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Peripheral Neuropathy Induced by Topiramate

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Abstract | **Case Report**

A 37-year-old female patient, hospitalized in May 2025 at Ar-Razi Hospital in Salé for cocaine withdrawal and depressive disorder, developed tingling and heaviness in all four limbs after six weeks of topiramate treatment at 100 mg/day. Clinical examination revealed no motor deficits, and laboratory tests (vitamin B9 and B12 levels) were normal. A cold electromyography (EMG) was requested post-discharge. Complete resolution of symptoms following a missed dose of topiramate suggested peripheral neuropathy induced by this medication, which was confirmed by the pharmacovigilance center. Topiramate was discontinued, resulting in near-complete symptom resolution. This case highlights the need for clinical vigilance regarding this rare side effect, particularly in non-conventional indications such as cocaine withdrawal. Interdisciplinary collaboration and reporting to pharmacovigilance centers are essential for better understanding this adverse effect.

Keywords: Peripheral neuropathy, Topiramate, Cocaine withdrawal.

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I. INTRODUCTION

Peripheral neuropathy is a condition characterized by damage to peripheral nerves, leading to tingling, numbness, or muscle weakness, primarily in the extremities. While often associated with causes such as diabetes, infections, or intoxications, drug-induced peripheral neuropathy is increasingly recognized, particularly with certain antiepileptic drugs like topiramate [1, 7].

Topiramate, a broad-spectrum antiepileptic, is used for epilepsy, migraine prophylaxis, and, less conventionally, in the management of substance use disorders, such as cocaine withdrawal [8]. Its side effects include cognitive impairment, weight loss, and, more rarely, peripheral neuropathy [2, 9].

The association between topiramate and peripheral neuropathy is rare but clinically significant, potentially impacting quality of life and requiring treatment adjustments. Compared to other antiepileptics like phenytoin or carbamazepine, where the link to neuropathy is well-documented, topiramate-related neuropathy is less reported, making clinical observations crucial [1, 10].

This article describes a case of topiramate-induced peripheral neuropathy in a patient hospitalized for cocaine withdrawal, aiming to explore its clinical presentation, pathophysiology, management, diagnostic challenges, and therapeutic strategies for this rare adverse effect.

II. CASE REPORT

A 37-year-old female patient was admitted to the Addiction Department of Ar-Razi Psychiatric Hospital in Salé in May 2025 for cocaine withdrawal and maintenance of abstinence. The diagnosis was cocaine use disorder comorbid with recurrent depressive disorder. The patient, a widowed mother of three with no occupation, had a history of multiple depressive episodes, a suicide attempt by medication overdose in 2024, and an appendectomy at age 15. No family history of neurological or psychiatric disorders was reported.

The patient was prescribed paroxetine 20 mg/day, topiramate 25 mg/day with gradual dose escalation, N-acetylcysteine (NAC) 1200 mg/day, and quetiapine 100 mg at night. At a dose of 100 mg/day of topiramate, after approximately six weeks of treatment, the patient experienced tingling in all four limbs, accompanied by a persistent sensation of heaviness throughout the day, without other associated neurological signs. Clinical examination showed normal tactile and pinprick sensitivity, with no evident motor deficits. Deep tendon reflexes were preserved.

A laboratory workup, including vitamin B9 and B12 levels, was conducted after consultation with internal medicine and returned normal results. A cold electromyography (EMG) was scheduled post-discharge.

The patient reported complete resolution of neurological symptoms after missing a single dose of topiramate, suggesting topiramate-induced peripheral neuropathy. After consultation with the pharmacovigilance center, similar cases were confirmed in the literature [1, 7]. Topiramate was gradually discontinued, and the patient was maintained on paroxetine 20 mg/day and NAC 1200 mg/day, with an adjusted dose of quetiapine for insomnia. At follow-up, the patient reported complete resolution of tingling and heaviness.

III. DISCUSSION

1. General Overview

Peripheral neuropathies involve damage to one or more peripheral nerves, resulting in sensory or motor symptoms of varying severity. Depending on the number and location of affected nerves, they are classified into mononeuropathies, multiple mononeuropathies, or polyneuropathies [4].

Causes of peripheral neuropathy are diverse, including mechanical factors (e.g., repetitive strain or injuries like carpal tunnel syndrome), autoimmune conditions (e.g., Guillain-Barré syndrome), metabolic disorders (e.g., diabetes), malignancies, infections (e.g., HIV, viral hepatitis), or chronic renal failure [11]. Certain medications (e.g., amiodarone, vincristine, dapsone) or therapies (e.g., immunotherapy, chemotherapy, radiotherapy) may also cause peripheral neuropathy. While not a common complication of topiramate, a few cases have been reported in the literature [1, 7, 9].

2. Epidemiology:

Topiramate-induced peripheral neuropathy is a rare adverse effect, with an estimated incidence of less than 1% based on pharmacovigilance data and case reports [1, 12]. It typically presents as distal, symmetrical sensory neuropathy, as observed in our case with tingling and heaviness in all four limbs.

Unlike other antiepileptics such as phenytoin or carbamazepine, which are well-known for causing neuropathies often due to folate deficiency or metabolic toxicity, topiramate-related neuropathy is rarely documented, highlighting the importance of clinical case reports [2, 10]. Available data suggest this adverse effect can occur at any age, with no clear predisposition related to sex or dose, although higher doses (e.g., 100 mg/day in our case) may increase the risk [13]. The rarity of this effect underscores the need for clinical vigilance, particularly in non-conventional uses like cocaine withdrawal, where topiramate is less commonly employed [8].

3. Pathophysiology:

Topiramate exerts its therapeutic effects through multiple mechanisms, including inhibition of voltage-gated sodium channels, enhancement of GABA activity, and antagonism of glutamate receptors. Peripheral neuropathy may result from direct toxicity to peripheral nerves, potentially due to disruption of mitochondrial function or oxidative stress causing axonal damage, primarily in sensory nerves [3, 14]. One study suggested that topiramate may impair mitochondrial protein synthesis, leading to energy dysfunction in axons, particularly in long, thin sensory fibers [1, 15]. In our case, the predominantly sensory symptoms without significant motor involvement align with the few reported cases, suggesting selectivity for sensory axons.

Concomitant use of paroxetine and NAC in our case was not associated with peripheral neuropathy in the literature, supporting topiramate as the likely cause. While cocaine itself can induce neuropathy, the absence of recent use and rapid symptom resolution after topiramate discontinuation rule out this possibility [16].

4. Clinical Presentation and Diagnosis:

Topiramate-induced peripheral neuropathy is characterized by sensory symptoms such as tingling, numbness, and, in some cases, burning pain, typically in a “glove-and-stocking” distribution [7]. In our case, the patient experienced tingling and persistent heaviness, which is less common but reported [1].

Diagnosis relies on three key elements:

- **Temporal relationship:** Symptoms appeared approximately six weeks after initiating topiramate, consistent with the typical onset of neurological adverse effects [9].
- **Exclusion of other causes:** Normal laboratory results (vitamin B9 and B12) and the absence of other risk factors (e.g., diabetes, autoimmune diseases, alcoholism) pointed to a drug-induced etiology.
- **Symptom resolution:** Complete resolution of symptoms after missing a single dose of topiramate strongly supports causality, rated as probable on the Naranjo scale [1, 17]. Contact with the pharmacovigilance center confirmed similar, though rare, cases in the literature.

5. MANAGEMENT

Management of topiramate-induced peripheral neuropathy primarily involves discontinuing the drug, as was done in our case with gradual tapering to avoid rebound effects, though this is less critical in non-epileptic indications like cocaine withdrawal [18]. Gabapentin, by modulating calcium channel activity, is effective in reducing paresthesia and heaviness. Other options, such as pregabalin or duloxetine, may also be considered [5]. Regular follow-up with nerve conduction studies is essential to assess recovery, which may be

partial or complete depending on the extent of axonal damage. Patients should be informed about the potential reversibility of symptoms and the need to avoid other neurotoxic medications [19].

6. Implications for Clinical Practice

This case highlights several clinical implications:

- **Increased monitoring:** Clinicians must remain vigilant for neurological symptoms, particularly sensory complaints, in patients on topiramate, especially in non-conventional indications like cocaine withdrawal, where data on adverse effects are limited [8]. Detailed history-taking and regular neurological examinations are recommended.
- **Interdisciplinary collaboration:** Collaboration between psychiatrists, neurologists, and pharmacovigilance centers is crucial for identifying and reporting rare effects. Reporting to the pharmacovigilance center in our case confirmed similar cases, emphasizing the value of pharmacovigilance databases [12].
- **Preventing recurrence:** Patients with topiramate-induced neuropathy should avoid other neurotoxic antiepileptics, such as phenytoin or lamotrigine, which have been linked to neuropathy in multicenter studies [6, 10]. In cocaine withdrawal, alternative therapies like NAC or non-pharmacological approaches should be prioritized when possible [20].
- **Patient education:** Informing patients about potential neurological side effects of topiramate can facilitate early detection and prompt management.

This case also underscores the challenges of using topiramate in emerging indications, where its safety profile is less established than in epilepsy or migraine. Further studies are needed to better define risk factors, including dose, treatment duration, and psychiatric or addiction comorbidities [13].

IV. CONCLUSION

Topiramate-induced peripheral neuropathy is a rare but clinically significant adverse effect requiring heightened clinician awareness. This case emphasizes the importance of recognizing sensory symptoms in patients on topiramate, conducting appropriate diagnostic workups, and promptly discontinuing the drug when neuropathy is suspected. Further studies are needed to elucidate the pathophysiology and identify risk factors for this condition. Regular neurological monitoring and patient education can improve outcomes for affected individuals.

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