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ISONIAZID THERAPY INDUCED PERIPHERAL NEUROPATHY

KEY WORDS: Isoniazid therapy, peripheral neuropathy, nerve conduction study

Dr. Biswadeb Ghosh Associate Professor, Dept. of General Medicine, Shri Ramkrishna Institute of Medical Sciences

Dr. Dinesh Virendra Lashkare Associate Professor, Dept. of General Surgery, Shri Ramkrishna Institute of Medical Sciences

Dr. Neelam Dinesh Lashkare Associate Professor, Dept. of Obstetrics & Gynaecology, Shri Ramkrishna Institute of Medical Sciences

Dr. Ankana Chakraborty* Assistant Professor, Dept. of Microbiology, Shri Ramkrishna Institute of Medical Sciences*Corresponding Author

ABSTRACT

Background: Isoniazid forms an integral part of first-line anti-tubercular therapy. However, peripheral neuropathy is a commonly-associated adverse event of isoniazid therapy. Neuropathy can progress to severe symptoms such as ataxia. Though millions of people are taking INH on a long-term basis, a minority of them are developing clinical neuropathy. Hence, chances are there that many more of them are having a subclinical form of peripheral neuropathy. **Methods:** A clinical and electrophysiological study was done on 60 subjects consisting of 30 patients of tuberculosis taking isoniazid for more than three months and 30 healthy controls of a similar age, sex and socio-economic status. Electrophysiological studies consisted of recording motor nerve conduction velocity, sensory nerve conduction velocity, amplitude and duration of action potential and terminal latency. Median nerves, ulnar nerves and sural nerves were tested bilaterally. A reduction of more than 10% in nerve conduction velocity in the cases was considered significant to label them as suffering from neuropathy (clinical/subclinical). **Results:** The difference in velocity from controls was found significant in both nerves (p-value < 0.001); that of amplitude is significant only in the sural nerve (p-value <0.05); that of terminal latency is also significant only in the sural nerve (p<0.01) and that of the duration of the action potential are insignificant in all the three nerves. **Conclusion:** Isoniazid therapy, unless given along with pyridoxine, produced neuropathy which may be clinical but is more often subclinical. Our study also suggested that sensory nerve conduction studies are more sensitive in detecting subclinical neuropathy.

Introduction:

Tuberculosis (TB) still remains a public health problem in India and worldwide. Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19. Reports suggest that a total of 1.6 million people died from TB in 2021[1]. As per WHO Global TB Report 2022, 21.4 Lakh TB cases were notified in India in 2021 which is 18% higher than in 2020[2].

However, TB is curable and preventable. Isoniazid forms an integral part of first-line anti-tubercular therapy. It is a prodrug activated by the catalase-peroxidase KatG, creating a variety of radicals and adducts that inhibit the production of the mycolic acids that make up the cell wall of Mycobacterium tuberculosis. This activity lends INH to being a potent bactericidal agent.

Several adverse effects are associated with isoniazid (INH) use. The most common side effects include gastrointestinal disturbances, a rash and/or pruritus. Peripheral neuropathy (PNP) is also an associated adverse event of isoniazid therapy. In vivo pyridoxine (B6) is converted into coenzymes which play an essential role in the metabolism of protein, carbohydrates, fatty acids, and several other substances, including brain amines. INH competitively inhibits the metabolism of pyridoxine resulting in decreased amounts of biologically active B6. This fact necessitates pyridoxine supplementation for the patients under treatment with INH.

Patients usually present with paresthesia which can be accompanied by muscle aches, occasionally muscular weakness, and can progress to more severe symptoms such as ataxia [3]. Risk factors for developing neuropathy after isoniazid therapy include old age, slow acetylator status, diabetes, renal failure, alcoholism, malnutrition, HIV infection, chronic hepatic failure, pregnancy, etc. [3].

Though millions of people are taking INH on a long-term basis, a minority of them are developing clinical neuropathy. Hence, chances are there that many more of them are having a subclinical form of peripheral neuropathy. Electrophysiological studies can detect subclinical peripheral neuropathy by demonstrating a reduction in the motor and sensory nerve conduction velocities.

Keeping these in mind, this study was done to estimate the burden of PNP on patients with isoniazid therapy using nerve conduction velocity and evoked potential responses.

Materials & Methods:

A case-control study was conducted in a tertiary care hospital comprising of 60 subjects. Thirty patients on INH therapy for more than three months with/without symptoms of neuropathy were included in the group of Cases. Thirty healthy individuals, age and gender-matched, of similar socio-economic status and similar dietary habits, who volunteered themselves were included in the control group.

Electrophysiological studies were conducted on both groups. It consisted of recording motor nerve conduction velocity, sensory nerve conduction velocity, amplitude and duration of action potential and terminal latency. Motor nerve conduction studies were done in the bilateral median and ulnar nerves while sensory nerve conduction studies were done in the bilateral median, ulnar and sural nerves. The latency, amplitude and duration of muscle action potentials were measured. Conduction velocity was determined using the following formula:

Conduction velocity = (Inter stimuli distance) / (Latency 1 – Latency 2)

Cases having symptoms of neuropathy in the form of tingling, numbness, paraesthesia, burning sensation or signs in the form of weakness, ataxia, diminished ankle jerks or diminished vibration sense were designated as clinical neuropathy. Patients having no symptoms of neuropathy but having a reduction in nerve conduction velocity by more than 10% in two or more nerves were considered to be having subclinical neuropathy.

Observation & Discussion:

Electrophysiological studies in the control group revealed the following results: Motor nerve conduction velocities were 59.32 ± 3.41 and 61.01 ± 3.34 M/sec, amplitudes were 9.21 ± 3.09 and 5.76 ± 1.53 mV, terminal latencies were 3.36 ± 0.38 and 2.51 V 0.56 mSec, and duration of action potentials were 11.22 ± 1.35 and 9.17 ± 1.80 mSec in the median and ulnar nerves respectively. The corresponding values in cases were 55.86 ± 3.51 and 56.60 M/sec, 8.53 ± 2.84 and 5.48 ± 1.43 mV, 3.62 V 0.33 and 2.63 ± 0.41 mSec and 11.38 ± 1.41 and 9.38 ± 1.84 mSec in the median and ulnar nerves respectively. Nerve conduction studies in affected cases were as follows: velocity 50.77 ± 1.67 and 51.53 ± 2.19 M/sec, amplitude 5.78 ± 2.07 and 4.79 ± 1.05 mV, terminal latency 3.65 ± 0.39 and 2.69 ± 0.41 mSec and duration of action potential 12.62 ± 2.06 and 12.30 ± 2.12 mSec in the median and ulnar nerves respectively.

The normal values for sensory nerve conduction studies were as follows: velocity 62.61 ± 3.51, 63.73 ± 3.49 and 52.12 ± 3.25 M/sec; amplitude 8.51 ± 3.56, 6.32 V 3.14 and 5.84 V 2.47 mV; terminal latency 2.40 ± 0.28, 2.12 ± 0.34 and 3.19 ± 0.36 mSec and duration of action potential 1.67 ± 0.41, 1.47 ± 0.41 and 1.44 ± 0.26 mSec in median, ulnar and sural nerves respectively. In affected cases, sensory nerve conduction studies were as follows: velocity 51.84 ± 2.76, 52.54 ± 3.52 and 40.91 ± 5.49 M/sec; amplitude were 5.75 ± 3.39, 3.74 ±1.93 and 2.50 ± 1.01 mV; terminal latency were 2.51 ± 0.36, 2.24 ±0.27 and 3.79 ± 0.51 mSec and duration of action potential were 1.75 ± 0.48, 1.54 ±0.47 and 1.51 ±0.37 mSec in median, ulnar and sural nerves respectively.

The difference in velocity from controls was found significant in both nerves (p-value < 0.001); that of amplitude is significant only in sural nerve (p-value <0.05); that of terminal latency is also significant only in sural nerve (p<0.01) and that of duration of action potential are insignificant in all the three nerves.

As per our study, sensory nerve conduction studies are more sensitive in detecting subclinical neuropathy in comparison to motor nerve conduction studies. It might be due to the fact that motor nerve conduction studies reflect the pathology of faster conducting i.e., larger diameter nerves fibre and its utility is comparatively limited where small fibres are involved [14].

Clinical features of neuropathy were present in 3.33% of patients and subclinical neuropathy was detected in 26.67% of cases. Older patients and those on INH for longer periods (six months) were more susceptible to the development of neuropathy. Diet played no role while concurrent pyridoxine therapy prevented the occurrence of neuropathy.

The incidence of PNP in INH-treated patients in cross-sectional studies revealed a rate ranging from 2 to 44% for an HIV-negative group [4, 5]. This distinction is relevant due to the fact that new cases of TB mainly occur in Asia and Africa in association with HIV, which regularly induces PNP either by itself or via HART, for example, treatment with nucleoside-reverse transcriptase inhibitors (NRTI) [4,5,6,7].

The pathophysiological background of INH-induced PNP is not well understood. It is likely that iso-nicotinic acid hydrazide interferes with vitamin B6 (pyridoxine) metabolism, leading to deficiency in biologically active B6 by inhibition of pyridoxine-dependent enzyme systems [8,9,10] Data from western countries reveal that rates of peripheral neuropathy in the general population have been noted to be around 1.1% but as high as 6% in the elderly [11]. Among persons with drug-susceptible TB (DS-TB), rates between 0 and 10% have been reported in the literature whereas for those with drug-resistant TB (DR-TB) much higher rates have been seen, with studies reporting rates between 13 and 17% [12,13].

Conclusion:

In this study, correlation of clinical findings with electrophysiological data revealed the following:

- Isoniazid even when given in low doses for more than 6 months produced neuropathy which may be clinical but is more often subclinical.
- Our study also suggested that sensory nerve conduction studies are more sensitive in detecting subclinical neuropathy in comparison to motor nerve conduction studies.
- Peripheral neuropathy due to isoniazid did not necessitate discontinuing the drug provided that the patients were following carefully and pyridoxine was included as part of the daily regimen.

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