CASE REPORT

Myristicin and phenytoin toxicity in an infant

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SUMMARY

A developmentally normal infant presented with repeated episodes of afebrile status epilepticus following nutmeg ingestion. He had developed two episodes of afebrile status epilepticus and had received different treatments earlier, but the details of treatment were not available. On admission, he redeveloped convulsions and loading doses of phenytoin, phenobarbitone and midazolam were administered. However, seizures persisted and extrapyramidal movements, nystagmus and visual dysfunction were noted. Iatrogenic phenytoin toxicity was considered and confirmed by drug levels. His symptoms completely disappeared after discontinuation of phenytoin therapy. The initial seizures were attributed to myristicin, an active component of nutmeg, because of the temporal association. However, the subsequent seizures were due to phenytoin toxicity caused by administration of multiple loading doses. This case highlights that nutmeg, a spice, can cause serious toxic effects like status epilepticus. Furthermore, treatment of status epilepticus with phenytoin can cause iatrogenic seizures due to its narrow therapeutic range.

BACKGROUND

Nutmeg, a spice, is commonly used as a carminative in India. It can cause seizures, sometimes refractory to treatment, due to its active component myristicin. In the infant being reported here, nutmeg administration had caused refractory seizures and the treatment of these seizures with multiple loading doses of anticonvulsants, especially phenytoin, led to iatrogenic phenytoin toxicity. Acute phenytoin toxicity can have central nervous system (CNS) manifestations and, very rarely, visual dysfunction. The toxicity is dose dependent and withdrawal of the drug, usually, results in complete resolution of the signs. This case is probably the first reported case of concomitant myristicin and phenytoin toxicity with a very rare manifestation of reversible phenytoin-induced visual dysfunction.

CASE PRESENTATION

A developmentally normal 3-month-old male infant presented to our institute with recurrent episodes of generalised tonic clonic seizures (GTCS). The infant had been treated for recurrent seizures at two other hospitals, for about 4 days, prior to admission to our institute. There was a history of administration of parenteral drugs at the previous two centres though there were no records available. On admission, his mother informed us that she had been giving a native medicine, nutmeg, ostensibly as a carminative, for several days and that the first convulsion was noticed a few hours following the

last ingestion of nutmeg. There was no history of preceding fever, vomiting, cranial trauma, ear discharge or bleeding from any site.

On examination, the infant was sedated with no signs of raised intracranial tension or focal neurological deficits. The pupils were equal and reacting normally to light. Fundus examination was normal. Other systems examination was essentially normal. The diagnostic work-up, including sepsis screen, blood sugar, electrolytes, renal function, liver function and calcium, was within normal limits. Brain MRI was normal. EEG, conducted 1 week after the admission, revealed θ waves appropriate for age, as background activity, along with mixed and δ activity. No paroxysmal discharges could be seen.

After admission to our centre, the infant developed 8–10 episodes of GTCS with up rolling of eyes and lip smacking movements along with a shrill cry. Seizure control could not be achieved with diazepam and two half loading doses of phenytoin, hence phenobarbitone and midazolam infusions were administered. He also developed nystagmus and extrapyramidal movements.

At this point in time, in view of multiple hospitalisations, non-availability of treatment details, persistence of seizures, nystagmus and choreoathetoid movements, the seizures were suspected to be due to iatrogenic acute phenytoin toxicity and the drug was withdrawn. Drug assay showed a markedly elevated serum level of phenytoin (greater than 40 $\mu\text{g/mL}$; normal range 10–20 $\mu\text{g/mL}$) thereby confirming phenytoin toxicity. After stopping the drug the seizures, extrapyramidal movements and nystagmus ceased within 24 h. Serum phenytoin levels, measured serially, documented a declining trend (table 1).

However, the infant was detected to have visual dysfunction, in the form of failure to follow light and focus on the mother's face. Pupillary reflexes, both direct and consensual, were sluggish. Flash visual evoked potential (VEP) showed P100 latency suggestive of an anterior visual pathway conduction defect in both right and left eyes (figure 1A, B). Electroretinogram (ERG) could not be conducted.

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Table 1 Serial serum phenytoin levels

Serial number	Serum phenytoin level ($\mu\text{g/mL}$)	Timing of test
1	>40	At admission
2	17.7	6 days later
3	<0.5	18 days later

Figure 1 (A) Flash visual evoked potentials (VEP)—right eye. (B) Flash VEPs—left eye.

OUTCOME AND FOLLOW-UP

At follow-up, after 2 weeks, the infant was seizure free, off anticonvulsants and neurologically normal.

DISCUSSION

This infant had the first episode of convulsions following nutmeg administration. Nutmeg is used as a native medication and is believed to have antidiarrhoeal and carminative properties. The active component in nutmeg is myristicin (5-allyl-1-methoxy-2,3-methylenedioxybenzene).¹ Myristicin is a weak monoamine oxidase inhibitor, which has both cardiovascular and CNS effects.^{1 2} It also has hallucinogenic properties making it a potential drug of abuse.

Poisoning due to myristicin is known to cause convulsions and delirium.³ This occurs 3–6 h following ingestion and the effect is known to last up to 72 h.^{1 2 4} This infant was given

oral nutmeg in the form of a paste for several days prior to the onset of convulsions. Since he was developmentally normal with no risk factors for convulsions like trauma, infection, etc, the cause for the initial episodes of seizures was probably the myristicin component of nutmeg. Estimation of serum levels of myristicin has been difficult due to the complexity of the process. The test could not be performed in this case.

The infant must have presented to the first hospital with refractory status epilepticus due to myristicin toxicity and would have been treated with loading doses of several drugs including phenytoin. We had also inadvertently administered loading doses of phenytoin in an attempt to control the second spate of seizures that were actually due to phenytoin toxicity, highlighting the importance of accessing details of treatment given.

Phenytoin toxicity usually has CNS effects like ataxia, nystagmus, slurred speech, decreased coordination and seizures.⁵ In

acute phenytoin toxicity, nystagmus is seen in 95%, ataxia in 88% and seizures in 19% of cases.⁶ Toxicity of phenytoin is attributable to several factors. Besides a narrow therapeutic range, differing pharmacokinetics at different serum levels can contribute to toxicity. At therapeutic concentrations, it follows first-order kinetics but once toxic levels are reached ($>20 \mu\text{g/mL}$), the kinetics changes to zero order causing slow elimination of the drug thereby enhancing toxicity.^{6,7} In addition, interindividual variation in metabolism exists and is attributed to CYP2C9 gene expression.^{8,9} There is also a high scope for iatrogenic phenytoin toxicity because of improper dosing since various oral preparations with grossly differing strengths are available.⁷

Early phenytoin toxicity manifests as vestibular and cerebellar signs. Seizures are caused only when the toxic levels reach $30 \mu\text{g/mL}$ or more, as in our case (more than $40 \mu\text{g/mL}$).⁶

Treatment of acute phenytoin toxicity is primarily withdrawal of the drug along with supportive care, that is, maintaining vital functions, activated charcoal, etc. Other modalities like plasmapheresis, haemodialysis and haemoperfusion have been used with varying success.⁹ Seizures are usually managed with benzodiazepines.

In the infant reported, most of the symptoms resolved within a week of stopping the drug indicating a dose-dependent toxicity. However the visual dysfunction, a rare manifestation of phenytoin toxicity, persisted for about 2 weeks.⁸ It may present either as blurred vision, xanthopsia, visual field constriction or external ophthalmoplegia.¹⁰ In this infant, the only clinically detectable abnormality was the inability to follow light and sluggish pupillary reflexes. Flash VEP showing prolonged P100 latency and ERG showing diffuse bilateral cone and rod dysfunction are diagnostic. The P100 latency seen in our case suggests an anterior visual pathway conduction defect. This is usually a reversible dysfunction with phenytoin toxicity unlike the permanent dysfunction seen in association with vigabatrin. In the follow-up, our case appeared to have normal vision in that he was looking and smiling at the mother and was able to follow light. Pupillary reflex also reverted to normal. However, follow-up VEP is required to assess complete recovery of function.

This case highlights the fact that nutmeg, a spice, can cause serious toxic effects like status epilepticus in infants. More importantly, the treatment of status with multiple loading doses of phenytoin can result in paradoxical seizures as it has a narrow therapeutic range.

Learning points

- ▶ Nutmeg, a spice, can cause significant central nervous system toxicity in infants.
- ▶ Phenytoin can cause refractory seizures at toxic levels.
- ▶ Phenytoin has a narrow therapeutic range, hence serum levels should be monitored periodically after loading doses and while on therapy.
- ▶ Reversible visual dysfunction can occur due to acute phenytoin toxicity.

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