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Cerebellar Syndrome as the Dominant Manifestation of Severe Chronic Phenytoin Toxicity

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ABSTRACT: **Background**: Phenytoin continues to be widely prescribed for seizure disorders despite its narrow therapeutic index and saturable hepatic metabolism, resulting in dose-dependent non-linear pharmacokinetics. Consequently, relatively small increases in dose may lead to disproportionate elevations in serum phenytoin concentrations and increase the risk of toxicity. Chronic phenytoin toxicity predominantly manifests with neurological features, including cerebellar dysfunction, nystagmus, dysarthria, and altered sensorium. As these manifestations are often nonspecific, drug toxicity should be considered in the differential diagnosis of patients presenting with unexplained acute or subacute cerebellar syndromes, particularly in those receiving long-term antiseizure therapy. Furthermore, the severity of neurological impairment in chronic phenytoin toxicity does not consistently correlate with serum phenytoin concentrations, making clinical assessment and therapeutic drug monitoring equally important. We report a case of chronic phenytoin toxicity presenting predominantly with cerebellar dysfunction despite markedly elevated serum phenytoin levels.

Case Presentation: A 50-year-old man with a seizure disorder on long-term phenytoin therapy (600 mg/day) presented with a one-week history of progressive gait imbalance, tremors, dysarthria, and altered sensorium. Examination revealed cerebellar signs, including gait ataxia, dysdiadochokinesia, intention tremor, horizontal gaze-evoked nystagmus, along with diffuse gingival hyperplasia. Magnetic resonance imaging of the brain excluded an acute cerebrovascular event. Serum phenytoin concentration was markedly elevated at 53.90 μg/mL, confirming chronic phenytoin toxicity. Phenytoin was discontinued and replaced with levetiracetam. The patient underwent one session each of hemoperfusion and hemodialysis. Serial therapeutic drug monitoring demonstrated a decline in serum phenytoin concentration to 24 μg/mL, which was accompanied by significant improvement in cerebellar signs and normalization of sensorium. He remained seizure-free and was discharged on levetiracetam with advice for regular follow-up.

Conclusion: This case highlights that chronic phenytoin toxicity may present

predominantly with cerebellar dysfunction despite markedly elevated serum phenytoin concentrations. Drug toxicity should remain an important differential diagnosis in patients with unexplained neurological symptoms, and therapeutic drug monitoring should complement clinical assessment to facilitate timely diagnosis and management.

INTRODUCTION

Phenytoin remains one of the most widely prescribed antiseizure medications because of its proven efficacy and cost-effectiveness in the management of focal and generalized tonic-clonic seizures. Despite its long-standing clinical use, phenytoin continues to present significant therapeutic challenges owing to its narrow therapeutic index, extensive protein binding, and complex pharmacokinetic profile. The drug is primarily metabolized by hepatic cytochrome P450 enzymes (CYP2C9 and CYP2C19). As metabolic pathways become saturated within the therapeutic range, phenytoin exhibits dose-dependent non-linear (Michaelis-Menten) pharmacokinetics, whereby relatively small increases in dose may result in disproportionate increases in serum drug concentrations and a heightened risk of toxicity.

The clinical manifestations of phenytoin toxicity predominantly involve the nervous system and may range from mild horizontal nystagmus to ataxia, dysarthria, tremors, confusion, and coma, depending on the severity of intoxication. Chronic toxicity is often characterized by progressive cerebellar dysfunction, while long-term therapy may also be associated with adverse effects such as gingival hyperplasia, peripheral neuropathy, osteopathy, and cerebellar atrophy. Because these neurological manifestations are nonspecific, phenytoin toxicity should be considered in the differential diagnosis of patients receiving long-term antiseizure therapy who present with unexplained cerebellar signs or altered mental status.

Although serum phenytoin estimation is an important component of therapeutic drug monitoring, the relationship between total serum phenytoin concentration and clinical severity is not always straightforward, particularly in chronic toxicity. Altered protein binding, individual pharmacokinetic variability, tissue distribution, and differences in free drug concentration may result in significant discordance between measured serum levels and neurological manifestations. Consequently, therapeutic decisions should be guided by careful clinical assessment in conjunction with serum drug concentrations rather than by laboratory values alone.

We report a case of chronic phenytoin toxicity presenting predominantly with progressive cerebellar dysfunction and altered sensorium despite a markedly elevated serum phenytoin concentration. This case highlights the importance of considering drug toxicity in the differential diagnosis of unexplained neurological presentations and reinforces the value of therapeutic drug monitoring alongside clinical correlation for timely diagnosis and appropriate management.

CASE PRESENTATION

Patient Information

A 50-year-old man with a known seizure disorder presented to the emergency department with a one-week history of progressive gait imbalance, bilateral upper limb tremors, slurring of speech, and altered sensorium. According to the patient's attender, he had been diagnosed with a seizure disorder 10 years earlier and was initiated on oral phenytoin. He remained seizure-free until one year prior to presentation, when he experienced a breakthrough seizure. Following this episode, the phenytoin dose was reportedly increased by a local physician to 100 mg, three tablets twice daily (600 mg/day). Although previous medical records and prescriptions were unavailable, the patient's attender produced the medication bottle confirming the reported dosage. The patient remained seizure-free thereafter until the onset of the present illness. There was no history of fever, headache, vomiting, recent head injury, alcohol intake, or concomitant medications known to interact with phenytoin.

Clinical Examination

On admission, the patient was disoriented to time, place, and person with a Glasgow Coma Scale (GCS) score of E4V4M6 (14/15). His blood pressure was 120/80 mmHg, pulse rate 60 beats/min, oxygen saturation 98% on room air, and he was afebrile.

Cognitive assessment using the Montreal Cognitive Assessment (MoCA) yielded a score of 14/30, indicating significant cognitive impairment.

General physical examination revealed diffuse gingival hyperplasia, suggestive of chronic phenytoin exposure.

Neurological examination demonstrated gait ataxia, impaired tandem walking, dysdiadochokinesia, bilateral intention tremor, horizontal gaze-evoked nystagmus, dysarthria, and impaired finger-to-nose coordination, consistent with cerebellar dysfunction. Cranial nerve examination was normal. Muscle bulk, tone, and power were preserved in all four limbs (Medical Research Council grade 5/5). Deep tendon reflexes were normal with bilateral flexor plantar responses. Sensory examination was unremarkable, and there were no signs of meningeal irritation.

Investigations

Baseline laboratory investigations, including complete blood count, renal function tests, liver function tests, serum electrolytes, coagulation profile, calcium, phosphorus, and blood glucose, were within acceptable limits and did not identify an alternative metabolic cause for the patient's neurological presentation.

Computed tomography of the brain showed no evidence of acute intracranial hemorrhage or infarction. MRI of the brain with MR angiography and venography demonstrated right mesial temporal sclerosis, chronic left cerebellar hemispheric infarct with hemosiderin deposition, and mild chronic small-vessel ischemic changes (Fazekas grade I), without evidence of acute infarction, intracranial hemorrhage, major vascular occlusion, or cerebral venous sinus thrombosis to explain the acute neurological deterioration.

In view of the prolonged exposure to high-dose phenytoin, characteristic cerebellar manifestations, and diffuse gingival hyperplasia, chronic phenytoin toxicity was suspected. Serum total phenytoin concentration was 53.90 µg/mL, confirming severe phenytoin toxicity.

Differential Diagnosis

The differential diagnoses considered included:

- Acute posterior circulation ischemic stroke
- Cerebellar infarction or hemorrhage
- Drug-induced cerebellar syndrome
- Metabolic encephalopathy
- Toxic encephalopathy
- Infective encephalitis
- Chronic phenytoin toxicity

The absence of acute neuroimaging abnormalities, normal metabolic evaluation, prolonged high-dose phenytoin exposure, diffuse gingival hyperplasia, and markedly elevated serum phenytoin concentration established the diagnosis of chronic phenytoin toxicity.

Final Diagnosis

Chronic phenytoin toxicity presenting with cerebellar dysfunction and altered sensorium secondary to prolonged high-dose phenytoin therapy (600 mg/day), confirmed by a serum phenytoin concentration of 53.90 µg/mL.

Management:

Phenytoin was discontinued immediately following confirmation of toxicity, and antiepileptic therapy was changed to levetiracetam.

Considering the severe neurological manifestations and markedly elevated serum phenytoin concentration, a multidisciplinary team comprising neurologists, nephrologists, and intensivists decided to proceed with extracorporeal therapy. The patient underwent two sessions of hemoperfusion alternating with two sessions of intermittent hemodialysis during the hospital stay.

Serial therapeutic drug monitoring was performed to assess treatment response. Following the first hemoperfusion session and subsequent hemodialysis, the serum phenytoin concentration decreased from 53.90 μg/mL to 24.60 μg/mL. After the second cycle of hemoperfusion followed by intermittent hemodialysis, the serum phenytoin concentration further declined to 16.20 μg/mL, reaching the therapeutic range. Throughout treatment, the patient received supportive care with close neurological monitoring and serial clinical assessment.

Outcome and Follow-up

A gradual improvement in neurological status was observed following extracorporeal therapy. Sensorium improved progressively, with recovery of orientation and cognition. Cerebellar signs, including gait ataxia, dysarthria, intention tremor, dysdiadochokinesia, and nystagmus, showed marked improvement in parallel with the reduction in serum phenytoin concentration. The patient remained seizure-free throughout hospitalization and was discharged in a clinically stable condition on levetiracetam, with advice regarding medication adherence, regular neurological follow-up, and periodic therapeutic drug monitoring.

DISCUSSION

Phenytoin remains one of the most commonly prescribed antiseizure medications because of its proven efficacy, availability, and affordability. Nevertheless, its clinical use is limited by a narrow therapeutic index and highly variable pharmacokinetics. Unlike most antiseizure medications, phenytoin exhibits capacity-limited (Michaelis–Menten) metabolism, in which hepatic CYP2C9 and CYP2C19 enzymes become saturated within or just above the therapeutic range. Consequently, relatively small increments in maintenance dose may produce disproportionate increases in serum drug concentrations, predisposing patients to chronic toxicity. Furthermore, because approximately 90% of circulating phenytoin is albumin bound, alterations in protein binding, hepatic metabolism, pharmacogenetic variability, and drug interactions contribute to marked interindividual differences in serum concentrations and clinical manifestations. These pharmacokinetic characteristics make phenytoin one of the few antiseizure medications for which individualized dosing and therapeutic drug monitoring (TDM) remain essential. (1–6)

Neurological manifestations constitute the hallmark of chronic phenytoin toxicity, with cerebellar dysfunction being the most characteristic presentation. Ataxia, dysarthria, nystagmus, intention tremor, dysdiadochokinesia, and cognitive impairment result from selective vulnerability of cerebellar Purkinje cells to prolonged phenytoin exposure. The largest systematic review to date by **Ferner et al.** evaluated 92 published cases and demonstrated that **ataxia was present in 96%**, **nystagmus in 70%**, and **dysarthria in 63%** of patients, with cerebellar atrophy identified in approximately two-thirds of those who underwent neuroimaging. Importantly, neurological recovery was variable, with many patients experiencing persistent disability despite discontinuation of phenytoin. (4,7,10)

Our patient demonstrated the classical clinical spectrum of chronic phenytoin neurotoxicity, presenting with progressive gait ataxia, dysarthria, horizontal gaze-evoked nystagmus, dysdiadochokinesia, intention tremor, altered sensorium, and cognitive impairment (MoCA score 14/30). In addition, diffuse gingival hyperplasia provided an important clue to prolonged phenytoin exposure. Gingival overgrowth is a well-recognized chronic adverse effect of phenytoin, although it does not correlate with serum drug concentration or neurological severity. Instead, it serves as a marker of long-term exposure and should prompt careful review of medication history in patients presenting with otherwise unexplained cerebellar syndromes. (7–9)

One of the most important observations in this case is the **poor correlation between serum phenytoin concentration and clinical severity**, a phenomenon that has been repeatedly described but remains under-recognized in routine clinical practice. Although total serum phenytoin concentrations above **20 μg/mL** are generally associated with toxicity, clinical manifestations are largely determined by the pharmacologically active free drug concentration rather than total serum concentration. Variability in albumin binding, renal function, hepatic function, pharmacogenetic polymorphisms, tissue distribution, and chronic neuroadaptation may all contribute to the marked clinicobiochemical dissociation observed in

chronic toxicity. Consequently, patients with concentrations exceeding **50 µg/mL** may remain conscious and predominantly exhibit cerebellar dysfunction, whereas others develop significant neurological impairment at comparatively lower concentrations. The systematic review by Ferner et al. similarly demonstrated substantial variability between serum phenytoin concentration, cerebellar symptoms, and radiological findings, emphasizing that clinical and radiological abnormalities do not consistently parallel biochemical measurements. (1–5,7,11,12)

Our patient illustrates this concept well. Despite a serum phenytoin concentration of **53.90 µg/mL**, he remained hemodynamically stable with a **Glasgow Coma Scale score of 14/15**, and cerebellar dysfunction predominated over profound depression of consciousness. Similar clinicobiochemical discordance has been described in recent case reports. Manoj et al. reported a patient with chronic phenytoin toxicity presenting predominantly with ataxia, highlighting the importance of therapeutic drug monitoring and the possible contribution of pharmacogenetic variability. Likewise, a recent **Radiology Case Reports** publication demonstrated significant neurological improvement following withdrawal of phenytoin despite established cerebellar atrophy, suggesting that early recognition may prevent irreversible neurological damage. (7,13,14)

The diagnosis of chronic phenytoin toxicity is frequently delayed because its manifestations overlap with several neurological disorders, particularly posterior circulation stroke, toxic-metabolic encephalopathy, cerebellitis, and neurodegenerative disease. In our patient, the acute onset of cerebellar dysfunction appropriately prompted neuroimaging to exclude posterior circulation ischemia. However, the absence of acute infarction, together with normal metabolic investigations and the presence of diffuse gingival hyperplasia, shifted attention toward drug toxicity. Confirmation by serum phenytoin estimation established the diagnosis. This case reinforces the importance of obtaining a meticulous medication history, particularly when previous medical records are unavailable. Verification of the medication bottle by the patient's attender proved invaluable in identifying prolonged administration of **600 mg/day** of phenytoin. (4,10,15)

Therapeutic drug monitoring was central to both diagnosis and management in the present case. Current recommendations advocate TDM in patients with suspected toxicity, dose escalation, breakthrough seizures, poor adherence, suspected drug interactions, or conditions likely to alter protein binding. Serial measurement of serum phenytoin concentration in our patient objectively documented progressive drug elimination and paralleled clinical recovery, supporting its value in monitoring treatment response rather than serving solely as a diagnostic test. Although total serum concentration should not replace clinical assessment, serial TDM provides an objective marker of drug clearance and may assist in determining the need for continued intervention. (1,2,16)

Supportive care remains the cornerstone of management for phenytoin toxicity. Nevertheless, the role of extracorporeal therapy has evolved over the past decade. Although phenytoin is highly protein bound, saturation of binding sites during severe intoxication increases the free fraction available for extracorporeal removal. Based on systematic review of the available evidence, the **EXTRIP Workgroup** recommends consideration of extracorporeal therapy in selected patients with severe poisoning, particularly those with prolonged coma or refractory neurological toxicity. Intermittent hemodialysis is the preferred modality because of its availability, while hemoperfusion remains an acceptable alternative. (4,17–19)

Our patient underwent **two sessions of hemoperfusion alternating with two sessions of intermittent hemodialysis**, resulting in a reduction in serum phenytoin concentration from **53.90 µg/mL** to **24.60 µg/mL**, and subsequently to **16.20 µg/mL**, accompanied by marked improvement in cognition and cerebellar function. Although spontaneous elimination after discontinuation of phenytoin undoubtedly contributed to the decline in serum concentration, the close temporal relationship between extracorporeal therapy and neurological recovery suggests a beneficial role in selected patients. Similar outcomes have been reported in recent literature. Felber et al. described successful use of intermittent hemodialysis in severe phenytoin overdose with rapid biochemical and neurological improvement, while the Indian case reported by **Sahoo et al.** highlighted the potential role of repeated charcoal hemoperfusion in accelerating recovery in severe phenytoin toxicity. (13,17–20)

In summary, this case highlights several clinically important messages. Chronic phenytoin toxicity should be considered in any patient receiving long-term phenytoin therapy who presents with unexplained cerebellar dysfunction, even in the absence of profound impairment of consciousness. Serum phenytoin concentration should always be interpreted in conjunction with the patient's neurological findings because significant clinicobiochemical dissociation may occur in chronic toxicity. Finally,

regular therapeutic drug monitoring, prompt withdrawal of phenytoin, and carefully selected use of extracorporeal therapies may contribute to favorable neurological outcomes when diagnosis is established early. (1,7,17)

Study	Serum Phenytoin (µg/mL)	Clinical Features	Management	Outcome	Clinical Significance
Ferner et al. (2022) Systematic review (92 cases)	Variable	Ataxia, nystagmus, dysarthria, cerebellar dysfunction	Phenytoin withdrawal ± supportive care	Variable recovery; some patients had persistent deficits	Demonstrated marked variability between serum phenytoin concentration, clinical presentation, and radiological findings.
Manoj et al. (2024)	Toxic level	Progressive ataxia, gait instability	Phenytoin withdrawal; therapeutic drug monitoring	Complete recovery	Highlighted the importance of therapeutic drug monitoring and possible pharmacogenetic variability.
Felber et al. (2024)	Markedly elevated	Severe neurological toxicity	Intermittent hemodialysis	Rapid neurological and biochemical recovery	Supported the use of hemodialysis in selected patients with severe phenytoin toxicity.
Sahoo et al. (2016, India)	Elevated	Altered sensorium and severe neurological toxicity	Repeated charcoal hemoperfusion	Significant neurological improvement	Suggested that repeated hemoperfusion may enhance recovery in severe phenytoin poisoning.
Present case	53.90 → 24.60 → 16.20	Progressive ataxia, dysarthria, intention tremor, dysdiadochokinesia, horizontal gaze-evoked nystagmus, altered sensorium, MoCA 14/30, gingival hyperplasia	Phenytoin withdrawal, levetiracetam, two sessions of hemoperfusion alternating with two sessions of intermittent hemodialysis	Marked neurological recovery with normalization of serum phenytoin concentration	Highlights clinicobiochemical dissociation in chronic phenytoin toxicity and demonstrates the role of serial therapeutic drug monitoring with combined extracorporeal therapy in selected patients.

Learning Points

- Chronic phenytoin toxicity may present predominantly with cerebellar dysfunction and altered sensorium, mimicking acute neurological disorders such as posterior circulation stroke.
- Serum phenytoin concentrations may not accurately predict the severity of chronic toxicity; therefore, treatment decisions should be guided by both clinical assessment and therapeutic drug monitoring.
- Early recognition, discontinuation of phenytoin, and appropriate use of extracorporeal therapy in selected patients can facilitate neurological recovery and improve clinical outcomes.

CONCLUSION

This case reinforces that chronic phenytoin toxicity remains an important and potentially reversible cause of cerebellar dysfunction in patients receiving long-term therapy. The marked discrepancy between serum phenytoin concentration and

clinical severity observed in our patient highlights the limitations of relying solely on biochemical measurements and emphasizes the importance of integrating therapeutic drug monitoring with careful neurological assessment. Recognition of clinical clues such as gingival hyperplasia, timely withdrawal of phenytoin, and individualized management, including extracorporeal therapy in selected patients, may facilitate neurological recovery and improve patient outcomes. Regular therapeutic drug monitoring and periodic reassessment of long-term phenytoin therapy remain essential to minimize preventable toxicity and optimize treatment safety.

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