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Treatment of Multi-drug Resistant Tuberculosis Causing Tubulopathy – Gitelman-like Syndrome

Treatment of multi-drug resistant (MDR) tuberculosis (TB) includes aminoglycosides and ethionamide. A 16-year-old girl presented with sudden onset of paralysis, dyselectrolytemia mimicking Gitelman syndrome, and ethionamide-induced hypothyroidism. Monitoring electrolytes during MDR-TB treatment is recommended to prevent life-threatening complications.

Keywords: *Hypothyroidism, Paralysis.*

Aminoglycosides are commonly used in multi-drug resistant (MDR) tuberculosis. Gitelman syndrome is associated with metabolic alkalosis, dyselectrolytemia with normal blood pressure, and has a high phenotypic variability. Kanamycin used in MDR tuberculosis can cause tubular dysfunction.

A 16-year-old girl presented with progressive weakness of all four limbs for 7 days, numbness and tingling sensations in the hand for 4 days and inability to hold neck for 1 day. There was no history of fever, trauma, backache, headache, loss of bladder/bowel control, parasthesias or similar episodes in the past. She was under treatment for MDR-TB since 2 months with kanamycin, cycloserine, ethionamide, levofloxacin, ethambutol and pyrazinamide. She had a family history of unexplained deaths in two of her six siblings. One sibling had died at the age of 24 during an acute diarrheal illness and the other sibling while on treatment for MDR-TB with similar regimen.

At presentation, she had bradycardia and was normotensive. Systemic examination revealed right sided effusion, generalized hypotonia, areflexia and a soft palpable goitre. Investigations revealed hypokalemia, hypocalcemia, hypomagnesemia, metabolic alkalosis with normal sodium, creatinine, complete blood counts and urine routine (***Table* I**). ECG showed prolonged QTc and PR interval and U waves. She was started on intravenous calcium gluconate, injection magnesium sulphate and intravenous potassium chloride. Paralysis and carpopedal spasms improved after 48-hours of intravenous replacement. Subsequent investigations showed vitamin D levels of 7.5 (normal 50-175), nmol/l and elevated PTH of 120 pg/mL (normal 10-60), and vitamin D3 was added on day 2. Fractional excretion of magnesium was 13.9%, with urinary chloride of 83 meq/L and 24-hour urinary calcium creatinine ratio of 0.21. Attributing these clinical manifestations to kanamycin, the drug was stopped on day 3. Gradually she improved over the next 5 days, intravenous replacements were converted to oral supplements and kanamycin was reintroduced on day 8. She also required thyroxine replacement for her hypothyroidism, which was attributed to ethionamide.

She was discharged in a hemodynamically stable condition on day 10. On follow up at 1 and 2 months, her electrolytes were normal, requiring 8 meq/kg/day of potassium supplement, 1500 mg/day of calcium and 1g of magnesium sulphate per week. As her TSH was still 16 mIU/L, thyroxine dose was increased to 75 mcg/day.

TABLE I LABORATORY PARAMETERS

Investigations	*Day 1*	*Day 3*	*Day 10*	*2 mo*
Serum potassium	2.0	2.5	3.5	4.0
Serum magnesium	1.0	1.1	1.4	1.7
Ionized calcium (4.0-5.0mg/dL)	3.5	3.7	4.0	4.5
pH, HCO3	7.6/ 35	7.56/ 34	7.4/ 30	7.45, 25
Free thyroxine	–	12	–	15
TSH	–	84	–	16
Anti-TPO Ab	–	Negative	–	–

TSH: thyroid stimulating hormone; Anti TPO Ab: anti thyroid peroxidise antibodies; – : not done; Free thyroxine Normal 12-22 pmol/L.

Though a strong possibility of familial Gitelman syndrome was suspected, we were unable to prove it due to lack of availability of definitive genetic testing. Gitelman syndrome, is a salt-losing tubulopathy characterized by metabolic alkalosis with hypokalemia, hypomagnesemia and hypocalciuria. Natural history of GS is heterogenous with varied degree of clinical symptoms, severity and age of presentation even if they have the same common mutation. Current literature warrants lifelong replacement of potassium, magnesium with or without potassium-sparing diuretics.

Drugs which can cause Gitelmans or Bartter like syndrome are aminoglycosides, prostaglandins, cisplatin and thiazides especially chronic abuse. Aminoglycosides bind to the negatively charged acidic component of the tubular epithelial cells [1]. Internalization of this complex results in altering various cellular processes and mechanism of absorption of various electrolytes. The important differential diagnosis is aminoglycoside induced nephrotoxicity (AIN). AIN was unlikely in our patient as she had alkalosis, normal creatinine, and urine examination did not reveal cells or casts. Previous report of a young female with MDR TB had similar clinical picture with kanamycin and she recovered completely with drug withdrawal [1]. Rarely Gitalman-like syndrome has been reported with Capreomycin, and Bartter like picture with Gentamycin. Both of them responded to drug withdrawal [2]. Gentamycin use causing Bartter like picture has been reported from Taiwan, where females were affected, and it resolved with stoppage of drug [3]. As is known that Gitalman or Bartter syndrome can have a varied course and can present later on in life, even if current electrolyte imbalance could be due to Kanamycin, these patients should be followed carefully for life as they can have life-threatening situations.

Ethionamide is not a commonly mentioned drug causing hypothyroidism [4]; though it causes goitrous hypothyroidism. This child was receiving ethionamide, for 2 months for MDR-TB before presentation. The recent onset thyroid swelling could be due to ethionamide induced goitrous hypothyroidism, which was associated with elevated TSH and low T4.

Physicians managing children with MDR-TB need to be aware of these possible side-effects of second-line anti-tubular drugs, and identify and stop the offending drugs if any dyselectrolytemia is found.

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