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Disulfiram Associated Peripheral Neuropathy in Patients with Alcohol Dependence Syndrome

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Type of Publication: Case Series

Conflicts of Interest: Nil

Abstract

Background: Disulfiram therapy can cause sensory and motor neuropathy. Speculation arises whether disulfiram is a causative or precipitating factor in alcohol-dependent individuals as they are vulnerable to neuropathy. There is limited data on disulfiram-associated neuropathy. This uncertainty highlights the need for further research to delineate the specific role of disulfiram in the development of neuropathy in this population.

Case presentation: Presenting a series of four cases illustrating disulfiram-related peripheral neuropathy: In the first case, a 31-year-old man underwent disulfiram therapy for three months and experienced acute symptoms of pain and gait disturbances, accompanied by difficulty walking due to right foot drop. The second case involves a 37-year-old man who developed numbness in his lower limbs while on disulfiram therapy. The third case features a 33-year-old male with sudden-onset reduced pain sensation in both lower limbs, affecting the dorsum of the foot and lateral shin area, along with diminished power in bilateral plantar dorsiflexion. Lastly, a 25-year-old male, after three months of disulfiram therapy, presented with one month

of symptoms indicative of peripheral neuropathy in the distal lower limb and proximal myopathy.

Conclusions: Disulfiram-associated neuropathy is often overlooked and can be challenging to distinguish from alcohol-induced neuropathy, given their shared characteristics as axonal neuropathies. Recognizing this side effect could facilitate early medication discontinuation, potentially minimizing neurological consequences.

Keywords: Disulfiram, Peripheral neuropathy, Axonopathy

Introduction

Disulfiram also known as tetraethyl thiuram disulfide, is a thiuram derivative, that is used in patients with alcohol dependence disorder as an aversive agent in the deaddiction phase. It works by inhibiting the oxidation of alcohol at the acetaldehyde stage. The resulting accumulation of acetaldehyde leads to uncomfortable symptoms, known as the alcohol-disulfiram reaction, which forms the basis for its therapeutic use. [1,2] Disulfiram-induced neuropathy affects approximately one in 15,000 individuals undergoing treatment for alcohol dependence, making it one of the most significant side effects of disulfiram therapy. The severity of disulfiram neuropathy ranges from mild to severe and is influenced by both the duration of exposure and the dosage administered. Axonal degeneration is a well-recognized pathological hallmark of disulfiram toxicity. In contrast, alcohol-induced neuropathy typically exhibits a slower progression compared to disulfiram-induced neuropathy. [1]

Various authors have suggested that the physiological response to disulfiram is dose-dependent and linked to the accumulation of carbon disulfide. Documented complications include central nervous system effects such as drowsiness, headache, fatigue, polyneuritis, and psychosis, as well as peripheral nervous system issues like peripheral neuritis and neuropathy. Disulfiram neuropathy is classified as a distal axonopathy, characterized by axonal degeneration. [2,3] Watson et al. reported that neuropathy typically develops gradually, with an average onset of 5–6 months after initiating disulfiram therapy. Symptoms generally improve progressively upon discontinuing disulfiram, with full recovery often achieved within a few months. Disulfiram-associated peripheral neuropathy is characterized by axonal degeneration. However, research suggests that disulfiram primarily exerts its toxic effects on Schwann cells and myelin. [4,5]

The mechanism underlying disulfiram-induced peripheral neurotoxicity remains unclear. However, factors such as drug dosage, duration of exposure, and comorbid conditions appear to influence both the occurrence and severity of symptoms, irrespective of age or gender. Recovery from disulfiram-induced neuropathy likely follows a trajectory largely determined by the initial extent of neurological impairment. [6] Rare reports have associated disulfiram use, particularly at doses of 500 mg/day or higher, with psychosis, catatonia, delirium, polyneuritis, peripheral neuropathy, and optic neuritis. Peripheral neuropathy has been observed with varied clinical presentations, including sensory, motor, or mixed deficits, often accompanied by polyneuritis. Complete recovery typically occurs within 1 to 5 months following the discontinuation of treatment. [7]

Although rare, disulfiram can occasionally cause moderate to severe progressive neuropathy, which is often misdiagnosed as alcohol-induced neuropathy and frequently goes unrecognized. Only a limited number of

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cases have documented axonopathy as a side effect of disulfiram use. This case series is presented to highlight the importance of considering disulfiram as a potential cause when evaluating patients with peripheral neuropathy in the context of alcohol dependence syndrome.

Case series:

Case 1: A 31-year-old man with a history of alcohol use for 18 years with features of dependence and average use of eight to ten units per day presented with sensory symptoms of difficulty gripping sandals and numbness of bilateral lower limbs for 2 months. He also had difficulty lifting his right foot off the ground and difficulty walking due to pain in bilateral lower limbs. The symptoms were insidious in onset and progressed gradually. He was on disulfiram therapy (250mg) orally for three months. With no prior history of medical illness. On examination, there was graded vibration loss of bilateral lower limbs and absent ankle jerk. The power of the ankle joint was reduced (Dorsiflexion 2/5, plantarflexion 3/5). He had a high-stepping gait. Laboratory Nerve conduction study showed Lower limb sensorimotor axonopathy (right more than left) and severe length-dependent motor neuropathy which was demonstrated by decreased amplitude in the compound motor action potential (CMAP) in right peroneal and bilateral tibial nerve and involvement of sensory nerve fibers as evidenced by absent sensory nerve action potentials (SNAPs) at right sural and left superficial peroneal nerve.

Case 2: A 37-year-old man presented to the psychiatric outpatient department with complaints of daily alcohol consumption of 4 to 8 units since 20 years of age, meeting the criteria for dependence. The patient was on disulfiram therapy orally (500mg) per day for 6 months during which he had continued his alcohol use. Over the past four months, he developed numbness and tingling in both feet, with symptoms that were acute in onset and gradually progressive. The patient had no prior history of medical illness. On examination, tandem walking was impaired, and had swaying while walking. Rhomberg's test was positive. He had no prior medical history of diabetes, heavy metal exposure, neurological impairments, or drug use. Laboratory investigations were within normal limits. A nerve conduction study showed absent CMAP in the right peroneal nerve and diminished CMAP in the left peroneal nerve. He was started on Gabapentin and over the next few weeks, his symptoms improved.

Case 3: A 33-year-old adult male with a history of three to five units of daily alcohol consumption for the past 12 years meeting criteria for dependence presented with complaints of burning dysesthesia, numbness, pain, and weakness of bilateral lower limbs in the last 5 months. It was gradually progressive. He was abstinent for the past 6 months during which he was on oral Disulfiram therapy of 500mg per day, with no prior history of medical illness. On examination, the power was reduced in bilateral ankle dorsiflexion (grade 4/5), and pain sensation was decreased over the bilateral dorsum of the feet and lateral shin. Lab investigations were within normal limits, including liver function tests, thyroid function tests, viral markers, Serum electrolytes, and electrocardiogram. The nerve conduction study was suggestive of right peroneal axonopathy. Disulfiram was discontinued and the Patient was started on Gabapentin and he was symptomatically better in 4 weeks.

Case 4: A 25-year male unemployed hailing from a nuclear family presented with alcohol use for 10 years with increased consumption of 6 to 8 units of alcohol per

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day meeting criteria for dependence for 8 years, presented with complaints of weakness of bilateral lower limbs, difficulty in standing up from squatting position, and paraesthesia of bilateral lower limbs since one month. The patient was on disulfiram therapy for 3 months on a dosage of 500 mg per day. The patient had a history of alcohol withdrawal seizures but no other significant medical conditions contributing to neuropathy. On examination, the power in both feet was 3/5, an antalgic gait was observed, and there was reduced plantar touch sensation bilaterally. Laboratory investigations were within normal limits. A nerve conduction study revealed bilateral tarsal tunnel syndrome. Following the discontinuation of disulfiram, gradual improvement in paresthesia and weakness was noted. The patient was then started on pregabalin, and a review after one month showed significant improvement in sensory symptoms.

Discussion

Distal axonopathy is a common symptom of disulfiram-associated neuropathy, and it is present in all four cases. The substantial drop in CMAP in the lower limbs, while sparing the upper extremities reveals the length-dependent character of the disulfiram neuropathy. Disulfiram neuropathy and alcoholic neuropathy might be difficult to tell apart clinically Disulfiram neuropathy is noted to be progressive with acute onset when compared to gradually progressive symptoms in alcohol-induced neuropathy. Sensory neuropathy and proximal myopathy were the most common symptoms present in all cases. In all our patients, nerve conduction studies confirmed the presence of axonopathy. The diagnosis is often made clinically and was confirmed with electrophysiological study.

Disulfiram exhibits neurotoxic effects independent of alcohol consumption. Unlike alcoholic neuropathy, which typically affects small fibers, disulfiram neuropathy primarily targets large-diameter sensory fibers. It often begins with symptoms such as distal paresthesia and numbness. [4] Subsequently, motor symptoms may manifest in the distal foot muscles, potentially progressing to significant weakness such as foot drop or quadriparesis, which is uncommon in alcoholic neuropathy unless there is concurrent thiamine deficiency. [1]

In all our cases patients' symptoms progressed at a higher rate than is usual for alcoholic neuropathy. After discontinuing disulfiram, both patients experienced clinical improvement in their symptoms. Electrodiagnostic tests revealed significant length-dependent axonopathy, with low distal compound muscle action potentials (CMAPs) in the lower extremities but normal CMAPs in the upper extremities. Additionally, their sensory nerve action potentials (SNAPs) were absent, indicating the involvement of both small and large fiber sensory nerves. This contrasts with previous reports of disulfiram neuropathy primarily affecting small fibers. [2] Distal axonopathy, a hallmark of disulfiram toxicity, was evident in these two cases. This condition was demonstrated by low CMAPs with relatively normal motor conduction velocities. The length-dependent nature of disulfiram neuropathy was highlighted by the severely decreased CMAPs in the lower extremities, while the upper extremities remained unaffected. Neither laboratory studies nor electrodiagnostic testing indicated demyelination. Research suggests that the causative agent of disulfiram neuropathy is carbon disulfide, a by-product of disulfiram metabolism. [1] Ansbacher *et al.* reported a

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case in which a sural nerve biopsy demonstrated neurofilamentous distal axonopathy and cited carbon disulfide as the responsible agent. Clinically, distinguishing disulfiram neuropathy from alcoholic neuropathy can be challenging. However, certain observations can aid in differentiation. Disulfiram neuropathy typically presents with an onset within weeks, whereas alcoholic neuropathy develops insidiously over several months. Additionally, the progression of symptoms is faster in disulfiram neuropathy compared to the slower progression seen in alcoholic neuropathy.[6] Symptoms of both types of neuropathy can exhibit similarities, such as symmetrical distribution, more severe involvement distally, and a decrease in ankle jerk reflexes. However, disulfiram neuropathy is distinguished by additional manifestations including muscle tenderness and abnormalities in distal limb sweating, which are not typically seen in alcoholic neuropathy. [7,8]

Clinical, electrophysiological, and pathological evidence suggests that disulfiram may induce a potentially reversible, dose-related axonal polyneuropathy. Given the confounding factor of alcohol-related neuropathy, further investigation into the specific effects of disulfiram on peripheral nerves is warranted.[9.10,11] One approach would be to perform electrodiagnostic studies before initiating disulfiram therapy to establish a baseline. If neuropathy and decreased compound muscle action potentials (CMAP) are observed after the commencement of disulfiram therapy, these changes could be more confidently attributed to disulfiram, as patients would have abstained from alcohol during treatment.

Conclusion

In conclusion, while disulfiram-induced peripheral neuropathy is a rare occurrence, it remains an important consideration in patients with alcohol dependence syndrome. Early recognition, based on clinical evaluation and supported by neurophysiological studies, is crucial for effective management. Discontinuation of disulfiram at the earliest sign of neuropathy typically leads to full recovery. To minimize the risk of adverse effects, disulfiram should be prescribed at the lowest effective dose, accompanied by regular neurological monitoring to safeguard patient well-being.

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