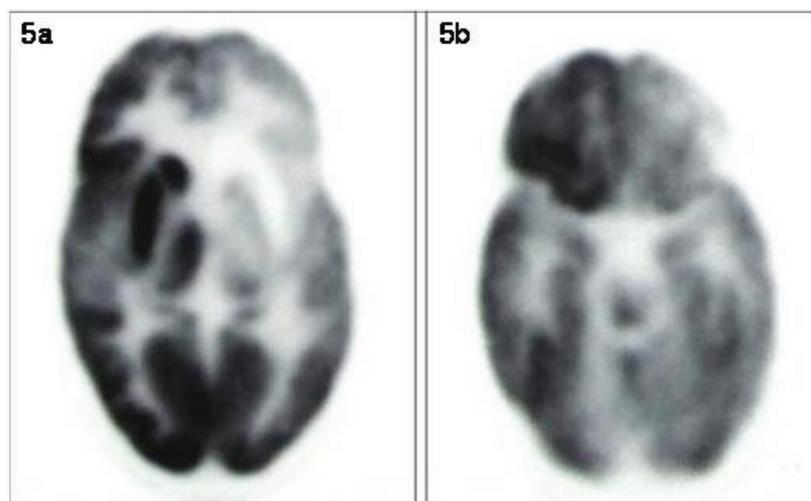


Figure 5 (a), (b). PET scan showed reduced metabolism in left fronto-parietal cortex and bilateral (right>left) cerebellar hemispheres suggestive of crossed cerebro-cerebellar diaschisis.

not the bilateral cerebellar hypometabolism. The bilateral cerebellar hypometabolism in our case may be attributable to PHT intoxication, supported by evidence of bilateral diffuse cerebellar atrophy on follow up MR imaging done at 6 months.

The phenomenon of ipsilateral cortical and contralateral cerebellar hypometabolism after basal ganglia bleed has been reported and mechanism proposed is interruption of connecting pathways causing a remote functional deactivation by a reduced excitatory input and a decreased blood flow.²¹ The phenomenon of diaschisis is usually asymptomatic, transient, and rarely leads to mild unilateral cerebellar dysfunction.^{22,23}

We finally hypothesize that acute PHT intoxication is responsible for persistent severe generalized cerebellar ataxia, cognitive and affective dysfunction along with bilateral cerebellar hypometabolism and atrophy; while diaschisis phenomenon is responsible for additional asymptomatic hypometabolism in right cerebellar hemisphere and left frontoparietal cortex. Also it is important to mention that in our case PHT was started prophylactically after basal ganglia bleed which is not as per recommendations.²⁴

We conclude that acute PHT intoxication may result in persistent ataxia with cerebellar cognitive affective syndrome with diffuse cerebellar atrophy, which is a rare phenomenon.

DISCLOSURE

Conflicts of interest: None

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