

Case reports

Acute visual dysfunction following phenytoin-induced toxicity

Archana THAKRAL¹, Radha SHENOY¹ and Dirk DELEU²

¹Department of Ophthalmology and ²Neurology Clinic, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman

Abstract

Purpose : To report that acute phenytoin toxicity may result in acute visual dysfunction.

Methods : A 19-year old man with cryptogenic simple partial and secondary generalized epilepsy developed blurred vision and xanthopsia after phenytoin loading for status epilepticus. Color blindness was found on testing with Ishihara's pseudo-isochromatic charts and visual fields (Goldmann perimeter) showed gross concentric constriction in both eyes. Flash visually evoked potentials showed prolonged P1 latency in both the eyes. Serum free-phenytoin concentration revealed toxic levels of phenytoin and no other etiology for retinopathy or optic neuropathy.

Results : Phenytoin was withheld and the patient experienced a partial recovery in conjunction with reduced serum levels of phenytoin. Ten months later flash visually evoked potentials were normal but electroretinogram confirmed diffuse bilateral cone and rod dysfunction.

Conclusion : Phenytoin toxicity may result in acute visual dysfunction a previously unreported phenomenon.

Key words : Phenytoin ; retinopathy ; optic neuropathy ; toxicity ; epilepsy.

Phenytoin is still one of the most effective drugs in the management of tonic-clonic and complex partial seizures, and their status epilepticus (Browne, 1997). Its wide pharmacokinetic variability and narrow therapeutic range often leads to toxicity which may present by variety of clinical symptoms and signs. We report the unique case of young epileptic man who presented features of acute visual dysfunction following phenytoin loading for generalized tonic-clonic status epilepticus.

Case report

A 19-year old student (weight 60 kg) had a 3-year history of cryptogenic simple partial and secondary generalized epilepsy. For the last three years he was successfully controlled with phenobarbital (120 mg/day) till he developed several partial seizures requiring adjustment in his anti-epileptic therapy. It was decided to change his treatment to topiramate 50 mg b.i.d., with which he became

seizure-free. Six months later he had a number of breakthrough secondary generalized seizures eventually resulting in status epilepticus. On admission he was treated with intravenous diazepam (10 mg), dexamethasone (8 mg bolus) and mannitol (200 ml over 8 hours) and received a phenytoin loading dose (1,000 mg over 20 min) followed by a maintenance dose of 300 mg/day. Two days later, the patient was brought to our attention, he complained of blurred vision and xanthopsia. Neurologic examination was normal except for the neuro-ophthalmologic findings (see below) and the presence of truncal ataxia. Best-corrected visual acuity was 3/200 (-3.25/-1.75 3 10°) in the right eye and 1/200 (-4.50/-0.50 3 165°) in the left eye. Pupillary reactions were preserved but bilateral sluggish in response to light reflex. Slit lamp examination, and intraocular pressures in both eyes were normal. Funduscopy showed bilateral normal optic discs, foveal reflexes and peripheral fundi, with minimal attenuation of both the arterioles and veins. Eye movements were normal but a right-sided gaze-evoked horizontal nystagmus was observed. Color blindness was noted on testing with Ishihara's pseudo-isochromatic charts (including the compliance testing plates). Visual fields (Goldmann perimeter) showed gross concentric constriction with object IV4e, in both eyes. Flash and pattern-reversal visually evoked potentials (VEP) showed prolonged P1 latency in both the eyes. Fluorescein angiography was normal in both eyes. General physical examination did not reveal any abnormality. Serum free-phenytoin concentration was 11.4 mmol/L (normal values 3.3-9.0 mmol/L). Routine blood chemistry (including electrolytes, liver and renal function, calcium, glucose, protein and albumin levels) and cell blood count were normal. Brain MRI was normal. Based on the diagnosis of drug-induced toxicity, phenytoin therapy was discontinued. Four days later all signs of phenytoin toxicity (nystagmus and ataxia) had disappeared and his visual symptoms had gradually improved ; he started reading again and his color vision improved substantially. His serum free-phenytoin concentration was 5.6 mmol/L. Ten days later his vision recovered to 20/40 in the right

eye and 20/60 in the left eye. Liver function tests remained normal. The patient was genotyped for *CYP2C9* by polymerase chain reaction, followed by restriction enzyme analysis and was found to be heterozygous for the *CYP2C9**1/*3 allele.

Any attempt to substitute phenytoin for other anti-epileptic drugs over the following months failed, resulting in reemerging partial seizures. In view of the good anti-epileptic response to phenytoin and the gradual improvement of his visual symptoms, a low dose phenytoin regimen was reinstated (200 mg/day) in combination with sodium valproate 250 mg t.i.d. His visual symptoms and signs continued to improve but he complained of reduced visibility at night. Ten months later ophthalmologic evaluation revealed: normal funduscopy, color vision (Farnsworth-Munsell 100-hue color test (F-100)) and visual fields in both eyes (Goldmann perimeter). Flash and pattern-reversal VEP was normal. The electroretinogram (ERG) consisted of flash and multifocal ERG under photopic, scotopic, and 30 Hz-flicker conditions. The results showed reduced amplitude of a and b waves in cone photopic and rod scotopic electroretinograms, and a delay in their latencies in both eyes. The amplitude of the 30-Hz flicker responses of the cones was delayed. Oscillatory potential in the light adapted conditions revealed latencies which were bilaterally prolonged. This indicated diffuse bilateral cone and rod dysfunction. Brain MRI with focus on optic nerve was repeatedly normal.

Discussion

Concentric peripheral visual field loss is most commonly observed in retinal disease, while loss of visual acuity, defective color vision and abnormal VEP (reflecting post-retinal neural functioning). Our patient presented features of both damage to the optic nerve and retina. The complex and diffuse pattern of retinal dysfunction observed in this patient consisted most likely of both retinal cone and rod system dysfunction. Despite this, retinal changes were minimal (slight narrowing of the retinal arteries), but normal retinal appearance has been reported in drug-induced toxicity (Beck, 1998). The visual field constriction and abnormal color vision observed in our patient were very similar to those seen in patients suffering from retinal dysfunction caused by other anti-epileptic drugs, vigabatrin and carbamazepine (Nousiainen *et al.*, 2000). The phenytoin-associated toxicity was most likely dose-dependent since reversal of the clinical symptoms and signs were observed after dose reduction and discontinuation.

The potential irreversible toxicity of vigabatrin on retinal function has been well established. (Krauss *et al.*, 1998) Reversible asymptomatic visual field defects and/or achromatopsia with

other anti-epileptic drugs, including tiagabine, carbamazepine, diazepam and progabide and phenobarbital have been the subject of anecdotal reports. Unlike in our patient, in all these reports the retinal dysfunction was the result of long-standing exposure to the anti-epileptic drug.

Lorenz and Kuck (1988) described bilateral reduced visual acuity and restricted visual fields in a 47-year-old woman with an inherited defect in the metabolism of phenytoin. She received 9 gram of phenytoin and had toxic levels for three months. Although VEP was abnormal the authors were not able to localize the level of the lesion. To explore the potential for genetic variability in cytochrome P450 liver enzyme activity that can lead to inter-person differences in response to phenytoin, genotyping was undertaken in our patient. The result indicated that he was *CYP2C9* heterozygous, which is not known to be associated with reduced phenytoin metabolism, and hence could not explain this acute phenytoin toxicity.

The negative effect of conventional anti-epileptic drugs (phenytoin, carbamazepine, sodium valproate) upon color vision discrimination has been well documented (Nousiainen *et al.*, 2000 ; Lopez *et al.*, 1999). Lopez *et al.* (1999) studied epileptic patients receiving anti-epileptic drugs in monotherapy. Although all these were asymptomatic with regard to color vision, 77% of them receiving phenytoin, 67% of them treated with carbamazepine and 33% of them taking sodium valproate had significant abnormalities in the blue-yellow axis. These findings were attributed to changes at the retinal processing level. Similar findings were reported by Bayer *et al.* (1997) who showed that phenytoin and carbamazepine could result in asymptomatic changes in retinal function lacking any correlation between degree of subclinical neurotoxicity and serum phenytoin concentrations. A thorough investigation of the influence of conventional anti-epileptic drugs on different aspects of visual perception in epileptic patients with clinical normal visual functions was undertaken by Paulus *et al.* (1996). Phenytoin provided the highest rate of abnormalities. Despite these studies, symptomatic visual disturbances (xantopsia, dyschromatopsia, blurred vision and constricted visual field defects) as observed in our patient are a unique feature of acute phenytoin toxicity.

Based on its saturable liver metabolism, phenytoin exhibits non-linear pharmacokinetic properties, which is responsible for a non-linear relationship between doses and plasma concentrations. Hence excessive increase in daily dosage, rapid intravenous loading, misuse of medication, alcohol abuse, concomitant liver disease and drug-drug interactions may lead to toxic phenytoin plasma concentrations with associated neurologic and non-neurologic manifestations (Browne, 1997). Dose-related neurological side effects such as nystagmus

is one of the most common and most frequently encountered manifestation, reported in over 85% of patients with toxic phenytoin plasma concentrations. Other dose-related neurologic manifestations in adults include movement disorders, ataxia, external ophthalmoplegia, periodic alternating nystagmus, downbeat nystagmus, hallucinations, paradoxical seizures, confusion and lethargy.

In conclusion, despite the lack of pretreatment perimetries and ERG, a causal relationship between phenytoin toxicity and acute retinal dysfunction in this patient is very likely. This case report highlights the importance of monitoring the serum levels of phenytoin during and after phenytoin loading. Furthermore, it could prompt systematic screening for retinal function in patients with long-standing and/or successive treatment of different anti-epileptic drugs with potential retinal toxicity.

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- Prof. D. DELEU, M.D., Ph.D., cF.A.A.N., F.R.C.P.,
Department of Medicine (Neurology),
P.O. Box 3050,
Hamad Medical Corporation,
Doha, State of Qatar.
E-mail : doc_deleu@hotmail.com.