Neuropsychiatric complications in a patient with tuberculosis

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Helen Joseph Hospital, Johannesburg South Africa
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Presentation

16 year old female - MX

- Bilateral suppurative lymphadenitis 5 months
- 7kg weight loss, night sweats, fever.
- 3 months ago:
  - Excisional lymph node biopsy: necrotizing granulomas consistent with mycobacterial infection
  - No mycobacterial cultures done on biopsy
  - First line TB therapy (rifampin, isoniazid, ethambutol, pyrazinamide)
- Initial improvement but then lymphadenopathy increased in size, and further weight loss
Past medical history

- HIV infection:
  - CD4: 52/mm$^3$
  - Viral load: 240 copies/ml
  - HIV diagnosed at age 7 and initiated ART – likely vertical transmission
  - Current ART regimen: tenofovir, lamivudine, lopinavir/ritonavir

- Tuberculosis at age 10 – treated for six months

- Hospital admission for pneumonia at age 12

- Social history: 10th grade student, good grades, had to stop school as a result of current illness, lives with both parents and two siblings, no alcohol or drug use
Management

- Differential diagnosis: **drug-resistant tuberculosis, lymphoma, non-tuberculous mycobacteria, poor adherence, sarcoidosis, bartonella, nocardia, actinomyces, toxoplasma, histoplasma**

- Fine needle aspirate done in clinic for:
  - Cytology
  - Gene Xpert MTB/RIF
  - Mycobacterial smear, culture, PCR, sensitivity testing
Xpert MTB/RIF result – available in 2 hours

MICROBIOLOGY

Tests requested: GeneXpert

Real time PCR for M. tuberculosis (GeneXpert):
PCRs result
Rifampicin

Mycobacterium tuberculosis complex detected
Resistant

This patient has presumptive MDR-TB. Please refer URGENTLY to an appropriate treatment facility. Send a 2nd sample for microscopy, TB culture and further susceptibility testing for confirmation.
### Xpert MTB/RIF

<table>
<thead>
<tr>
<th>RECEIVED FROM PATIENT</th>
<th>INACTIVATION</th>
<th>INOCULATION INTO XPERT MTB/RIF CARTRIDGE</th>
<th>INSERTED INTO GENEXPERT MACHINE</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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- Cartridge-based PCR diagnostic test
- Identifies presence of *Mycobacterium tuberculosis* and rifampicin resistance
- Can be used at the point of care or scaled up for use in reference laboratories – can be done by a lay person
- Results available in 2 hours
- Implemented as first-line test for TB in South Africa in 2012
South Africa

HIGH TB BURDEN | HIGH HIV BURDEN | HIGH MDR-TB BURDEN

Estimates of TB burden\textsuperscript{a} 2013

<table>
<thead>
<tr>
<th></th>
<th>NUMBER (thousands)</th>
<th>RATE (per 100 000 population)</th>
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<tbody>
<tr>
<td>Incidence (includes HIV+TB)</td>
<td>450 (410–520)</td>
<td>860 (776–980)</td>
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Reported cases of RR-/MDR-TB 2013

<table>
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<tr>
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<th>NEW</th>
<th>RETREATMENT</th>
<th>TOTAL\textsuperscript{b}</th>
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<tbody>
<tr>
<td>Cases tested for RR-/MDR-TB</td>
<td>258 401</td>
<td></td>
<td></td>
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<tr>
<td>Laboratory-confirmed RR-/MDR-TB cases</td>
<td></td>
<td>26 023</td>
<td></td>
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<tr>
<td>Patients started on MDR-TB treatment</td>
<td></td>
<td>10 663</td>
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WHO TB report 2013
Drug-resistant TB management

- South African uses a standardized drug resistant TB regimen
  - Kanamycin (6 months)
  - Ethionamide
  - Terizidone
  - Moxifloxacin
  - Pyrazinamide
  - (Isoniazid while awaiting isoniazid sensitivity results)
2 week follow up visit

- Feels much better
- Tolerating injectable kanamycin
- Lost 0.7 kg, complaining of nausea and vomiting from ethionamide
- Lymph nodes no longer draining pus
- Blood tests: $K = 3.1$, GFR=85
- Given potassium supplementation and anti-emetic to take with ethionamide
1 month follow-up visit

- Nausea improved
- Gaining weight 1.4 kg in two weeks
- Culture sent at first visit – no growth – no further resistance information
  - Lymph nodes decreased in size, FNA attempted but unsuccessful
- Feels ready to go back to school
- High frequency hearing loss noted on audiometry testing
  - Kanamycin dosing frequency reduced to three times weekly
2 months

- Frantic phone call from mom
  - Odd behavior: fearful, visual & auditory hallucinations, wandering around the house at night, combative and violent towards family, paranoid.
  - Tried to harm herself, attacked her grandmother with a knife.

- Taken to a private hospital emergency room at night

- Advised treating clinician that this was likely side effect of terizidone and would resolve quickly with discontinuation of the drug
Cycloserine and Terizidone – neuropsychiatric side effects

- Cycloserine discovered in 1952
  - Bacteriostatic
  - Prevents cell wall synthesis via enzymatic inhibition.
- Used extensively worldwide in the treatment of drug-resistant TB
- Reported rates of psychiatric side-effects 20-33%: mania, insomnia, anxiety.
- Psychosis occurs in up to 13%
- Symptoms resolve rapidly with discontinuation of the drug

Doherty General Hospital Psychiatry 2013
Helmy Scan J Respir Dis 1970
Jancik Scan J Respir Dis 1970
Bankier Can Med Assoc J 1965
2.5 months (clinic)

- Discharged from hospital

- Symptoms have not improved: paranoid, self-harm, hallucinations, unable to care for self, disinhibition, insomnia, emotionally labile.

- Mom has taken time off from work to care for her as she is unable to feed, dress, bathe herself and cannot be left alone.

- Unusual for terizidone psychosis, typically resolves quickly

- Admitted for further workup
Inpatient work up

Tests
- FBC – WBC 3.54, Hemoglobin 12.6, platelets 273
- CRP – 26
- Renal function and electrolytes normal
- Liver function tests – normal
- TSH – 1
- CD4 = 95/mm³
- VL < 50 copies/ml
- RPR negative
- ANA titer < 1:40

CT Brain normal

Lumbar puncture: 0 WBC, 0 RBC, India Ink and cryptococcal latex antigen negative, VDRL negative, Xpert MTB/RIF negative

Assessed by psychiatry: initiated risperidone add venlafaxine

Discharged home
3 months (clinic)

- No improvement in symptoms: not sleeping at night, paranoid, ongoing auditory and visual hallucinations

- Medication list
  - Kanamycin *(case reports of aminoglycoside psychosis, not in TB)*
  - Ethionamide *(case reports of psychosis - rare)*
  - Terizidone
  - Isoniazid *(well described psychiatric side effects, case series)*
  - Moxifloxacin *(case reports of fluoroquinolone associated psychosis – not in TB)*
  - Pyrazinamide
  - Stavudine
  - Lamivudine
  - Lopinavir/ritonavir
Most often seen in those with an “antecedent history of unstable personality”

Symptoms: psychomotor activity, restlessness, irritability, muscle jerking, hallucinations, usually persecutory.
TOXIC PSYCHOSIS DUE TO ISONIAZID

BY HOWARD DUNCAN AND DAVID KERR

Department of Medicine, Postgraduate Medical School, Hammersmith Hospital, London
Present address: Royal Victoria Infirmary, Newcastle upon Tyne

- Case series 38 patients
- Prodromal period of a few days when mental and muscular irritability, tremor and twitching are present.
- The psychosis has no specific pattern, but confusion, mania, hallucinations and paranoid delusions are all common.
- Recovery is usual if the drug is withdrawn, **but may take several months**. Approximately a third of patients had some residual symptoms.
Psychiatric effects of isoniazid

- Isoniazid was found to have anti-depressant effects in patients with tuberculosis in early clinical trials
  - Belongs to same class of hydrazine compounds as mono-oxidase inhibitors
  - Paved the way for the development of anti-depressants

- Frequency of psychiatric side effects of isoniazid: 1.9/100

- Case reports describe a prodromal in the weeks prior to the emergence of the psychosis, characterized by anxiety, emotional lability and facial twitching

- Mechanism (theory) – action as a monoamine-oxidase inhibitor could induce a manic psychosis

Doherty General Hospital Psychiatry 2013
What to do?

- Decision made to stop TB treatment completely - ? Isoniazid related psychosis
- ART continued
- Risperidone dose increased 1 mg in the morning and 2 mg at night
- Venlafaxine continued
3.5 months (clinic)

- Auditory and visual hallucinations improve, paranoia has stopped, she’s sleeping, able to feed and bathe herself.
- Flat affect, very quiet
- Family relieved
4 months (private hospital)

- Family becomes alarmed because she starts “shaking” and “feeling hot” and becomes very rigid.

- Taken to private hospital and admitted to neurology service. Sparse records from hospital admission:
  - EEG done – no seizure activity
  - MRI done - normal
  - Risperidone, venlafaxine, ART continued
  - Valproic acid added
4.5 months (clinic followup)

- Off TB treatment for 1 month
- Has lost 2 kg
- Flat affect, rigid tone, fine tremor
- Psychiatry consulted – extrapyramidal side effects from risperidone
  - risperidone, venlafaxine, valproic acid stopped
- Given haloperidol 2.5 mg
- Rigidty, tremor resolved
Drug Interactions

lopinavir + venlafaxine
Lopinavir increases levels of venlafaxine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Significant interaction possible, monitor closely. Potential for increased toxicity.

moxifloxacin + risperidone
Moxifloxacin and risperidone both increase QTc interval. Potential for dangerous interaction. Use with caution and monitor closely.

moxifloxacin + venlafaxine
Moxifloxacin and venlafaxine both increase QTc interval. Potential for dangerous interaction. Use with caution and monitor closely.

venlafaxine + isoniazid
Venlafaxine and isoniazid both increase serotonin levels. Potential for dangerous interaction. Use with caution and monitor closely.

venlafaxine + risperidone
Venlafaxine will increase the level or effect of risperidone by affecting hepatic enzyme CYP2D6 metabolism. Potential for interaction, monitor.

ritonavir + lamivudine
Ritonavir and lamivudine both increase risk of immune reconstitution syndrome. Potential for interaction, monitor.

ritonavir + stavudine
Ritonavir and stavudine both increase risk of immune reconstitution syndrome. Potential for interaction, monitor.

lamivudine + stavudine
Lamivudine and stavudine both increase risk of immune reconstitution syndrome. Potential for interaction, monitor.

risperidone + venlafaxine
Risperidone and venlafaxine both increase QTc interval. Potential for interaction, monitor.

orphenadrine + risperidone
Orphenadrine and risperidone both increase sedation. Potential for interaction, monitor.
risperidone drug interactions

- **Ritonavir** + risperidone - significant interaction.
  - Increases the level or effect of risperidone by P-glycoprotein (MDR1) efflux transporter.
  - Also minor interaction via hepatic enzyme CYP2D6 metabolism.

- **Venlafaxine** + risperidone
  - Venlafaxine will increase the level or effect of risperidone by affecting hepatic enzyme CYP2D6 metabolism
5 months (clinic)

- Mom confused by multiple medication changes, gives her risperidone in error instead of haloperidol.
- Developed tremor, rigidity. Resolved when switched back to haloperidol.
- Re-challenged with TB treatment but isoniazid omitted.
- Kanamycin, moxifloxacin, pyrazinamide, ethionamide successfully re-introduced. Ethambutol and PAS were added as additional drugs.
- Progressive high frequency hearing loss on audiometry testing.
- Kanamycin stopped,
- Linezolid obtained by special petition to hospital
5.5 months (clinic)

- Mood stabilized.
- Progressive high frequency hearing loss on audiometry testing.
- Kanamycin stopped
- **Linezolid** obtained by *special petition to hospital*
<table>
<thead>
<tr>
<th>Group</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Group 1: first-line agents – <em>good drugs!</em></td>
<td><strong>Rifampin</strong> (1967), isoniazid (1952), ethambutol (1961) pyrazinamide (1952)</td>
</tr>
<tr>
<td>Group 2: aminoglycosides</td>
<td>Kanamycin, amikacin, capreomycin, streptomycin (1948)</td>
</tr>
<tr>
<td>Group 3: Fluoroquinolones</td>
<td>Moxifloxacin, levofloxacin</td>
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<tr>
<td>Group 4: bacteriostatic second-line agents</td>
<td>cycloserine/terizidone (1952), ethionamide (1956) Para-aminosalicylic acid (PAS) (1944)</td>
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<tr>
<td>Group 5: Agents with unclear role in the treatment of drug-resistant TB</td>
<td>Clofazimine (1954), linezolid, amoxicillin/clavulanate, imipenem, high dose isoniazid</td>
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<tr>
<td>New agents!</td>
<td><strong>Bedaquiline</strong> (2012), delaminid (2014)</td>
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7 months

- Back in school good grades
- CD4= 130, viral load< 50 copies/ml.
- Psychosis resolved, mood stabilized, aggression and paranoia resolved.
- Haloperidol stopped.
- Exhibits mild disinhibition
- Being followed by psychiatry
- No further extrapyramidal side effects.
- High frequency hearing loss, not affecting speech frequencies
- Gained 11 kg