

# Nutmeg and Phenytoin toxicity in an infant



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3 month old male infant presented with

- Acute onset of multiple episodes of seizures – 2 days duration
- Seizure type – vacant stare with tonic posturing of limbs, lasting for a few seconds associated with loss of consciousness



- Treated with parenteral drugs at 2 other hospitals prior to admission at our institute
- Treatment details not available
- No preceding fever, cranial trauma, ear discharge or bleed from any site
- The baby had been fed paste made from nutmeg (*jadikkai*), prior to onset of seizures



- 1<sup>st</sup> born to 3<sup>rd</sup> degree consanguineous parentage
- Born at 36wks, forceps delivery, IUGR, birth weight 2.4 kg
- Normal antenatal and postnatal period
- Developmentally normal

## On examination

- Afebrile
- No neurocutaneous markers
- Vitals stable
- CNS: drowsy, pupils were normal & reacting equally to light, no meningeal signs, AF level, no deficits, fundus – normal
- CVS: Grade 3/ 6 systolic murmur 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> ICS
- RS & PA: Normal





## Investigations

- Sepsis screen – Negative
- Blood sugar, calcium, magnesium, RFT, LFT, serum electrolytes – Normal
- EEG and MRI brain – Normal
- ECHO – Bicuspid aortic valve, mild aortic stenosis



## Course in hospital

- After admission – 8 to 10 episodes of GTCS with lip smacking
- Two half loading doses of phenytoin given
- Seizures were controlled only after starting phenobarbitone and midazolam infusion



- Phenobarbitone and phenytoin maintenance continued
- Baby was noted to have nystagmus, extrapyramidal movements and shrill cry
- Did not follow light; sluggish pupillary reactions
- Did not focus upon or smile at the mother







In view of

- Multiple hospital admissions
- H/o administration of multiple injections
- Recurrence of seizures
- Nystagmus
- Extrapramidal movements

Phenytoin toxicity suspected



- Serum phenytoin levels –  $>40 \mu\text{g}/\text{ml}$  (toxic range)  
normal –  $10 - 20 \mu\text{g}/\text{ml}$
- Phenytoin was withdrawn and phenobarbitone continued

- Nystagmus – resolved within 48 hours
- Involuntary movements started improving within 72 hours
- Vision improved, in that baby could focus on and smile at mother, in about a week
- Repeat serum phenytoin – 17.7  $\mu\text{g}/\text{ml}$  (therapeutic range; done after a week of stopping the drug)



## At discharge

- Seizure free
- No involuntary movements or nystagmus
- Visual dysfunction persisted (did not follow light)
- VEP – P 100 latency suggestive of anterior visual pathway defect
- Discharged on oral phenobarbitone





## Follow up after 2 weeks

- Baby was focusing and smiling at his mother
- He was able to follow light
- Pupillary reactions were normal
  
- Serum phenytoin level –  $< 0.5 \mu\text{g}/\text{ml}$



# Discussion



- Proximate cause for acute symptomatic seizures – probably nutmeg (*jadikkai*) ingestion
- Anti diarrheal and carminative agent
- Active component – Myristicin; weak MAO inhibitor with CVS and CNS effects
- Hallucinogen
- Poisoning causes convulsions, delirium and blurred vision
- Assay not widely available

*Simple and rapid determination of myristicin in human serum. Dawidowicz AL, Dybowski MP. Forensic toxicology 2012*





- Phenytoin is a commonly used AED; iatrogenic toxicity is also common
- Factors responsible for dose related toxicity
  - ✓ Narrow therapeutic index
  - ✓ Complex pharmacokinetics
  - ✓ Inter individual variability in metabolism and clearance
  - ✓ Drug interactions
  - ✓ Improper dosing

## Phenytoin pharmacokinetics in infancy



- Neonates and early infancy – reduction in the activity of rate controlling enzymes of phenytoin biotransformation
- Increased free phenytoin fraction in plasma and tissues



## Dose related toxicity:

- 20 - 25  $\mu\text{g}/\text{dl}$  – Nystagmus on lateral gaze
- 30  $\mu\text{g}/\text{dl}$  – Ataxia and diplopia
- $>30 \mu\text{g}/\text{dl}$  – Dysarthria, seizures
- $>40 \mu\text{g}/\text{dl}$  – lethargy, drowsiness, rarely asterixis



## **Clinical manifestations of Phenytoin toxicity**

- GIT – nausea, vomiting, abdominal distension, ileus
- CVS – tachycardia, arrhythmias
- Renal failure

## CNS toxicity

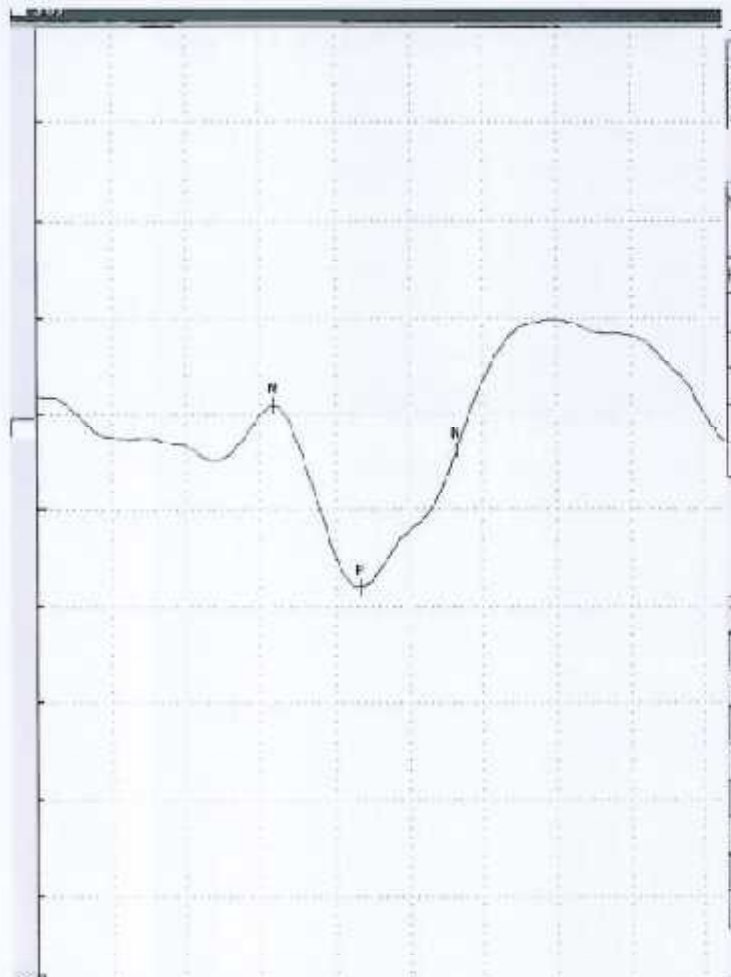
- Dizziness, vertigo, lethargy, **altered mental status**
- Dysdiadochokinesia, ataxia
- **Choreoathetosis**, dystonia
- Dysarthria
- **Seizures**
- Opsoclonus, cerebellar atrophy
- Reversible focal neurological deficits





## Ocular toxicity due to phenytoin

- Blurred vision, **visual loss (reversible)**
- Xanthopsia
- Colour blindness
- Concentric visual field constriction
- **Nystagmus**
- Diplopia
- External ophthalmoplegia
- **Sluggish pupillary reflexes**



Lead	Ampl	Filter	Velocity
1	300	F	100uV
2		F	1mV
3		GA	500uV
4		PE	10uV

**STIM Settings**  
 Rate 1Hz  
 Location Right

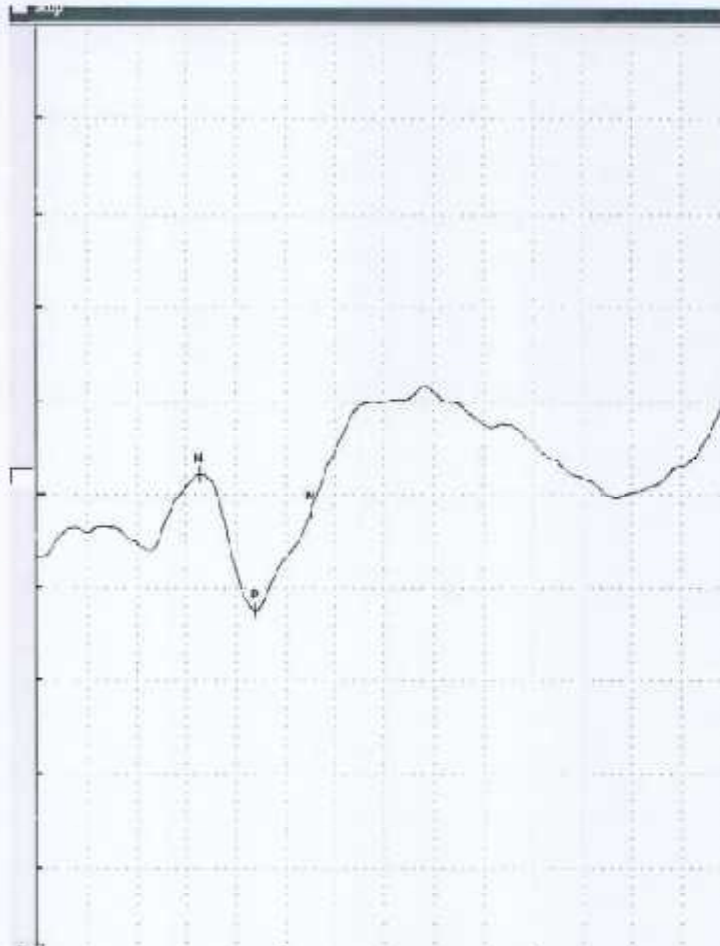
No.	Annotation	Latency(ms)						
		N1	F	N1	N2	(none)	(none)	(none)
H1	Right side	95.4	130.2	165.2				

Type	From	To	From	To	From	To	From	To
Interval	N2	N2	N2	N2	N2	N2	N2	N2
A1								
Amplitude	N2	N2	N2	N2	N2	N2	N2	N2
A1								
Interval	N2	N2	N2	N2	N2	N2	N2	N2
B1								
Amplitude								
B1								

Find Obj  
 - Pause  
 - Analysis

**Patient Information**  
 ID No.: 4506      Name: Baby, Rithish  
 Sex: Male      Age: 5months      Height: 2094434      Weight: 17664  
 Refer Dept.: Pvt      Physician: Pvt  
 History: H/O Seizures

**Examination Information**  
 Side: Right  
 Date: 10/9/2013 No.  
 Examined by:  
 Comment: Right side



Presc	Ampl	Rate	Filter
1	200	45	0
2			
3			
4			

**STIM Settings**  
 Rate 1Hz  
 Location Right

No	Annotation	Latency(ms)						
		N	P	N	N2	(none)	(none)	(none)
A1	Left side	87.8	132.0	165.6				

Type	From	To	From	To	From	To	From	To
Interval	-N2	N2	N2	N2	N2	N2	N2	N2
A1								
Amplitude	+N2	N2	N2	N2	N2	N2	N2	N2
A1								
Interval	-N2	N2	N2	N2	N2	N2	N2	N2
B1								
Amplitude	+N2	N2	N2	N2	N2	N2	N2	N2
B1								

**Patient Information**  
 ID No.: 4606  
 Sex: Male  
 Refer Dept.: Pvt  
 History: H/O Seizures

Name: Baby. Rithish  
 Age: 5months Height: 209434 Weight: 17594  
 Physician: Pvt

**Examination Information**  
 Side: left  
 Date: 10/9/2013 No.  
 Examined by:  
 Comment: Left side





## **Treatment of phenytoin toxicity**

- Symptomatic
- Seizures managed with benzodiazepines
- Plasmapheresis
- Hemodialysis
- Hemoperfusion

### **Follow up:**

MRI brain after 6 months to look for cerebellar atrophy

# Take Home Message



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

# References



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**THANK YOU**