

Neuropathy in Patients on Linezolid and High Dose Isoniazid based Regimen for Drug Resistant Tuberculosis

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ABSTRACT

Introduction: Drug resistant Tuberculosis (DR-TB) is a major hurdle in the eradication and control measures of national tuberculosis programme. The DR – TB management are not only expensive, but also toxic with poor outcomes. This article highlights the severity of neuropathy in DR-TB patients in correlation with EMG and NCV studies which is first of its kind.

Material and methods: The Department of Respiratory Medicine at LTMGH (Sion, Mumbai) studied 12 patients of tingling and numbness while on DR-TB regimen. These patients underwent Neurological Evaluation and Nerve Conduction Studies (NCS).

Results: The results of analysis based on their drug regimen and NCS were suggestive of predominantly sensory type of neuropathy.

Conclusions: The causative drug clinically was high dose Isoniazid and Linezolid which were withheld and subsequently patients improved clinically on withdrawal of these drugs and supportive treatment.

Keywords: Peripheral Neuropathy; MDR-TB; XDR-TB

INTRODUCTION

Multidrug Resistant Tuberculosis is a major public health concern for World Health Organization (WHO).¹ India alone accounts for 2.79 million cases of Tuberculosis in the world (2016). Drug Resistant tuberculosis account for 4.1% in new cases and 19% in re-treatment cases globally. Drug resistant Tuberculosis treatment is associated with a spectrum of side effects including gastro-intestinal, skin reactions and neuropsychiatric involvement. This study highlights the neuropathic complaints of patients on drug resistant tuberculosis treatment and its correlation with neurophysiologic studies. The treatment of drug resistant tuberculosis is prolonged and hence cumulative toxicity of drugs are more likely to cause adverse events than diseases which have shorter treatment. Drugs like Linezolid do not cause serious adverse events like bone marrow affection and retinal toxicity when given for indications for bacterial infections. Neuropathy is especially common with Linezolid treatment for more than four weeks.² Peripheral neuropathy is more common with Isoniazid in patients who are diabetic, pregnant, immunocompromised host and chronic alcoholics. Prophylactic dose of pyridoxine helps to prevent neuropathy in the above patients. Drug resistant tuberculosis results in various adverse effects involving various systems which makes completing the two year regimen very difficult. The use of newer drugs like Bedaquiline and Delamanid

has helped to shorten the duration of treatment but they are still investigational drugs requiring Conditional Access Programme (CAP).

Current research aimed to study the neuropathic symptoms of patients on treatment of drug-resistant tuberculosis and to correlate the symptoms with their neurophysiologic study.

MATERIAL AND METHODS

Patients of Drug Resistant Tuberculosis in a tertiary care institute in the Respiratory Medicine Department of Lokmanya Tilak Municipal Medical College (Sion, Mumbai) were followed up prospectively in outpatient department for side effects related to treatment for a period of 2 years (2016-2018). Since the neuropathic complaints were less common in the given follow up patients of 200 drug resistant patients, all patients with neuropathic complaints were included in the study. The drug history was carefully taken and noted.

Inclusion Criteria

All patients with neuropathic complaints (tingling and numbness) in either upper or lower limbs were included in the study.

Exclusion Criteria

All patients with Diabetes and HIV (Human Immunodeficiency Virus) were excluded so that confounding factors were excluded.

All patients were evaluated based on their neuropathic complaints by Neurologist in this hospital and appropriate tests were advised. Patients of tingling and numbness of hands or feet were evaluated by Neurologist including their clinical examination. These patients were advised Nerve Conduction studies by the Neurologist. These studies were conducted during their symptoms by an Electrophysiologist. The Nerve Conduction studies were performed on both upper limbs and lower limbs. Tests were conducted for both

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sensory and motor neuropathy. Severity of nerve conduction defects were graded based on their action potentials evoked during the procedure. The symptoms were correlated with these reports based on upper and lower limbs, severity of the defects and sensory or motor nerve defects. Subsequently, the reports were evaluated by Neurologist and appropriate symptom relief medications.

RESULTS

12 patients of Drug Resistant Tuberculosis on appropriate Regimen under National Programme (Programmatic Management for Drug Resistant Treatment - PMDT) complained of tingling and numbness in the limbs. They had no other illnesses. The patients presented with these complaints ranging from 3 months to 9 months after starting treatment. These patients underwent Nerve Conduction studies (NCS). All these patients were treated with Linezolid based regimen. 8 patients were also on High dose Isoniazid in their treatment regimen.

Of these 12 patients, 3 patients had symptoms of tingling and numbness; however they had normal nerve conduction reports.

Of the remaining 9 patients, all patients had sensory type of neuropathy. 1 patient had an additional motor neuropathy too. Majority of the patients had axonal type of Neuropathy (6/9 patients). Of the 9 patients with sensory neuropathy, 3 patients had absent sensory nerve conduction in bilateral lower limbs; (Table 1 & 2) while 5 patients had markedly diffuse sensory polyneuropathy in bilateral lower limbs. (Table 3 & 4) One patient had only mild sensory polyneuropathy in lower limbs.

Of these 9 patients, 3 patients had Upper limb absent nerve potentials in bilateral median and ulnar nerves too. 2 patients had mild sensory polyneuropathies; while rest 4 had normal upper limb nerve conduction studies.

NCS	Frequency
Normal NCS	3
Sensory Type of Neuropathy	9
Motor Type of Neuropathy	1
Axonal Type of Neuropathy	6

Table-1: Analysis of Nerve Conduction Studies (NCS)

Lower Limb Involvement	9
Upper Limb Involvement	5

Table-2: Upper & Lower Limb Involvement

Absent Sensory Nerve Conduction	3
Markedly Diffuse Sensory Polyneuropathy	5
Mild Sensory Polyneuropathy	1

Table-3: Severity of Conduction Defects in Lower Limbs

Absent Sensory Nerve Conduction	3
Mild Sensory Polyneuropathy	2
Normal study	4

Table-4: Severity of Conduction Defects in Upper Limbs

Only one patient had motor neuropathy in bilateral lower limbs.

These patients with neuropathy symptoms were evaluated by Neurologist. Subsequently, a clinical decision of withholding Linezolid^{2,3,4} and high dose Isoniazid from their regimen was taken. These patients had decreased symptoms over a period of one month and continued on a modified regimen as per PMDT. These drugs were not re-introduced in the regimen. Patients were also treated with high dose Pyridoxine (Vitamin B6), other multivitamins and Tablet Pregabalin 75 mg in more symptomatic 3 cases. Those patients with poor regimen for drug resistant tuberculosis on excluding the above drugs, were reinforced with other alternative and sensitive drugs based on their drug sensitivity pattern. Symptoms preceded in 3 patients as they had normal nerve conduction studies.

DISCUSSION

Patients of Drug Resistant Tuberculosis have various side effects while on treatment with second line anti tuberculosis drugs. Neuropathy symptoms in second line drugs are primarily due to High dose Isoniazid and Linezolid based on clinical grounds.^{5,6,7} The treatment involved withdrawal of these drugs from the regimen and supportive treatment like high dose pyridoxine and other vitamin supplements. Severe cases required use of Pregabalin for symptomatic relief. Linezolid may cause neuropathic symptoms, bone marrow suppression (thrombocytopenia, bicytopenia and aplastic anemia) and toxic amphyopia.^{5,6} The neuropathy so developed does not resolve completely despite withdrawal of the drug as noted in all our patients. The symptoms may be debilitating enough to carry out even routine household activities resulting in significant impairment. This affects patients' quality of life. Thus, patients while they start getting better from TB disease while on these second line anti TB drugs; they deteriorate functionally due to worsening neuropathic symptoms. Similar to study conducted by Shin SS et al (2003), where 10 patients had lower limb neuropathy symptoms and all sensory; in our study, 9 patients had lower limb and 5 patients had both upper and lower limb neuropathic symptoms. (3 patients had normal NCS). None of our patients had complete resolution. Withdrawal of Linezolid and high dose Isoniazid helped in alleviating symptoms along with supportive care from Neurology medications. Previous studies with co-relation to Nerve Conduction studies have not been done in the past. These patients recovered in terms of Tuberculosis (culture negative) while on continuation of the rest of the regimen. Even in the study by Singh et al (2019)⁸, Linezolid based regimen showed neuropathic symptoms in 14 out of 33 patients on drug resistant TB, of these 2 patients required permanent discontinuation from their regimen. In the article published by Joseph Kass and Wayne Shandera (Aug 2010)⁹, the use of antituberculous drugs (first and second line) may hamper compliance of the patients due to its central and peripheral nervous effects. Similarly, in the study by Arnold et al (Jan 2016), peripheral neuropathy account for 13-17% of patients on drug resistant tuberculosis. The drugs may

affect sensory, motor or autonomic nerves producing various symptoms of peripheral neuropathy. This was highlighted in our study with co-relation with Nerve Conduction studies. It is worthwhile to note that symptoms of neuropathy precede the development of neurophysiological changes in the Nerve Conduction studies (3 cases in our study). This fact is well known in Diabetic neuropathy.

All the above patients were non-diabetic and did not suffer from Human Immunodeficiency virus (HIV). They did not have any prior symptoms of neuropathy at baseline making drug induced peripheral neuropathy as the most likely diagnosis. Abatement of symptoms on withdrawal of neuropathic drugs (Linezolid and high dose Isoniazid) adds to the clinical diagnosis.

CONCLUSION

Multi drug Resistant Tuberculosis treatment is associated with adverse reactions like neuropathic symptoms. The causative drugs were clinically high dose Isoniazid and Linezolid. The symptoms were correlated with predominantly sensory type of neuropathy in both upper and lower limbs. Withdrawal of these drugs and symptomatic treatment helps patient improve significantly though not completely. Symptoms of neuropathy precede changes in nerve conduction studies.

Limitations of the study

The numbers of patients evaluated were small. Follow up Nerve conduction studies could not be undertaken as patients are still on treatment with modified regimen for drug resistant tuberculosis. The specific drug responsible (Linezolid OR High dose Isoniazid) could not be attributed as both have potential to cause neuropathy and both were withdrawn from the drug regimen to alleviate symptoms of neuropathy.

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