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### Paraparesis following commencement of Anti Tuberculosis drugs for latent Tuberculosis. Case report and review of literature

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#### ABSTRACT

A 43 year old female Patient, with recently diagnosed latent Tuberculosis (TB), started On anti- TB drugs (Isoniazid, Rifampicin), came with symptoms of Motor and sensory polyneuropathy only 4 weeks after starting the drugs. Extensive investigations were pursued. Nerve conduction study showed Features of Guillain- Barre syndrome (GBS). After stopping the Anti TB medications, patient symptoms Improved. This gives us an idea that Anti TB medications can itself trigger GBS. The Association of TB and GBS will be reviewed in Literature as well as the differentials and management.

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## Background:

Tuberculosis (TB) is a disease caused by a germ called *Mycobacterium tuberculosis* that is spread from person to person through the air by droplets.

Clinical manifestations include active TB, latent TB, Reactivation TB and Miliary TB

Latent Tuberculosis (TB) means that the patient has been previously exposed to TB but does not have the active disease and is not infectious. The diagnosis of latent TB is made when there is a positive tuberculin skin test or Quantiferon test and active Pulmonary TB is ruled out by negative Sputum Acid fast bacilli stain.

Acute immune mediated Polyneuropathies come under the umbrella of Guillain Barre Syndrome. It is a demyelinating disease of peripheral nerves and has many variants like Acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, Miller fisher syndrome, paraparesis variant to name a few. The diagnosis is made by Lumbar puncture, which shows high protein with normal cell counts called "Albuminocytological dissociation" and Nerve conduction studies. The prognosis is fair usually but in some cases can lead to Life threatening respiratory muscle weakness and breathing difficulty. Its treatment is mainly Intravenous Immunoglobulin or plasmapheresis. (1-2)

## Case Presentation:

We report a 43-year-Old female, Recently Diagnosed as Latent TB and started on Anti TB medication (Rifampin and isoniazid with pyridoxine) 4 weeks ago. Patient presented with 5 days history of feeling weak in both lower limbs and numbness in upper and lower Limbs as well as some generalized pain in upper and lower extremities. Patient was unable to walk at time of presentation. Examination revealed intact Cranial nerves. Decreased MRC scale of grading power in Lower limbs bilaterally 2/5 and distal upper extremity 4/5. There was decreased

sensation in lower limbs bilaterally below the ankle and distal upper extremity. No sensory level. No cerebellar or sensory ataxia. Cerebellar signs negative. Plantars were down going. Reflexes could not be elicited all over. No muscle tenderness was there. Patient was complaint with her Anti TB drugs including pyridoxine. (rifampin 600mg daily, isoniazid 300 mg daily, pyridoxine 40 mg daily)

Initial labs showed WBC count  $12 \times 10^3/\text{UL}$  (Normal values:  $4-10 \times 10^3/\text{UL}$ ), Hgb 10.3 gm/dL (Normal values-12-15 gm/dL), Plt  $207 \times 10^3/\text{uL}$  (Normal values -150- 400  $\times 10^3/\text{UL}$ ), Urea 3.8 mmol/L (Normal values- 3.2 - 7.4 mmol/L), Creatinine 66  $\mu\text{mol/L}$  (Normal values- 50-98  $\mu\text{mol/L}$ ), ALT 191 U/L (Normal values 0 -55 U/L), AST 259 U/L (Normal values 5 -34 U/L), T bil 25  $\mu\text{mol/L}$  (Normal values 3.4-20.5  $\mu\text{mol/L}$ ). Thyroid profile was normal. MRI spine could not reveal any significant abnormality. Patient was continued on Pyridoxine as Isoniazid induced Peripheral neuropathy was a possibility, but did not show much improvement. Lumbar puncture was done which was unremarkable.

Patient was started on Pyridoxine replacement. Anti TB drugs were stopped from admission because of drug induced increase in liver enzymes. Pyridoxine was discontinued after few days. Patient's pain and sensation improved during hospital stay. The weakness in lower extremities was still the same but did not progress. 2 weeks later patient had Nerve conduction study which showed Length dependent axonal polyneuropathy that was going with early Guillain barre syndrome of axonal variant. The patient could not tolerate electromyography and refused a repeat Lumbar Puncture.

The increased Liver function test (LFT) was attributed to drug induced hepatic dysfunction. After stopping Anti TB drugs, Patient's LFT trended down.

Patient did not receive Intravenous immunoglobulin (IVIg) due to patient's reluctance despite explaining the

consequences. Patient was discharged as she wanted to travel back to home country. Patient could walk with walking frame upon discharge.

### **Discussion:**

Guillain- Barre syndrome is an auto immune condition that affects the peripheral nerves. It has many variants, some of which can cause mild motor or sensory weakness to some causing respiratory compromise. Its incidence is around 1-2 /100,000 population. It is more common in males and its incidence increases with age (1-2). The triggers can vary from, Infections such as Campylobacter, HIV, drugs, viral infection such as CMV, Zika virus. Negligible Association with Influenza vaccine and few reports with meningococcal vaccine have been seen. (3-8).

TB has many neurological manifestations. In about 1% of individuals with *Mycobacterium tuberculosis* infection, central nervous system (CNS) involvement develops This includes intracranial involvement including meningitis, tuberculomas, Brain abscess, TB encephalopathy, And spinal involvement such as Pott's spine or Pott's paraplegia which is spinal vertebral involvement of TB causing paraplegia, Spinal meningitis and non-osseous spinal tuberculoma. (9-10)

First line Anti TB drugs are Isoniazid, Rifampin, Pyrazinamide, ethambutol. Second line drugs are mainly Fluoroquinolones, Aminoglycoside, Linezolid, Cycloserine, ethionamide. (11-13)

Isoniazid's main side effect is that it causes peripheral neuropathy , agranulocytosis and pancreatitis rarely. Isoniazid induced Psychosis, convulsive seizures are reported as well (14) Pyridoxine is given to prevent symptoms of peripheral neuropathy. Rifampin makes secretions orange, Agranulocytosis, thrombocytopenia, leukopenia, flu like syndrome. Pyrazinamide is the most hepatotoxic. The side effects include hyperuricemia, arthralgia, rarely rhabdomyolysis. Ethambutol causes retro bulbar neuritis and risk is greater in patients

with kidney failure and in elderly individuals with impaired renal function. Retro bulbar neuritis is reversible when the symptoms are detected early and the drug is immediately discontinued. All of the ANTI TB drugs can cause Liver injury ranging from transient rise in Liver enzymes to Hepatotoxicity (13)

Regarding Neurological side effects From 1<sup>st</sup> Line therapy, Isoniazid common side effect is peripheral neuritis. Ethambutol can cause degeneration of Optic chiasma and nerve leading to impairment of visual acuity. From 2<sup>nd</sup> Line therapy, Aminoglycosides are associated with flaccid paralysis. (14)

Our Patient came with symptoms of Paraparesis and sensory symptoms in upper and lower limbs. Isoniazid induced peripheral neuropathy can cause it. The fact that patient was on Pyridoxine already, was compliant with the medication and that isoniazid was started just 4 weeks ago, made it less likely. There is case report of motor predominant polyneuropathy with isoniazid in literature which should be kept in consideration (15). Patient had areflexia in all limbs. Patient's Anti TB were stopped and pyridoxine was started considering Pyridoxine deficiency due to isoniazid. The pyridoxine was stopped as well after few days with no improvement in symptoms. The areflexia and sensory symptoms Made GBS as our primary differential to rule out for which we proceeded with lumbar puncture, nerve conduction study and electromyography. Isoniazid Induced motor predominant neuropathy was less likely due to very recently started Anti TB and was ruled out by Nerve conduction study. Patient's Anti TB medication were stopped and Patient's weakness Improved during hospital stay. No respiratory compromise happened. Patient was able walk with walking frame at time of discharge.

Nerve conduction study was done which revealed Length dependent axonal polyneuropathy which was consistent with early Guillaine barre syndrome of axonal variant.

Guillain barre syndrome is one of very rare association with TB. Anti TB drugs triggering it or The Infection itself is not known fully. There are a few case reports Of Guillain barre syndrome in association with pulmonary TB. We found around 6 reports. Almost all of the association have been with active TB or disseminated TB rather than Latent TB. In a review of 1100 cases of GBS, Leneman reported tuberculosis as an associated illness in eight cases (16).

In one of the case reports, patient was diagnosed with Active TB, started on Anti TB therapy, later presented with Bilateral lower limb weakness and Nerve conduction studies revealed features of Guillain barre syndrome. Except our patient was being treated for latent TB. (17)

In case reports by Vyravanathan and Senanayake, in which they reports 2 cases of Of TB with Guillain barre syndrome, the proposed mechanism is cell mediated Hypersensitivity reaction to TB bacteria (18) .

In another report by Peiris, Wickremasinghe and Chandrasekara, Tuberculous Bacteria were found in nerve roots at Necropsy in a patient with GBS suggesting TB polyradiculitis. (19)

Our Patient never had any bowel or bladder symptoms, so TB polyradiculitis was less likely.

Multiple reports of GBS associated with TB have been seen in literature. The mechanism of association is not well known and multiple hypothesis have been suggested. The possibility of anti TB drugs as a trigger for GBS has never been Discussed. In our patient, who was on Anti TB (Isoniazid, Rifampicin) for Latent TB, We thought that one of the drugs Itself can be a trigger for Guillain Barre syndrome. We stopped the anti TB, and Patient's symptoms improved within 3 weeks with physiotherapy. Patient went home with Walking frame .

In our opinion, The possibility of any Anti TB

drug Triggering GBS itself should be considered as well.

### Conclusion :

The association of Anti TB with GBS is not clear but we need to be vigilant that Patients coming with Symptoms of polyneuropathy after starting Anti TB, should not be just taken as Isoniazid induced Pyridoxine deficiency related Polyneuropathy or Isoniazid induced motor predominant polyneuropathy. Further investigations should be pursued and GBS should be ruled out. We need to Consider Anti TB drugs as a trigger for Guillain Barre syndrome as well.

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