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Case Report

Dissociation between vibration and joint position sensation in a case of metronidazole-induced reversible axonal polyneuropathy

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Abstract

Axonal neuropathy is an important neuropathic entity with guarded prognosis globally. Metabolic, inflammatory, vasculitis, infections, drugs and toxins are common causes of axonal neuropathy. Metronidazole is a commonly used anti-anaerobic and anti-protozoal medication in tropical countries having diverse utility. The neurological manifestations of metronidazole toxicity is diverse. The sensation of joint position and vibration ascend via common pathway of dorsal column tract. However, certain diseases can affect selective modality of sensation in the form of dissociation between vibration and joint position sensation. In this case report, we discuss a person presenting with distal paresthesia and tried to explore the various treatable aetiologies of axonal sensorimotor polyneuropathy in a 45 year-old man. A proper history and clinical examination can guide to exclusion of various clinical aetiologies.

Keywords: Axonal, Polyneuropathy, Metronidazole, Favourable, Dissociation.

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1. Introduction

Axonal neuropathy is an important common neuropathic entity with guarded prognosis worldwide.[1] The common aetiologies include diabetes mellitus, systemic lupus erythematosus, axonal variants of Guillain barre syndrome, toxins & drugs.[2] Metronidazole is a commonly used anti-anaerobic and anti-protozoal medication in tropical countries having diverse utility.[3] Metronidazole is an important cause of axonal neuropathy having favourable prognosis. The sensation of joint position and vibration ascend via common pathway of dorsal column tract. However, the receptors, central pathways in the spinal cord and final end-point for joint position and vibratory sensations are not identical. Hence, some neurological disorders can affect selective modalities and can result in dissociation between joint position and vibration.

2. Case Description

A 45 year-old-male, vegan, policeman of urban residence presented with insidious onset gradually progressive pain with tingling sensation in both feet for 6 months. There was no history of weakness, backache, radicular pain, neck pain, difficulty in vision, ocular pain or discharge, redness of eye, diplopia, facial pain or numbness, difficulty in chewing/swallowing/speaking, difficulty in hearing or change in voice. There is no history of fever, headache, altered sensorium or behaviour, memory loss, convulsions or abnormal movement of body. However, he denied of joint pain, rash, photosensitivity, raynaud phenomena, hair loss, urethral discharge, significant weight loss, cough. His bowel and bladder habits were unremarkable and there was no history of ingestion/inhalation of any abusive substance or history of high risk behaviour. He has no history of similar illness, diabetes mellitus, hypertension, vasculitis, and contact to tuberculosis or trauma. His general examination revealed pulse of 76/min, regular, blood pressure 130/84mm

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Hg, respiratory rate of 14/min, temperature of 97.4F, absence of pallor, icterus, clubbing, edema, significant lymphadenopathy, thyroid swelling, rash, hypopigmented patch, abnormal nail changes with normal tongue and oral cavity. His nervous system examination showed normal higher functions, cranial nerve examination including fundus, normal motor examination, including deep tendon reflexes and flexor plantar response bilaterally. Sensory examination revealed diminished vibration sensation, impaired pain, touch and temperature with intact joint-position sensation below ankles symmetrically without other sensory deficit. Rhomberg sign was negative. The cerebellar functions were normal with absent signs of meningeal irritation and peripheral nerves weren't palpable. The other systems were normal.

At this time, nerve conduction studies should be performed to elucidate the pattern of involvement objectively in terms of extent, distribution, severity and distribution of nerves. His nerve conduction study revealed axonal distal sensorimotor polyneuropathy affecting bilateral tibial, common peroneal and sural nerve amplitudes (reduced) with normal latencies, conduction velocities and preserved F waves. He was worked up extensively in the line of predominant sensorimotor polyneuropathy. His blood investigations showed hemoglobin of 13.8g/dl, wbc count 7900/cumm, with normal differential count, platelet count 1.9 lakhs/cumm, with mean corpuscular volume of 84fl, ESR 15 mm AEFH, blood sugar 98mg/dl, Hba1c 5.9, alanine transaminase 26 IU/l, aspartate transaminase 33 IU/l, alkaline phosphatase 102 mg/dl, bilirubin 0.56 mg/dl, creatinine 0.86 mg/dl, urea 16 mg/dl, sodium 142 mmol/l, potassium 4.6 mmol/l, calcium 9.3 mg/dl, thyroid stimulating hormone 1.28 IU/ml, vitamin B12 level of 340 pg/ml, C reactive protein 2 mg/l. His vasculitic workup (antinuclear antibody) including RH factor and anti-CCP antibody and serum protein electrophoresis were normal. His cerebrospinal fluid examination was also normal.

The aetiology for such involvement was not clear even after extensive workup for the same. So we reviewed back history of the patient where he revealed self-intake of oral metronidazole tablets (400 mg strength) thrice daily for last 15 months (total cumulative dose of 15 grams) for recurrent painful oral aphthous ulcers of 3 years. The diagnosis of metronidazole-induced chronic axonal predominant sensorimotor polyneuropathy was made in view of high cumulative dosage of the medicine ingested by the patient with temporal evolution of symptomatology and negative screen for other possible causes of the same. Patient was counselled about his illness and advised to immediately stop the medication. He was additionally advised to have gastromedicine consultation for aphthous ulcer if recurrence occurs. His imaging of brain and spine with contrast were performed to evaluate any other possible subclinical neurological involvement due to metronidazole toxicity but scans were normal. He has experienced substantial clinical improvement during follow-up at 3 months and was completely asymptomatic at 6 months.

3. Discussion

This patient of chronic predominant sensorimotor symmetric axonal polyneuropathy was diagnosed with metronidazole-induced polyneuropathy and counselled about risk of its prolonged use and advised to immediately stop the medication after which he improved substantially over months. The uniqueness in this case was the evidence of dissociation between impaired vibration sense and intact joint position sensation.

The approach of chronic polyneuropathy can be divided into various classifications like symmetric and asymmetric pattern; acquired and hereditary; sensory, motor, sensorimotor, autonomic and mixed; axonal and demyelinating; large fibre, small fibre and mixed involvement. Acquired etiologies include metabolic disorders like diabetes mellitus, toxins, drugs, infections, autoimmune conditions, paraneoplastic disorders. Axonal neuropathy is an important common neuropathic entity with guarded prognosis worldwide.[1] The common aetiologies include diabetes mellitus, systemic lupus erythematosus, axonal variants of guillain barre syndrome, toxins & drugs.[2] Metronidazole is commonly used anti-anaerobic and anti-protozoal medication in tropical countries having diverse utility.[3]

Metronidazole is a 5-nitroimidazole synthetic compound that inhibits microbial nucleic acid synthesis with central nervous system penetration with low drug resistance and high cost-effectiveness.[4] The exact mechanism of neurotoxicity is unclear but primarily related to axonal degeneration caused by inhibition of neuronal protein synthesis by metronidazole–mediated RNA binding, accumulation of free radicals, dysregulation of neurotransmission of GABA by metabolites, nutrition-deficiency-like neuropathy, production of nitro-radical anions and semiquinone during reactions between catecholamines and metronidazole.[5] Neurological adverse effects are theoretically rare but there are several case reports of diverse phenomena with metronidazole.[6] The neurological spectra of metronidazole toxicity in listed in **Table 1**.

Table 1:

CNS	PNS
a. Encephalopathy	a. Distal sensory/ sensorimotor polyneuropathy
b. Cerebellar syndrome	b. Autonomic neuropathy
c. Seizure	
d. Optic neuropathy	
e. Reversible splenial lesions syndrome	

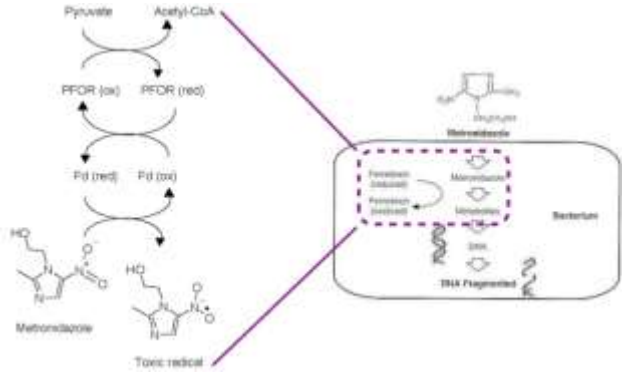

Figure 1: Pathogenesis of metronidazole toxicity

Electro-diagnostic tests can aid in pattern of neuropathy.[7] It has been suggested that neurological toxicity may be related to prolonged administration, high doses, or high cumulative doses of metronidazole.[8] There is no specific tests for diagnostic correlation at present and clinical diagnosis with exclusion with substantial recovery with stoppage of drug favours the diagnosis of neurological complication of metronidazole toxicity. However, brain magnetic resonance imaging finding of bilateral T2/Flair signal changes of dentate nuclei, splenium part of corpus callosum are a characteristic feature as reported (wernicke's encephalopathy is the important differential diagnosis here).[6,9] After stopping the drug, encephalopathy, cerebellar syndrome and peripheral neuropathy can show excellent prognosis(over days to weeks).[10] In contrary, a case report by Peng et al., persistant sensory complaints affected occupational status even after 6 months of drug stoppage.[11] The neurotoxic effect of metronidazole can be considered to be underappreciated due to lack of insight and awareness.[12]

Most toxic neuropathies including medication-induced forms, principally induce axonal degeneration in a "dying back" pattern disproportionately affecting the distal segments of the most vulnerable long nerves. Peripheral neuropathy in the form of axonal degeneration is a rare side-effect seen with chronic intake of metronidazole. This entity has a favourable outcome with drug discontinuation in due course of time. In this case report, we discuss a person presenting with distal paresthesia and tried to explore the various treatable aetiologies of axonal sensorimotor polyneuropathy. The uniqueness of this case is the clinical outcome of an axonal polyneuropathic diagnosis after discontinuation of the offending drug observed at 3 month follow-up.

Another prominent observation, as mentioned earlier is the dissociation between impaired vibratory and intact joint position sensation, which is carried by common dorsal column tract afferent ascending pathway upto the somatosensory cortex.[13] There are a few evidences that the central pathways in the spinal cord for position and vibratory sensations are not identical.[14] Despite the fact that the core routes that mediate joint position and vibration perception appear to be the same, they end on separate thalamic and cerebral cortex neurons. These sensory functions are also mediated by different receptors. Some neurological conditions impact one of these sensory functions while leaving the other partially or entirely unaffected. However, Netsky described a patient with syringomyelia in who had a decreased vibration feeling but a normal joint position sensation where he noticed a normal dorsal column with the evidence of demyelination in lateral funiculus.[15] Hence, he inferred that the ascending fibres for vibration sensation splits into dorsal column and lateral funiculus. Furthermore, patients with multiple sclerosis, rheumatoid cervical myelopathy, and brainstem infarction reported similar presentation of reduced vibratory sensation and intact joint position sensation.[16]

4. Conclusion

Metronidazole is an important cause of axonal neuropathy. Metronidazole induced axonal neuropathy has favourable prognosis. Metronidazole is an effective medicine that is widely used off-label drug prescribed in day-to-day life. However, rampant use of this beneficial medicine should not be advocated. A proper history and clinical examination can guide to exclusion of various clinical aetiologies.

5. Source of Funding

None.

6. Conflict of Interest

None.

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