Anti-NMDA-receptor encephalitis: One patient’s journey through the mental health system and acute medicine in search of diagnosis and treatment.

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RECOVERY

Expectations

Reality
First contact with psychiatric Triage: Day 1.

• 30 year old married housewife of 3 small children – 8, 7 & 4
• Rapid CMI check – No public mental health history
• Nil private psychiatrist or psychologist.
• Nil history of head injury.
• P/C received from husband
• Urgent referral of wife to Mental Health Service.
• Husband’s parents have taken the children for the night – concerned for their safety. Husband concerned for his safety and the safety of his wife.
• Client has no known history of suicidal ideation, DSH or homicidal ideation.
History

• Treated for Depression for 10 years by GP.
• No previous history of psychosis.
• Depressive illness stable in past 8 years.
• Good physical health.
• Current medication: Effexor 150mg.
• Husband has urgently driven back from a local holiday today with wife & kids.
• Wife trying to jump out of car. Was reporting she was seeing and speaking to her dead father all the way back during the journey.
Presenting condition

- Husband reports “strange peculiar behaviour”
- Rapid deterioration in mental state over 2 days.
- Client presenting with poor tolerance of others, increasingly irritable, tearful and an increase in anger.
- Reports visual and command auditory hallucination from her father.
- Deceased father telling her to kill a family member, to run away and not to seek help.
- Client’s behaviour is unpredictable.
Referred to CATT, Category C referral.

- On assessment, client is screaming and crying.
- Acutely psychotic.
- Responding to visual/auditory hallucinations.
- Client asked if CATT clinicians were aliens.
- At risk of accidental self harm and accidental harm to others due to impaired judgment and insight.
- Request and Authority to Transport completed.
ED, Medical Clearance and Admission to Psychiatric Unit.

- Section 9 upheld in ED
- ITO confirmed the following day, Section 12.
- Routine bloods: NAD.
- Medically cleared in ED.
- Code grey, Mechanical Restraints used.
- Admitted to psychiatric unit, ICU.
- Identified that there is a family history of mental illness: Mother schizophrenia, Father BPAD & brother psychosis.
Day 4: Medical Admission

• Metabolic deterioration.
• Hypotension (76/51) – required a met call
• Tachycardia (115-150)
• Fever (40)
• Transferred to WGH ED for possible Neuroleptic Malignant Syndrome & Serotonin Syndrome
• Prescribed IV antibiotics and fluids.
• Psychotropic medication not settling patient’s presentation.
• Suspected encephalitis, unknown cause.
Encephalitis

Typically an acute altered level of consciousness with signs of inflammation

Can be confirmed by imaging, lumbar puncture or by blood

Where did it come from?
## The causes of inflammation

<table>
<thead>
<tr>
<th>Cause</th>
<th>Infectious</th>
<th>Autoimmune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal</td>
<td>Murray Valley</td>
<td>NMDA receptor antibody associated</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Herpes Simplex</td>
<td>VGKC receptor antibody associated</td>
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<tr>
<td>Paraneoplastic</td>
<td>West Nile</td>
<td>Hashimoto’s encephalitis</td>
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<tr>
<td>Post-infectious</td>
<td>Japanese</td>
<td>Rasmussen’s encephalitis</td>
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<tr>
<td>HIV encephalitis</td>
<td>Tick Borne</td>
<td>Paraneoplastic</td>
</tr>
<tr>
<td>Chronic</td>
<td>Mycoplasma</td>
<td>Encephalitis lethargica</td>
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<tr>
<td>Inflammatory</td>
<td>Enteroviral</td>
<td></td>
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<tr>
<td>Bacterial</td>
<td>Western or Eastern Equine</td>
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</table>
What is Anti NMDA Receptor Encephalitis?

• First identified and given a name in 2007 when the cause was finally identified (Syndrome identified prior to 2007).
• A novel autoimmune and paraneoplastic disease often presenting as acute psychosis.
• An acute form of encephalitis.
• Viewed as a mysterious and often life threatening disease which affects the lives of mostly young women.
• The majority of patients are admitted to psychiatric hospitals misdiagnosed.
• Many patients can be admitted to ICU.
• Patients have potential for near-complete recovery with early diagnosis and intervention.
A Paraneoplastic Syndrome

- Is a disease or symptoms that is the consequence of the presence of cancer in the body, but not due to the presence of cancer cells.
- It can be what the tumor excretes (hormones or cytokines) or by an immune response.
- Theses cancers are associated with the breast, ovarian and lung.
**Teratoma Tumour**

- Is an encapsulated tumour with tissue or organ components.
- Normally Benign
- Reported to contain hair, teeth, bone, brain, thyroid, liver tissue and very rarely eyes, torso, hands, feet or other limbs.
- Usually benign, although several forms are malignant.
- Teratoma tumour is thought to be present at birth.
Auto-immune response attacks the NMDA receptors in the brain.

• The body sees this tumour like a foreign type of tissue and mounts an attack.
• Immune response produces antibodies against the NMDA receptors that are in the tumour.
• The immunological system is tricked and subsequently is misdirected in attacking the NMDA receptors in the brain.
Back to patient. Risk assessment on Medical Ward.

- Absconding Risk
- Tachycardia 110, BP stabilized at 120/70.
- Violent and Aggressive.
- Mechanical Restraints used practically 24/7.
- Division 1 nurse with psych experience 1:1 observer.
- Agitated, constantly singing ‘Purple Rain’
- Reporting hearing her father in the next room shouting abuse at her, derogatory auditory hallucinations.
- Tearful and distressed
Medical

• Day 8: MRI NAD (Half of patients with Anti NMDAR have no abnormalities on MRI).

• Day 20: Lumbar puncture confirmed encephalitis, presence of anti-NMDA-R antibodies (Gold standard for diagnosis).

• Day 22: Pelvic CT and Ovarian ultrasound indicated abnormality with right ovary.

• Day 30: A mass on pt’s right ovary was removed
Treatment

• High dose Immunosuppression therapy.
• Nil response in 7-30 days: $2^{nd}$ line immunosuppression therapy.
• Anti-inflammatory medication.
• Treating the offending agent (operation to remove ovary & teratoma tumour).
• Chemotherapy.
• 20% of patients relapse caused by a recurrent teratoma that cannot be located.
Results of tumour on day 36

- Bowel cell (epithelial cells)
- **Neuron cells**
- Bone
- Teeth
- Solid and cyst-like structures with epidermis, dermis, adexal structures and fat.
- Intestinal type epithelium
- Hair
Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies
What do we know about anti NMDA receptor encephalitis

- Young: Adolescents or young adult
- Age range is 23 months to 76 years in literature
- Of all known cases 81% Females (54% have ovarian teratoma) and 19% Males
- Early Neuropsychiatric presentation
- Seizures; Psychosis; Confusion; Memory loss
- Rapid deterioration of mental state: 1-14 days.
- Altered level of consciousness
- Autonomic dysfunction; Movement disorders, Coma.
- Few studies in literature on medication management to relieve distressing psychotic symptoms.
3 stages of NMDA-Receptor Encephalitis

Prodromal stage

Begins with nonspecific fever, diarrhoea, vomiting, headache or upper respiratory symptoms.
2nd Stage of illness

- Appear between 1-21 days after prodromal symptoms.
- 72% - 83% of patients present with psychiatric symptoms i.e. psychosis, delusions, hallucinations.
- 76% - 82% of patients have presented with seizures (generalised or complex partial)
- Amnesia, confusion, memory, depression, paranoid thoughts, and visual or auditory hallucinations.
3rd Stage of illness

- Decreased level of consciousness, lethargy, seizures, hypoventilation, autonomic instability, and dyskinesia's.
- Central hypoventilation and autonomic instability often require intensive care unit for ventilation support ranging from 2 to 40 weeks.
- Coma or death.
Back to the patient

• Significant improvement in mental state 3 days post tumour removal (Day 33).
• One week post tumour removal (Day 37): Taken off section 12, now voluntary status.
• 1:1 observer ceased (Day 39)
• Initially managed with low doses of Seroquel, no prn.
• During admission medication slowly changed from Seroquel to Valproate, Olanzapine & Clonazepam. No prn.
• Day 60: Cease all psychotropic medication. Gradual weekly reduction and cessation.
Day 60 of Medical Admission

• Transferred to Rehab ward
• Cognitive impairment secondary to inflammation of brain.
• Presents with slow speech. Poor concentration, impaired short & long term memory. Nil psychotic symptoms.
• Will need long term rehabilitation. Discharged back home.
• Nil mental health follow up post discharge.
Management pathway

Consider alternative diagnosis

NMDAR antibody testing (serum and CSF)

Positive

MRI, CT, or ultrasound studies*

Tumour absent

Methylprednisolone plus IVlg or plasma exchange

Little or no response

Rituximab, cyclophosphamide or both

Good response

Supportive care, chronic immunosuppression,† yearly tumour surveillance

Tumour present

Tumour removal plus methylprednisolone plus IVlg or plasma exchange

Good response

Supportive care, yearly tumour surveillance

Consider alternative immunosuppressants,‡ yearly tumour surveillance

Supportive care, chronic immunosuppression,† yearly tumour surveillance
Implications for practice

Research by Ko Tsutsui et al 2012:

• Random testing of 51 cases of patients diagnosed with schizophrenia or schizoaffective disorders.

• 4 patients tested positive for anti NMDAR encephalitis.

• Most of their symptoms are resistant to pharmacological treatments but respond relatively well to ECT.
References

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