Disturbances in the mind and the body
A case report on the challenge of multiple side effects in the treatment multi-drug resistant tuberculosis

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Introduction:
Medications used to treat multi-drug resistant tuberculosis (MDR-TB) have significant toxicity that adds complexity to the management of these patients. This case report describes the challenge of managing a patient of Lithuanian origin with MDR-TB who experienced multiple side effects to anti-tuberculous drugs including a hypomanic episode whilst on cycloserine and also a discussion around neuropsychiatric complications of cycloserine.

Presentation and treatment:
The patient, a 44 year old woman originally from Lithuanian but living in the UK for the past 7 years, was initially diagnosed with pulmonary tuberculosis in January 2017 at her local district general hospital. Her ability to communicate in English was very limited and an interpreter was required to communicate with her. In March PCR based drug susceptibility testing demonstrated resistance to rifampicin, isoniazid and ethambutol and culture demonstrated streptomycin resistance. Later samples were found to be pyrazinamide resistant. She was then transferred to the regional MDR-TB centre to be established on a new treatment regime of amikacin, prothionamide, cycloserine, moxifloxacin, linezolid and clofazimine.

Her treatment was complicated by multiple side effects as seen in the table. These led to a 6 month long admission being required to develop a tolerable treatment regime that controlled the patient's MDR-TB. Her final treatment regime consisted of bedaquiline 200mg three times a week , levofloxacin 500mg od , clofazimine 100mg od, prothionamide 500mg od, linezolid 400mg od.

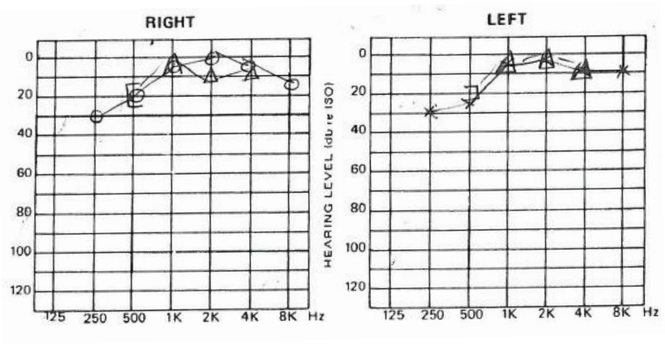
Side effect	Responsible drugs	Required action
Nausea and vomiting	Prothionamide, clofazimine, quinolones	Dose reduction and for a period split doses of prothionamide. Addition of PPI and antiemetics.
Mild transaminitis	prothionamide, moxifloxacin or linezolid	Monitoring of LFTs and exclusion of other causes of hepatitis.
QT prolongation	Moxifloxacin, levofloxacin, clofazimine	Moxifloxacin switched to levofloxacin. Clofazimine dose reduced. Levofloxacin dose reduced. Changed other non-TB QT prolonging drugs. Weekly ECGs.
Hypothyroidism	prothionamide	Treatment with levothyroxine.
Hearing loss	amikacin, capreomycin	Initially amikacin stopped and meropenem with co-amoxiclav started. Later capreomycin stopped as further hearing loss and bedaquiline started.
Subclinical peripheral neuropathy	prothionamide or linezolid	Pyridoxine dose increased and symptoms monitored.
Hypomania with psychotic features	cycloserine	Stopped. Early psychiatric review and treatment with diazepam and olanzapine. Olanzapine later switched to aripiprazole due to long QT concerns. Adjustments to environment. Daily interpreter to aid communication.
Anaemia and leukopenia	linezolid	Initially held for 1 week and then restarted at a lower dose with careful monitoring.
Skin discolouration	clofazimine	Patient informed of side effect prior to starting and educated regarding sun exposure risks.
Kidney injury	capreomycin	Stopped and bedaquiline started.
Visual changes	linezolid	Regular visual acuity and colour disclination checks. Ophthalmology review.

Cycloserine and psychiatric side effects:
Psychiatric disturbances due to cycloserine have been recognised since the drug was first used since it was discovered and used to treat TB in the 1950s (Lewis, 1957). These commonly manifest as depression or psychosis but the overall rate of these adverse drug reactions leading to discontinuation of cycloserine remains low at 5.7% (Hwang, 2013). Mania and hypomania are much less commonly reported side effects, but other cases where mania is the predominant feature have been reported. A neurobiological mechanism has been proposed with cycloserine acting as a partial agonist of NMDA receptors that are part of the glutamatergic system that contributes to mood (Bakhla, 2013).

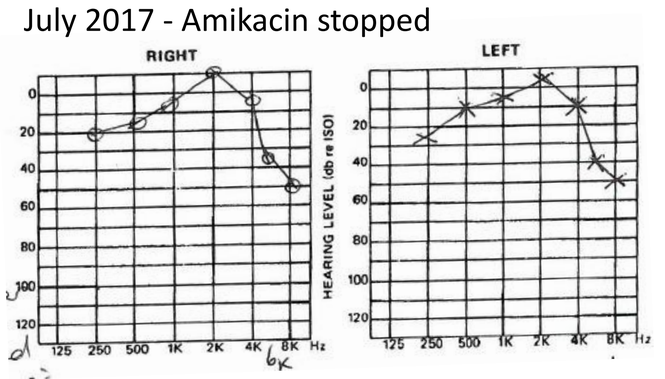
In this case the psychiatric opinion was that the patient's hypomania was multifactorial with factors such as prolonged time within an isolation ward, language barriers, separation from family and difficulty in understanding aspects of her MDR-TB treatment contributing to her altered mental state. The hypomanic episode had significant impact on the patient's anti-tuberculosis leading to a treatment interruption of all medications lasting 2 weeks, removing cycloserine from her anti-tuberculous drug regime and ongoing refusal of meropenem due to a fixed belief that this had made her confused. The episode resolved with treatment with antipsychotic medications and benzodiazepines. Alongside this medical therapy significant alterations were made to the patient's environment, such as being provided with her own fridge and laptop and being moved to an isolation room with a view outside the hospital, and also efforts to increase continuity of care including a daily interpreter.

Patient audiograms

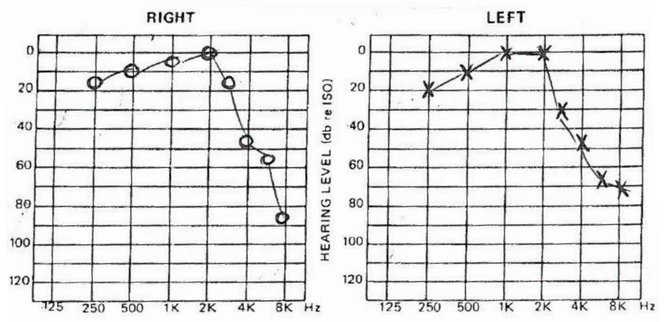
April 2017 - Baseline



July 2017 - Amikacin stopped



September 2017 - Capreomycin stopped



Learning points:
- MDR-TB treatments have significant side effect profiles that can result in prolonged hospital admissions to find a tolerable regime.
- Cycloserine can cause patients to develop psychiatric disturbances such as psychosis, depression and mania.
- Taking a broader approach and considering other factors, such as the patient's environment and communication difficulties, that may contribute to an altered mental state and compliance during the treatment for MDR-TB is an important part of addressing these issues.

References
Lewis WC, Calden G, Thurslan J R, Gibson WE. Psychiatric and neurological reaction to cycloserine in the treatment of tuberculosis. Dis Chest 1957; 32: 172–177.
Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. Int J Tuberc Lung Dis. 2013;17(10):1257–66.
Bakhla AK, Gore PS, Srivastava SL. Cycloserine induced mania. Ind Psychiatry J 2013;22:69-70

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