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Ataxia as an Adverse Drug Reaction: A Case Series

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Abstract: ***Background: Ataxia is a clinical syndrome resulting from cerebellar dysfunction, presenting with gait imbalance, dysmetria, dysdiadochokinesia, and nystagmus. While structural, metabolic, and autoimmune causes are well recognized, drug-induced ataxia remains underdiagnosed despite being potentially reversible. Methods: We report a case series of three patients presenting with acute cerebellar ataxia associated with recent drug exposure. Clinical evaluation, laboratory investigations, serum drug levels, and neuroimaging were performed. Structural causes were excluded, and outcomes were assessed following drug withdrawal. Results: Three cases of drug-induced ataxia were identified. Phenytoin toxicity (44 µg/mL), likely potentiated by valproate, caused acute cerebellar signs in a young female. Carbamazepine-induced ataxia occurred in an elderly male despite therapeutic levels, suggesting individual susceptibility. Metronidazole-induced encephalopathy presented with characteristic bilateral dentate nucleus hyperintensities on MRI. All patients showed significant clinical improvement after discontinuation of the offending drug. Conclusion: Drug-induced ataxia is an important, reversible cause of cerebellar dysfunction. Early recognition through detailed medication history and timely drug withdrawal can prevent unnecessary investigations and ensure favorable neurological recovery.***

Keywords: Drug-induced ataxia; Cerebellar dysfunction; Phenytoin toxicity; Carbamazepine neurotoxicity; Metronidazole encephalopathy

1. Introduction

Ataxia is a clinical syndrome characterized by impaired coordination of voluntary movements, manifesting as gait imbalance, dysmetria, dysdiadochokinesia, and oculomotor abnormalities such as nystagmus. It arises from dysfunction of the cerebellum and its pathways, with etiologies that range from structural lesions and metabolic disturbances to infectious, autoimmune, hereditary, toxic, and drug-related causes. Identifying the underlying mechanism is crucial, as the management and prognosis vary widely.

Among the reversible causes, drug-induced ataxia is frequently under-recognized yet not uncommon, with reported incidence ranging from 3% to 40% among exposed populations, particularly with antiepileptic medications[1, 5]. Several medications- particularly antiepileptic drugs, sedatives, chemotherapeutic agents, and certain antibiotics—can impair cerebellar function through direct toxicity, altered neurotransmission, or metabolic effects. Phenytoin and carbamazepine, two commonly prescribed antiepileptic agents, remain the most well-documented offenders due to their narrow therapeutic windows and complex pharmacokinetics[4, 9]. Toxicity often manifests acutely with gait ataxia, limb incoordination, and gaze-evoked nystagmus, even in the absence of structural abnormalities on neuroimaging.

Early recognition of drug-induced ataxia is essential because timely adjustment or discontinuation of the offending agent typically leads to full neurological recovery. This case series highlights three patients who developed acute cerebellar ataxia secondary to drug toxicity, emphasizing the importance of maintaining a high index of suspicion in patients presenting with new-onset ataxia and on multiple medications.

2. Literature Survey

Drug-induced ataxia has been widely reported with antiepileptic drugs such as phenytoin and carbamazepine due to their narrow therapeutic index. Studies report incidence ranging from 3% to 40% depending on drug exposure and patient susceptibility. Metronidazole-induced encephalopathy is well documented with characteristic MRI findings involving dentate nuclei[2,3].

Previous literature highlights:

- Dose-dependent toxicity (phenytoin)
- Idiosyncratic reactions (carbamazepine)
- Cumulative toxicity (metronidazole)

However, underdiagnosis remains common due to overlap with primary neurological disorders.

3. Problem Definition

Drug-induced ataxia is frequently overlooked despite being reversible. There is a need to:

- Recognize drug-related causes early
- Differentiate from structural cerebellar disease
- Avoid unnecessary investigations
- Prevent permanent neurological damage

4. Methodology / Approach

This study is a descriptive case series conducted in a tertiary care hospital. Three patients presenting with acute cerebellar ataxia and a history of recent drug exposure were included.

All patients underwent:

- Detailed clinical evaluation
- Comprehensive drug history assessment
- Laboratory investigations (CBC, renal and liver function tests, electrolytes)
- Serum drug level estimation (where applicable)
- Neuroimaging with MRI brain

Structural causes of ataxia were excluded in all cases. A diagnosis of drug-induced ataxia was made based on:

- Temporal association with drug exposure
- Exclusion of alternative etiologies
- Clinical improvement following withdrawal of the suspected drug

Patients were managed by discontinuation of the offending agent and supportive care, and outcomes were assessed based on resolution of neurological symptoms during follow-up.

5. Results & Discussion

The following cases illustrate how commonly prescribed medications can produce acute cerebellar dysfunction, often mimic primary neurological disease yet remaining entirely reversible with timely recognition.

Case 1: Phenytoin-Induced Acute Cerebellar Ataxia

A 19-year-old female presented with difficulty in walking for 4 days and no complaint of fever, vomiting, vertigo, altered sensorium, limb weakness, or involuntary movements. She had significant past history of intellectual disability and generalized tonic–clonic seizures since childhood and had been treated for Pott's spine 3 years back.

On examination, she was vitally stable. Gingival hypertrophy was noted. Neurological evaluation revealed truncal ataxia, broad-based gait, postural instability, bilateral gaze-evoked horizontal nystagmus, dysmetria, and dysdiadochokinesia. Tone, power, reflexes, sensation, and plantar responses were normal. Routine laboratory tests including CBC, renal and liver function tests, electrolytes, and CPK were within normal limits.

Further history revealed that the patient had been receiving levetiracetam, valproate, and clonazepam for long-standing seizure disorder, and phenytoin was added to this regimen two months prior to presentation. MRI of the brain and spine were normal. Serum phenytoin level was 44 µg/mL (therapeutic range: 10–20 µg/mL), confirming toxicity. The occurrence of phenytoin toxicity was likely potentiated by concomitant valproate therapy, which inhibits phenytoin metabolism and increases the free (unbound) phenytoin fraction. Phenytoin was discontinued, and doses of the remaining antiepileptic medications were optimized, resulting in rapid clinical improvement.

The patient demonstrated rapid improvement, with resolution of nystagmus and marked reduction in ataxia and dysmetria following drug withdrawal within 6 days.

Case 2: Carbamazepine-Induced Cerebellar Dysfunction

A 64-year-old male presented with complaints of difficulty in walking, imbalance, and slurred speech for 3 days. There was no history of fever, trauma, loss of consciousness, seizures, or other focal neurological deficits. He was a known case of ischemic heart disease and hypertension for 5 years and recently diagnosed with trigeminal neuralgia for which he was started on carbamazepine 300 mg/day seven days earlier.

On examination, he was alert and oriented, with mild dysarthria, horizontal gaze-evoked nystagmus, and ataxic gait. Power, tone, deep and superficial reflexes, cranial nerves, and sensory examination were normal. Dysmetria and dysdiadochokinesia were present. Laboratory tests including CBC, electrolytes, LFT, RFT, blood sugar, TSH, ECG, and ABG were normal.

Serum carbamazepine level was 7.92 µg/mL (therapeutic: 4–12 µg/mL). MRI Brain with angiography (pre- and post-symptom onset) revealed a vascular loop of the right superior cerebellar artery abutting the trigeminal nerve, but no parenchymal lesions. No acute infarct or haemorrhage was identified.

Based on the clinical picture, temporal association, drug level, and normal imaging, carbamazepine-induced cerebellar ataxia was diagnosed. The drug was discontinued, resulting in complete resolution of neurological symptoms within 72 hours, confirming carbamazepine toxicity as the cause.

Case 3: Metronidazole-Induced Encephalopathic Ataxia

A 53-year-old male presented with complaint of difficulty in walking for 2 days. He had no complaint of altered sensorium, focal neurological deficits, or seizures. The patient had undergone drainage of the liver abscess via a pigtail catheter 3 months back and had been receiving high-dose metronidazole (>2 g/day).

Neurological examination revealed left-sided dysdiadochokinesia, with otherwise normal tone, power, reflexes, sensory findings, and plantar responses. CBC, RFT, LFT, electrolyte panel were all within normal limits.

Electrophysiology (EMG-NCV) showed demyelinating motor > sensory polyneuropathy, raising suspicion for drug-related neurotoxicity.

MRI Brain with Contrast demonstrated T2/FLAIR hyperintensities in the bilateral dentate nuclei with diffusion restriction, a classic finding of metronidazole-induced encephalopathy[2], [3], [7].

Metronidazole was discontinued immediately, after which the patient showed significant clinical improvement, with progressive resolution of ataxia over 10 days.

6. Discussion

Common Mechanisms of Drug-Induced Ataxia

Drug-induced ataxia results from disruption of cerebellar circuitry, Purkinje cell function, vestibulo-cerebellar integration, or cerebellar output pathways. Based on the presented cases, the following five common mechanisms can be identified:

1) Voltage-Gated Sodium Channel Inhibition

Several neuroactive drugs, particularly antiepileptics such as phenytoin and carbamazepine, exert their therapeutic effect through blockade of voltage-gated sodium (Na^+) channels[6]. However, excessive inhibition impairs high-frequency firing of cerebellar Purkinje cells, which are critical for maintaining inhibitory output to deep cerebellar nuclei. Suppression of Purkinje cell activity disrupts timing and coordination of motor signals, leading clinically to dysmetria, gait imbalance, dysdiadochokinesia, and gaze-evoked nystagmus. Because Purkinje cells rely heavily on rapid sodium-dependent action potentials, they are particularly vulnerable to concentration-dependent toxicity.

2) Alteration of GABAergic Neurotransmission

Cerebellar coordination depends on finely regulated inhibitory signaling mediated by gamma-aminobutyric acid (GABA). Several drugs may impair GABA release or disrupt inhibitory cerebellar pathways. Reduced inhibitory tone leads to cerebellar disinhibition and impaired modulation of motor output. This manifests as truncal instability, limb incoordination, saccadic abnormalities, and oscillopsia. Both direct interference with GABAergic neurons and indirect effects on synaptic transmission contribute to this mechanism.

3) Disruption of Cerebellar Output Pathways

The dentate nuclei and superior cerebellar peduncles serve as major efferent pathways transmitting cerebellar signals to motor cortex and brainstem structures. Toxic injury to these structures—either functional or structural—impairs cerebellar output. In the metronidazole case, selective involvement of the bilateral dentate nuclei with T2/FLAIR hyperintensities illustrates this mechanism clearly. Interruption of cerebellar output pathways produces prominent limb ataxia, dysarthria, and gait disturbance, even in the absence of diffuse cortical involvement.

4) Metabolic or Electrolyte-Mediated Cerebellar Dysfunction

Certain drugs induce secondary metabolic derangements that impair neuronal function. Carbamazepine may cause syndrome of inappropriate antidiuretic hormone secretion (SIADH), leading to dilutional hyponatremia. Even moderate reductions in serum sodium can produce gait instability, confusion, and cerebellar incoordination. Similarly, mitochondrial dysfunction and oxidative stress, as seen with metronidazole, impair cellular energy production in metabolically active cerebellar neurons, particularly Purkinje cells and dentate nuclei. These metabolic insults compromise neuronal signaling and synaptic transmission, resulting in reversible ataxia.

5) Dose, Duration and Pharmacokinetic-Related Neurotoxicity

Drug-induced ataxia often reflects concentration-dependent toxicity. Agents with narrow therapeutic indices and complex pharmacokinetics are particularly implicated. Phenytoin demonstrates non-linear (zero-order) kinetics[9]., where small dose increases can produce disproportionate rises in serum levels due to metabolic saturation. Drug–drug interactions (e.g., valproate increasing free phenytoin levels) further amplify toxicity. In other cases, cumulative exposure or prolonged high-dose therapy leads to selective vulnerability of cerebellar structures, as observed with metronidazole. Importantly, ataxia may occur even within therapeutic serum ranges due to inter-individual variability, age-related physiological changes, or impaired drug clearance.

Here in all three cases Drug-Specific Mechanism (One Key Mechanism for Each Drug) are as follows:

1) Phenytoin- Non-Linear Pharmacokinetics with Purkinje Cell Suppression
   Phenytoin toxicity is strongly linked to its zero-order metabolism[9]. Once hepatic enzymes become saturated, minor dose changes or metabolic interactions can produce marked elevation in serum concentration. Excessive sodium channel blockade suppresses Purkinje cell firing, leading to impaired cerebellar cortical output. This explains why gait ataxia and nystagmus are often early and prominent manifestations of phenytoin toxicity.
2) Carbamazepine – Neurotoxicity from Active Epoxide Metabolite Accumulation
   Carbamazepine is metabolized to carbamazepine-10,11-epoxide, an active neurotoxic metabolite[5], [10]. Accumulation of this metabolite- due to hepatic dysfunction, drug interactions, or rapid dose titration- can prolong or exaggerate cerebellar toxicity. Notably, neurotoxicity may occur even when parent drug levels remain within the therapeutic range, reflecting the contribution of metabolite-mediated effects on cerebellar neurons.
3) Metronidazole – Selective Dentate Nucleus Toxicity with Intramyelinic Edema
   Metronidazole-induced ataxia is characterized by selective involvement of the dentate nuclei. The drug and its metabolites cause axonal swelling, intramyelinic

edema, and mitochondrial dysfunction, particularly in metabolically active cerebellar structures. This selective vulnerability explains the characteristic bilateral dentate nucleus hyperintensities[2,3,8] seen on MRI and the prominence of limb ataxia and dysarthria. Importantly, this injury is typically reversible with prompt drug discontinuation.

7. Conclusion

Drug-induced ataxia is a clinically significant, frequently overlooked, and potentially reversible cause of acquired cerebellar dysfunction. A wide range of medications can impair cerebellar and vestibular pathways through direct neurotoxicity, altered neurotransmission, metabolic derangements, or cumulative tissue injury, often in the absence of structural abnormalities on neuroimaging.

The occurrence of drug-induced ataxia may be dose-dependent, particularly with agents that have a narrow therapeutic index or concentration-dependent effects on neuronal ion channels and synaptic transmission. However, ataxia can also occur at therapeutic doses due to individual susceptibility, pharmacokinetic variability, drug–drug interactions, impaired clearance, or age-related physiological changes, indicating that toxicity is not exclusively dose-dependent.

In addition, certain drugs produce cerebellar dysfunction in a duration- or cumulative dose-dependent manner, especially with prolonged exposure, leading to selective vulnerability of cerebellar structures. Importantly, early recognition and prompt withdrawal or dose adjustment of the offending agent usually results in complete or substantial neurological recovery, whereas delayed diagnosis may lead to persistent or irreversible cerebellar damage.

A high index of suspicion, careful medication history, and timely intervention are therefore essential in all patients presenting with new-onset ataxia, as drug-induced etiologies represent one of the most preventable and treatable causes of cerebellar ataxia[1,8].

8. Future Scope

- Larger cohort studies to determine incidence
- Development of drug-monitoring protocols
- Increased clinician awareness to reduce misdiagnosis
- Integration of pharmacogenomics in predicting susceptibility

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