October 2015

Isoniazid induced motor-dominant neuropathy

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CASE REPORT

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Abstract

Isoniazid though a very effective treatment for tuberculosis can cause severe motor-dominant neuropathy which can be reversible with pyridoxine supplementation. A 45-year-old female diagnosed with psoas abscess, culture positive for mycobacterium tuberculosis, was started on anti- tuberculous treatment with four drugs, including isoniazid at a dose of 5 mg/kg/day. Three months later she developed severe motor weakness of lower limbs with loss of ankle and knee reflexes. She was treated with vitamin B6 injections and isoniazid treatment was continued. Her motor weakness gradually improved in a few months, but mild sensory impairment persisted even after two years. There is need for vigilance regarding neurological effects of isoniazid in seemingly low-risk individuals in whom development of symptoms should raise the suspicion about slow acetylator status. Timely therapeutic intervention with high-dose vitamin B6 can reduce the long-term morbidity associated with this easily reversible condition.

Keywords: Isoniazid, Neuropathy, Pyridoxine, Anti tuberculous therapy.

Introduction

The World Health Organisation (WHO) ranks Pakistan 5th among the "high tuberculosis (TB) burden countries". About 420,000 new cases are reported every year in the country[1] and most patients are treated with recommended first-line anti-TB drugs that include isonicotinylhydrazine (INH) or isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. Isoniazid typically causes a sensory peripheral neuropathy which presents with burning and numbness of the extremities. In a few cases, sensory symptoms may progress rapidly with the development of ataxia and motor weakness. Isoniazid acts as a competitive inhibitor of pyridoxine (B6), making its biologically active form less available for proper functioning of nerve cells.[2]

The incidence of isoniazid-induced neuropathy is very low, ranging from 0.2-2% in the general population.[2] This susceptibility appears to be highest in the elderly, during pregnancy, in chronic alcoholics, malnourished, human immunodeciciency virus (HIV) infected individuals and patients with slow acetylator genotype.[3] Therefore guidelines recommend vitamin B6 prophylaxis only for the above-mentioned high-risk patients.[4-6]

In line with a case reported from Tunisia in 2012,[4] we report a case of a middle aged female who developed severe axonal sensory and motor neuropathy leading to quadriparesis three months after she was started on anti-TB treatment (ATT) without vitamin B6 prophylaxis.

Case Report

A 45-year-old woman, a teacher by profession, presented with sudden onset of numbness and muscle weakness of limbs with one-week history. Her symptoms had started with difficulty in rising from a chair progressing to weakness of the upper limbs as well. She had been diagnosed with a psoas abscess three months earlier at a local hospital that was drained and was found to be culture-positive for mycobacterium tuberculosis after which the intensive phase of ATT using four drugs (isoniazid 5mg/kg, rifampicin 10mg/kg, pyrazinamide 25mg/kg and ethambutol15mg/kg) was given for two months. Her symptoms started during the early part of her continuation phase with two drugs (isoniazid and rifampicin). She did not receive any vitamin B6 supplementation alongside ATT. Her only co-morbid condition at the time of treatment was hypertension which was controlled on an angiotensin-converting-enzyme (ACE) inhibitor lisinopril10mg. The patient had no history of immunodeficiency, diabetes, renal failure, hepatic dysfunction, human immunodeficiency virus (HIV) infection. She was a non-smoker and did not use alcohol. She denied any recent upper respiratory tract infections or fever. She appeared to be recovering well from her tuberculosis infection as evident from a history of weight-gain and resolution of fever. She presented to the clinic in a wheelchair unable to walk or bear weight. Her vitals were stable with a body mass index (BMI) of 26kg/m^2. General physical examination was unremarkable. Neurological examination revealed sensorimotor tetra paresis with a muscle strength of 4/5 in all extremities. Achilles and patellar tendon reflexes were reduced. Peripheral joints were free. There were

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decreased touch sensations with total loss of proprioception in both upper and lower limbs. Cranial nerves were intact. There was no deglutition or breathing difficulty. With symptoms involving all four limbs, she was diagnosed with INH-induced B6 deficiency with a differential of Guillian Barre Syndrome (GBS). An urgent consultation was sought from neurologist and she was empirically started on vitamin B6 injections.

A complete blood count (CBC) ordered at the time of presentation showed mildly low haemoglobin of 10.2gm/dl. All other laboratory investigations, including lactate dehydrogenase (LDH), creatinephosphokinase (CPK), erythrocyte sedimentation rate (ESR), liver enzymes Alanine transaminase (ALT) and thyroid stimulating hormone (TSH) were within normal limits.

Electromyography was also ordered which showed severe axonal sensorimotor polyneuropathy with slow conduction velocities of bilateral peroneal motor nerves and nerves supplying right tibias anterior muscle. After review of all investigations, injectable vitamin B complex was continued, and amitriptyline gabapentin was prescribed for neuropathic pain. Physiotherapy was initiated. The patient showed rapid improvement in muscle weakness one week after initiation of B6 injections by demonstrating an ability to stand on her own. Subsequent visits showed further improvement with increasing ability to bear weight and ambulate. She was later switched to oral pyridoxine at a dose of 100mg/day and physiotherapy was continued. Over the next several months she continued to show improvement with decreasing motor dysfunction. She, however, continued to have mild sensory deficit in all limbs, lower more than upper, and power deficit in the small muscles of her feet.

At two-year follow-up she was able to climb stairs with minor difficulty, but continued to have mild numbness and tingling in her toes. Power returned to 5/5 in both upper and lower limbs.

Discussion

Numerous studies have identified isoniazid as a cause for peripheral neuropathy.[2,3] Practically, however, the incidence of peripheral neuropathy among patients receiving isoniazid at conventional doses is reported to be very low, ranging from 0.2-2%.[3] This neuropathy is most common in high-risk patient population that includes slow acetylators, patients with HIV, diabetes, chronic renal failure, pregnant and lactating women, malnourished and elderly patients, alcoholics, patient on certain medications that antagonize B6 effect like hydralazine, cycloserine, penicillamine and antiretroviral drugs.[2,3] The guidelines of WHO, Centers for Disease Control and Prevention(CDC), the American Thoracic Society (ATS), therefore, recommend 10-25mg per day pyridoxine prophylaxis along with isoniazid to prevent the onset of neuropathy in these high-risk groups.[4,5] Local guidelines from Pakistan also do not recommend B6 prophylaxis for low-risk groups despite this disease being highly endemic.[6] Our patient despite being a low-risk candidate for INH-induced neuropathy developed severe motor dominant polyneuropathy that was later on reversed with pyridoxine supplementation.

There is no report to our knowledge that patients with no risk factors developed severe motor dominant neuropathy after the use of isoniazid. However, literature search has identified two case reports of isoniazid-induced neuropathy in the presence of one or more underlying risk factors. The first, published in 2006, mentioned the case of a 42-year-old French female, diagnosed as HIV, who developed sensori-motor neuropathy three months after commencement of isoniazid therapy for presumed tuberculosis. Assuming a slow acetylator status for her, the dose of INH was reduced, and vitamin B6 supplementation resolved the neuropathy completely.[7] The second case report published in 2012 in Tunisia described a patient who developed motor neuropathy just two weeks after the start of INH.[8] In this case, however, a BMI of 18kg/m^2 may have contributed to an increased risk of neuropathy. In our case the nutritional status as well as BMI were well within normal range. In the absence of a low BMI and known co-morbidities, low acetylator status of our patient was another consideration, but laboratory testing is not readily available to check acetylator status in our part of the world.

National and regional guidelines on tuberculosis do not recommend pyridoxine prophylaxis in low-risk patients probably as it adds approximately Rs1500 (USD15.2) per patient for every six months of treatment. In addition, the low incidence of neuropathy with isoniazid use and its reversibility with therapeutic doses of pyridoxine goes against the argument of routine prescription of pyridoxine as prophylaxis.

However, a concern in our part of the world is that many patients get lost to follow-up or present late after symptoms manifest, primarily due to financial reasons or lack of health awareness. Would it be prudent, therefore, to also provide prophylaxis to low-risk patients who have poor health awareness, an understanding of drug side effects and are at risk for getting lost to follow-up? Another question arises whether presence of other micronutrient deficiencies commonly found here makes

patients more vulnerable to the side effects of ATT.

Our patient, despite getting a timely diagnosis and treatment, recovered but was left with some residual deficits.

The solution maybe for physicians to perform a meticulous review of risk factors in all patients undergoing ATT without pyridoxine supplementation, educate them regarding potential side effects of ATT so that they may seek early medical attention.

Conclusion

The case highlights the need for vigilance regarding neurological effects of INH in seemingly low-risk individuals. Healthcare providers need to assess nutritional status before starting ATT. More importantly, all patients receiving ATT should be educated about the risk of neurological side-effects of INH and the need for early reporting so that timely therapeutic intervention can reduce the long-term morbidity associated with this easily reversible albeit rare condition.

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