

## Phenytoin Toxicity Manifesting as Acute Psychosis: An Uncommon Side Effect of a Common Drug

### Abstract

Antiepileptic drug-induced psychotic disorder represents an iatrogenic, adverse drug reaction. Phenytoin has rarely been shown to be a causative agent of acute psychosis in patients. We present such a rare case of short term use of phenytoin causing toxicity manifesting as acute psychosis and complete recovery following phenytoin withdrawal.

**Keywords:** *Acute psychosis, phenytoin toxicity, rare side effect*

### Introduction

Patients with epilepsy have increased vulnerability to psychiatric comorbidity including psychotic disorders.<sup>[1]</sup> Antiepileptic drug (AED)-induced psychotic disorder (AIPD) represents an iatrogenic, adverse drug reaction. The prevalence of AIPD has been reported to range from 1.0% to 8.4% in clinical trials of AEDs.<sup>[2]</sup> Various AEDs have been associated with either a positive or a negative effect as pertaining to psychiatric manifestations such as topiramate, vigabatrin, levetiracetam, tiagabine, and zonisamide have been associated primarily with adverse psychotropic effects, while gabapentin, pregabalin, lacosamide, and lamotrigine demonstrated a more beneficial psychotropic profile, especially with regard to affective symptoms.<sup>[2]</sup> Phenytoin has rarely been shown to be a causative agent of acute psychosis in patients. We present such a rare case of phenytoin toxicity leading to acute psychosis and complete recovery following phenytoin withdrawal.

### Case Report

A 26-year-old male presented to our institute with a complaint of a headache with diminution of vision for the past 3 months. He had no comorbidities and no history of any behavioral abnormalities or any chronic drug intake. On examination, his visual acuity in the right eye was 6/18 and in the left eye was 6/60 as per Snellen

chart. On confrontation method, he had right temporal and left inferior and nasal field cuts. Imaging revealed an intra-axial left parieto-occipital region space occupying lesion, with heterogeneous enhancement and with perilesional edema with mass effect. He was started on phenytoin 300 mg in HS dosing and was scheduled for surgery. Subsequently, he underwent left occipital craniotomy and gross total tumor excision. He received one dose of steroids (Injection Dexamethasone 4 mg) intraoperatively, with no steroids being given postoperatively. The postoperative period was uneventful, and he was discharged in a stable condition. Biopsy revealed Glioblastoma Multiforme. Ten days later, the patient again presented to our emergency department in an agitated state with a history of unwarranted aggression toward his relatives. He had delusions of persecution with irrelevant, excessive talking and no insight into his behavior. He had severe gait ataxia. Physical examination revealed he had horizontal nystagmus. Investigations including complete blood count, liver function tests, renal function tests, fasting blood sugar, serum electrolytes, serum Vitamin B12, and folic acid, X-ray chest and computed tomography were all normal. His cerebrospinal fluid examination revealed red blood cell-170, white blood cell-5 (100% polymorphs), sugar-51 (blood sugar-121), and protein-71. The patient was initially suspected to have partially treated meningitis and was started on anti-meningitis treatment. However, his symptoms did not improve. On a suspicion of phenytoin toxicity, his serum levels

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were checked which revealed excessively high levels of >40 µg/ml. Phenytoin was stopped, following which the patient improved and he was discharged. At 2-week follow-up, the patient was normal, with no further episode of similar behavior. Repeat phenytoin values at follow-up were within the normal range.

## Discussion

Phenytoin is one of the most widely prescribed antiepileptic in developing countries because of being cheap and widely available. In the 1980s, phenytoin was promoted as an anti-depressant.<sup>[3]</sup> Although phenytoin is now rarely used as a psychotropic agent, a controlled study did show efficacy for mania.<sup>[4]</sup>

Phenytoin toxicity depends on the route of administration, duration, exposure, and dosage. Phenytoin metabolism is dose-dependent. Elimination follows first-order kinetics (fixed percentage of drug metabolized during a per unit time) at the low drug concentrations and zero-order kinetics (fixed amount of drug metabolized per unit time) at higher drug concentrations. This change in kinetics reflects the saturation of metabolic pathways. Thus, very small increments in dosage may result in adverse effects. The earliest signs of phenytoin toxicity are typically horizontal nystagmus and unsteady gait. More severe toxicity results in slurred speech, along with a gradually worsening mental status typified by lethargy, confusion, sedation, psychomotor slowing, mild cognitive impairment, and depression. Other side effects from phenytoin include gingival hyperplasia, hirsutism, hypocalcemia, osteomalacia, drug rash, cardiovascular effects such as bradycardia and hypotension. An acute encephalopathy and paradoxically seizures may develop with toxicity (blood phenytoin (PHT) levels, >40 µg/mL).<sup>[5,6]</sup>

Adverse effects with phenytoin use manifesting in various psychiatric disorders or behavioral symptoms have been reported earlier. Acute psychosis as caused by phenytoin toxicity has been rarely reported. McDanal and Bolman<sup>[7]</sup> reported a case of chronic epileptic patient on long term phenytoin use, who presented with psychotic behavior, with no other symptoms of phenytoin toxicity, with below normal phenytoin levels (<5 µg/ml), although the patient did improve following phenytoin withdrawal. Gatzonis *et al.*<sup>[8]</sup> reported the case of acute psychosis developing in a case of trigeminal neuralgia, which improved after stopping phenytoin, although serum levels were again normal. Borasi *et al.*<sup>[9]</sup> are the only ones who report a chronic epileptic with a history of 15 years of phenytoin intake, presenting with acute psychosis and raised serum levels of the same, who improved after stopping phenytoin. Our case is the only one where a short history of the recommended dosage of phenytoin intake is associated with acute psychosis.

Treatment with most of the commonly used AEDs is associated with reduced folate or vitamin B12 serum

levels.<sup>[10,11]</sup> Psychiatric disorders that may be diagnosed in patients having vitamin B12 deficiency include depression, bipolar disorder, panic disorder, psychosis, phobias, and dementia.<sup>[12-14]</sup> Our patient, though, had normal Vitamin B12 and folate levels, ruling this out as a cause of his psychosis.

Chen *et al.*<sup>[15]</sup> in their study on psychotic disorders caused by AEDs found that four factors are associated with AED-AIPD: Female gender, temporal lobe involvement and use of levetiracetam, and a negative association with carbamazepine. Disorganized behavior and thinking were predominant in AED-AIPD. Patients with AED-AIPD differed from non-AED-AIPDs in having better outcome along with a shorter duration of psychotic episodes. None of their AIPD patients demonstrated a chronic course of psychosis. Nadkarni and Devinsky hypothesized that epileptiform discharges may mimic electroconvulsive therapy in a focal area, and discharge suppression by AEDs may lead to psychopathology.<sup>[16]</sup> Trimble suggested that there is a disturbance of monoamine metabolism in these patients, and speculated that an increase in central dopamine activity caused by AED medication may increase their risk of developing psychoses.<sup>[17]</sup> However, no absolute mechanism of action has been found till date.

## Conclusion

The WHO defines an adverse drug reaction as “A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or the modifications of physiological function.” A “serious adverse reaction means an adverse reaction which is fatal, life-threatening, disabling, incapacitating, or which results in or prolongs hospitalization.” Acute psychosis caused by phenytoin has been previously unknown or incompletely documented. There is a possible causal relationship between the adverse event and the drug, and such an adverse event is debilitating for the patient and prolongs the hospital stay. Thus, acute psychosis as a manifestation of phenytoin toxicity should be kept in mind and be evaluated for in patients presenting with such symptoms.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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