

Anti N-methyl-D-aspartate Receptor Encephalitis

Case of the week

7/6/12

Mr CL, 17yo male

- PMHx: ADHD → known to developmental pediatrician, Tx with atomoxetine, suffers from tic's secondary to atomoxetine
- SHx: attending high school, expected to finish HSC and attend university. Lives with supportive parents + brother. Brother Dx with Aspergers. Non-smoker, nil significant ETOH intake

- 19/5/12: presented to Concord Hospital with 1/52 headache and fevers → Dx with ?viral meningitis → D/C home, nil antivirals
 - LP: protien 0.5 glucose 4; mononuclear 6; erythrocytes 2, clear and colourless
 - Non-con CT-B: no acute intracranial changes
- At home developed persistent fevers + headache, some slurred speech
- 28/5/12: BIBA from school with behavioral disturbances and confusion. Admitted RPAH.
 - Nil focal neurology at admission.
 - LP: nil organisms; prot 0.36; WCC 35; lymphocytes 70%; neutrophils 20%; monocytes 10%
 - Commenced on ceftriaxone + acyclovir

- 29/5/12: increasing delirium (rambling, shouting, hyperactive)
 - Unable to perform MRI d/t agitation
 - EEG: excessive artifact, some possible R hemispheric slowing
- 30/5/12: GA for MRI which found increased signal intensity on FLAIR in subarachnoid space → ? Meningitis
- 31/5/12 – 2/6/12: ongoing behavioral decline on ward
 - Commenced on IVIg (intragam 30gm IV daily) and methylprednisolone (1mg IV daily)
- 1/6/12: Dx confirmed of anti-NMDAR encephalitis on CSF + serum
 - Ceftriaxone + acyclovir ceased
 - Testicular U/S: bilateral epididymitis
- 2/6/12: became mute, incontinent of urine and faeces
 - Supporting own airway but concern of rapid decline given known Dx of anti- NMDAR encephalitis
 - T/F BICU for neuro-obs + potential airway support

- At admission to BICU noted to be confused, hypertonic, hyper-reflexic, with down going planters, GCS 11 (E4V1M6)
- GCS fluctuating from 5- 11
- 3/6/12:
 - commenced on levetiracetam by neurology 500mg BD
 - noted to have self limiting periods of bradypnea, resistance to passive movement, unresponsiveness, rhythmic asymmetrical upper and lower lip movements, intermittently verbalizing
 - ongoing poor oral intake, commenced on Promote feeds
- 5/6/12: PET scan found no foci of abN glucose metabolism in the torso to suggest an underlying high- grade tumor
- 6/6/12: HBcAb and HBsAb +ve, HBsAg –ve, now awaiting HBV DNA
 - Considering commencing retuximab

Anti- NMDAR Encephalitis

- NMDA receptors are ligand-gated cation channels, which play a crucial role in synaptic transmission and plasticity. The receptors are heteromers of NR1 subunits that bind glycine and NR2 subunits that bind glutamate.
- NR1 and NR2 combine to form receptors subtypes with distinct pharmacological properties, localisation and ability to interact with intracellular messengers.
- NMDAR encephalitis is a disorder associated with antibodies against NR1-NR2 heteromers and results in a characteristic neuropsychiatric syndrome.
- It's first described in 2005 as a syndrome of psychiatric Sx, decreased consciousness and hypoventilation in association with ovarian teratomas, in which specific autoantibodies to the NMDAR were identified.
- It has changed the diagnostic approach to clinical problems as diverse as catatonia, subacute memory disturbance, seizures, abN movements and limbic encephalitis.

Frequency

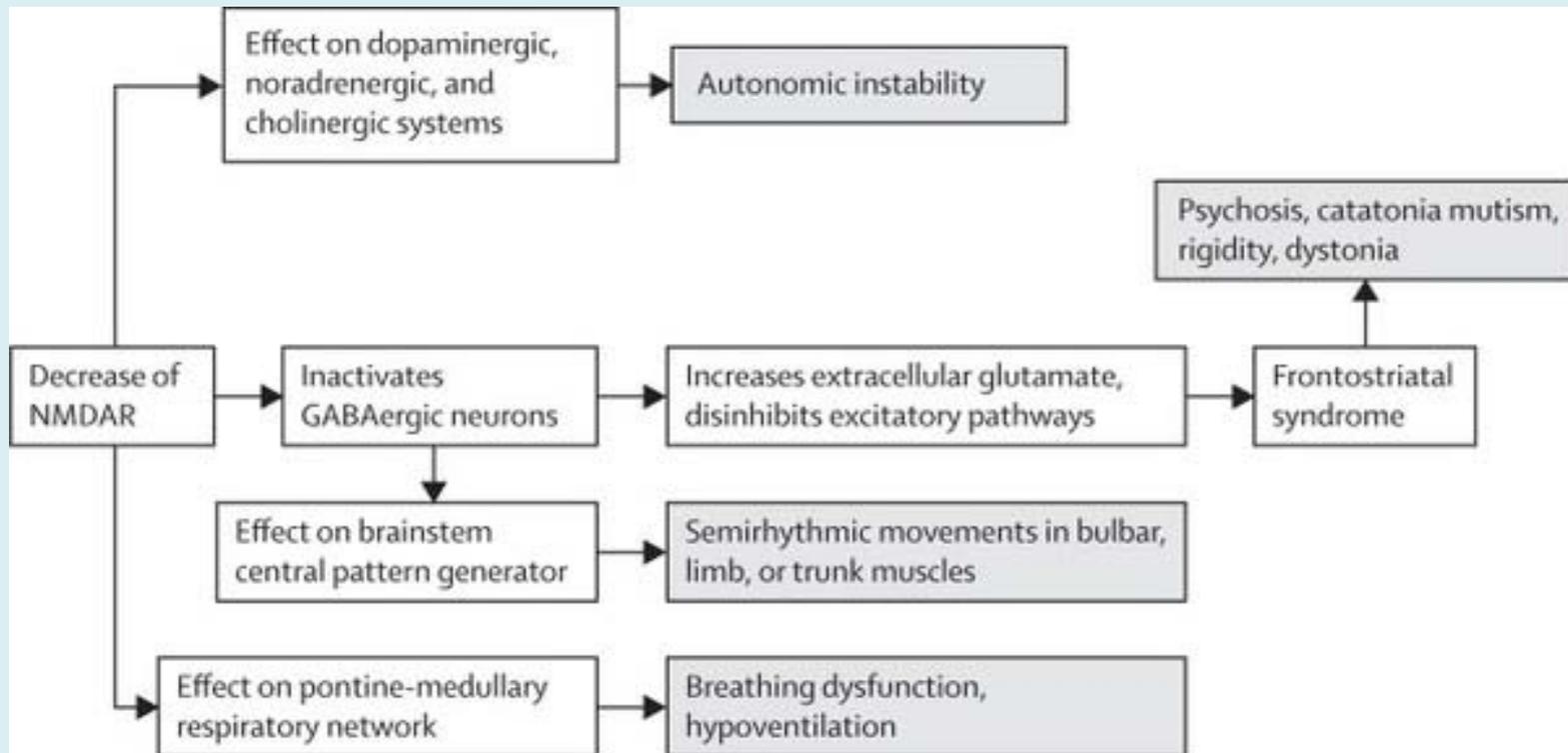
- Exact incidence of NMDAR encephalitis is unknown. In a retrospective analysis of encephalitis of unknown origin, NMDAR antibodies were identified in 1% of patients aged between 18- 35 admitted to ICU.
- A UK multicenter based prospective study of causes of encephalitis showed that 4% of patients had anti- NMDAR encephalitis.

The Clinical Course

- Antibodies against the NR1 subunit of the NMDAR are assoc with a characteristic syndrome that develops in several stages of illness and recovery.
- ~70% of patients have prodromal Sx of headache, fever, N&V, diarrhoea or URTI. Within <2/52 patients develop psychiatric symptoms of anxiety, insomnia, fear, grandiose delusions, hyper-religiosity, mania, and paranoia, social withdrawal and stereotypical behaviour. Rapid disintegration of language from reduction of verbal output and echolalia to frank mutism.
- This initial phase of illness is usually followed by decreased responsiveness that can alternate between periods of agitation and catatonia.
- At this stage abN movements and autonomic instability usually manifest. Oro-lingual- facial dyskinesias are the most characteristic movements but other types might occur with limb and trunk choreoathetosis, elaborate motions of arms and legs, oculogyric crisis, dystonia and rigidity.

- The most frequent autonomic manifestations include hyperthermia, tachycardia, hypersalivation, HTN, bradycardia, hypotension, urinary incontinence, and erectile dysfunction.
- Hypoventilation requiring respiratory support occurs as the patient becomes comatose but can occur earlier when the level of consciousness is relatively preserved.
- Autonomic storms can fluctuate from tachycardia to bradycardia and long lasting cardiac pauses, which in some patients require a temporary pacemaker.
- Motor or complex seizures develop at early stages of disease. Frequency and intensity of the seizures decrease as the disease evolves.
- There can also be a dissociative responses to stimuli noted (i.e. patients resist eye opening, but show no response to pain)
- Clinical examination of the patient reveals a diffuse encephalopathy indicating dysfunction of subcortical structures, limbic regions, amygdale and frontostriatal circuitry.
- Patients without tumours have periods of unconsciousness and confusion that can be longer or worse than are those of patients with tumours

Clinical Correlates



Clinical correlates of antibody-mediated decrease of NMDAR
The figure is based on data from animal models of pharmacological or genetic decrease of NMDAR

Diagnostic Tests

- The diagnosis of anti-NMDAR encephalitis is confirmed by the detection of antibodies to NR1 subunit of the NMDAR in serum or CSF.
- The CSF is initially abN in 80% of patients and becomes abN later in the disease in most other patients. Findings include: moderate lymphocytic pleocytosis, normal or mildly increased protein concentration and in 60% of patients CSF specific oligoclonal bands. Most patients have intrathecal synthesis of NMDAR antibodies.
- After treatment or in advanced stages of the disease, the CSF antibodies usually remain elevated if there is no clinical improvement, while serum antibodies may be substantially decreased by treatments. The titer of CSF antibodies appears to correlate more closely with the clinical outcome.
- All 431 patients had antibodies in serum + CSF. And it reported that if diagnosis was delayed or if patient had already received Tx antibodies might only be detectable in CSF.

- Brain MRI is unremarkable in 50% of patients. In the other 50% T2 hyperintensity can be seen in hippocampi, cerebellar or cerebral cortex, frontobasal regions, basal ganglia, brain stem and infrequently spinal cord. The findings are usually mild or transient and can be accompanied by subtle contrast enhancement in the affected areas or the meninges. F/U MRI is either normal or show minimum change despite the severity and duration of Sx.
- EEG is abN in most patients, usually showing non-specific slowing and disorganised activity sometimes with electrographic seizures. This activity is not assoc with abN movements and does not respond to antiepileptic drugs. Monitoring with video EEG is important to diagnose and Tx seizures appropriately.
- Brain biopsy does not provide a diagnosis of anti-NMDAR encephalitis. Biopsies in 15 patients showed normal or non-specific findings, including peri vascular lymphocytic cuffing sparse parenchymal T cell infiltrates or microglial activation

Sex, Tumour Association and Potential Triggers of the Immune Response

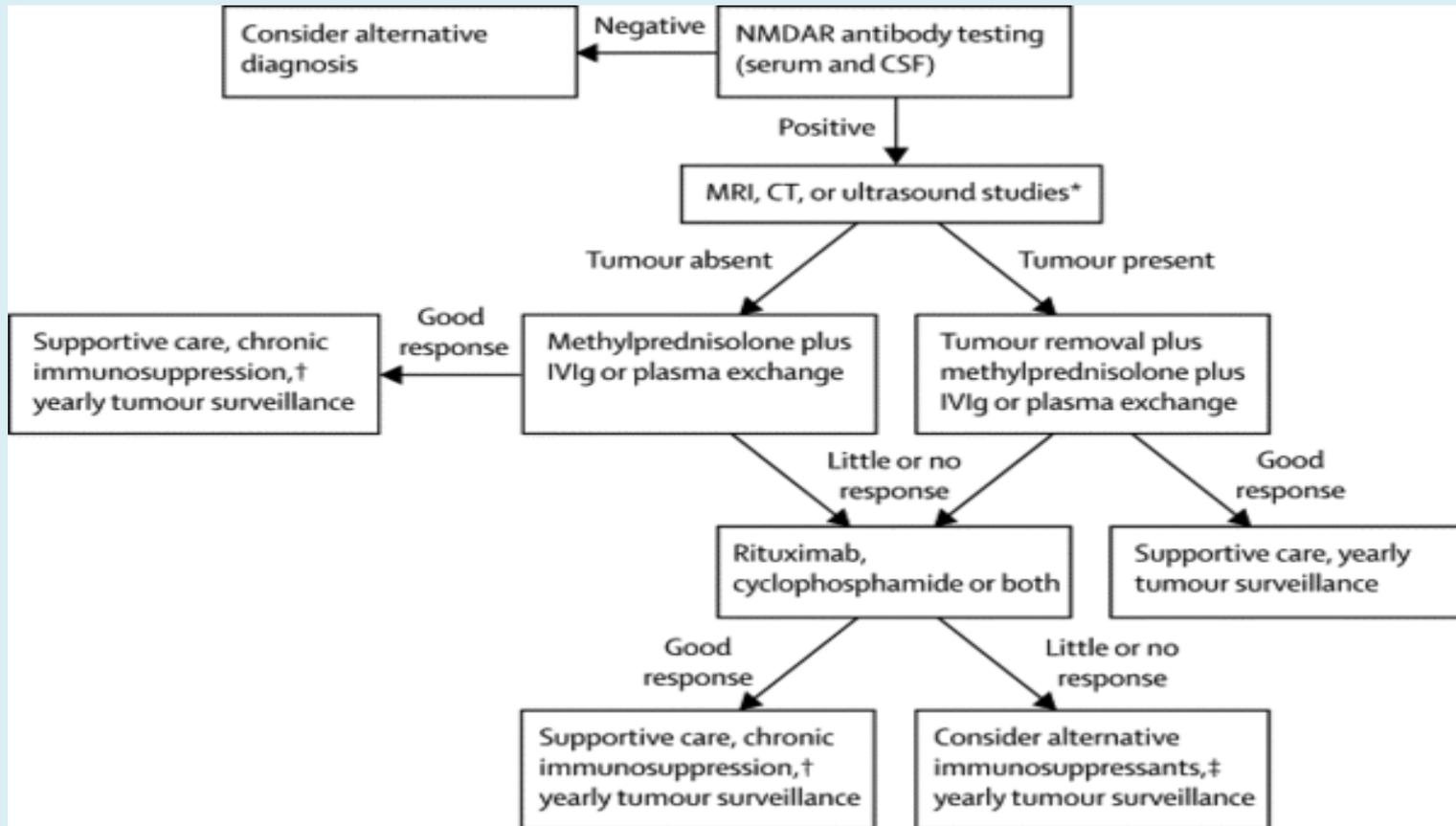
- ~80% of patients with anti-NMDAR encephalitis are women.
- Detection of underlying tumour is dependent on age, sex and ethnic b/g.
- The younger the patient, the less likely a tumour will be detected. In females older than 18yrs the frequency of underlying teratomas is high. Black women are more likely to have an underlying ovarian teratoma than patients of other ethnic groups.
- Only ~5% of males older than 18yrs had an underlying tumour.
- Detection of tumours other than teratoma is not common
 - 2% (neuroblastoma, Hodgkin's lymphoma)
- Based on this the 1st concern in female patients should be screening for an ovarian teratoma: CT/MRI/pelvic + transvaginal ultrasound and tumour markers
- Non-specific systemic infections or vaccinations can act as an adjuvant of the autoimmune response. Those implicated included: influenza H1N1; booster vaccinations for tetanus, diphtheria, and pertussis

Treatment, Outcome and Relapses

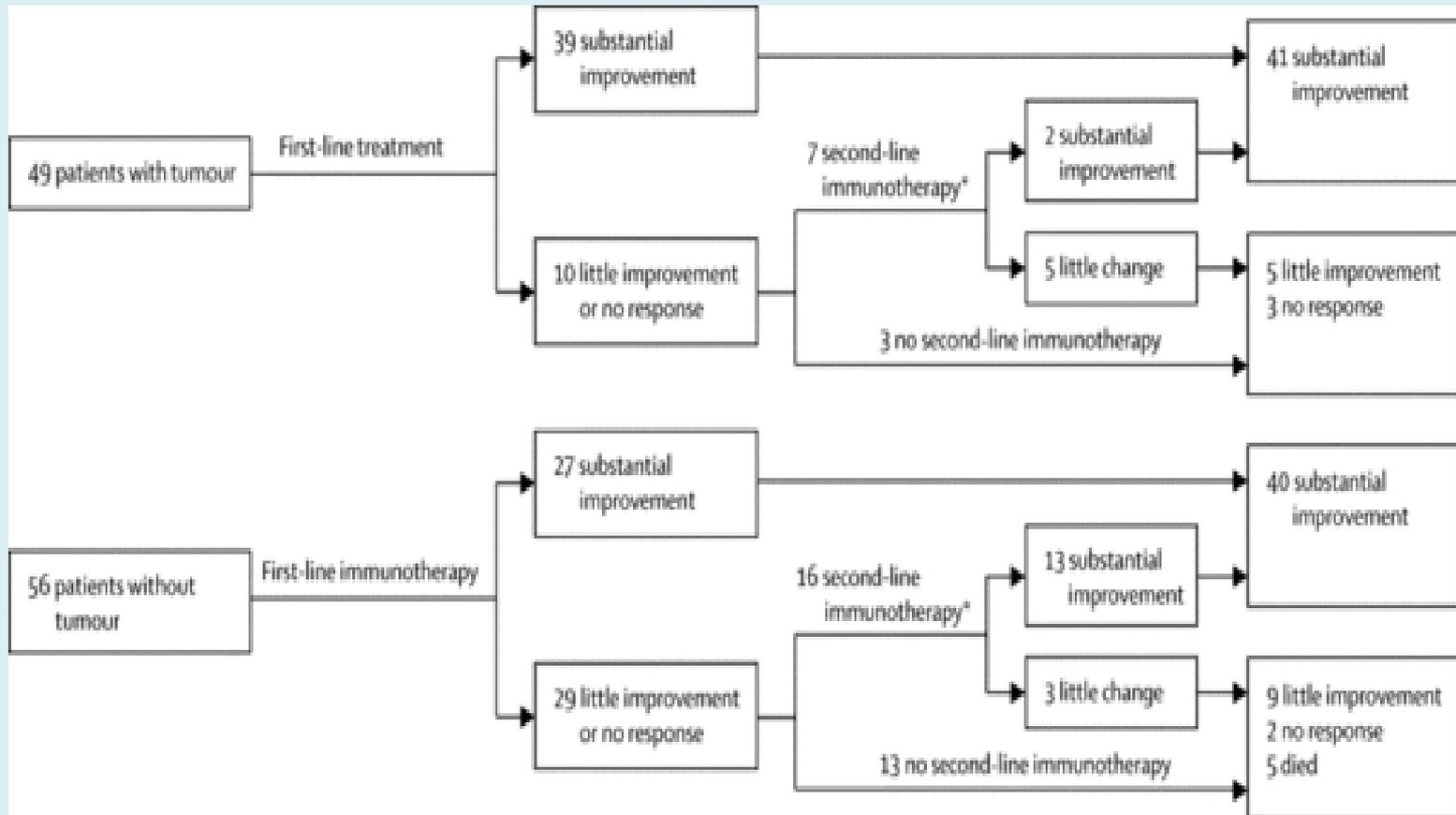
- ~75% of patients with NMDAR antibodies recover or have mild sequelae. All other patients remain severely disabled or die.
- Mx should initially focus on immunotherapy and detection and removal of a teratoma.
- Most patients receive corticosteroids, IVIg or plasma exchange as 1st line immunotherapy.
 - These Tx have enhanced effectiveness and speed of action when patients have an underlying tumour that is removed.
- In patients without a tumour or with delayed Dx, additional Tx with 2nd line immunotherapy (rituximab +/- cyclophosphamide) is usually needed.
- 80% of patients with a tumour (mostly teratoma) had substantial improvement after tumour removal and 1st line immunotherapy, only 48% of those without a tumour had a similar degree of improvement after 1st line immunotherapy and needed 2nd line immunotherapy more often. Overall, 2nd line immunotherapy resulted in substantial improvement in 65% of patients.

- Reports exist of patients with predominant psychiatric manifestations that were given ECT. One patient's disorder resolved without further Tx, but others only had definitive improvement after immunotherapy or removal of underlying tumour.
- Spontaneous neurological improvement has been reported, but usually occurs at the expense of longer hospital stay and slower recovery

Proposed Tx Algorithm



Treatment outcomes



Treatment and outcome in 105 patients comparing presence and absence of tumour and the use of second-line immunotherapy

Recovery

- Recovery occurs as a multistage process that happens in the reverse order of Sx presentation.
- Patients slowly wake from coma as their autonomic functions stabilize respiration recovers and dyskinesias subside → they are able to follow simple commands and can have appropriate interactions → recover verbal functions.
- During the recovery period patients can become psychotic and agitated again, calming as they further recover.
- Social behaviour and executive functional Sx are usually the last to improve and recovery can be incomplete or delayed by many months
- For the acute stage of disease, many patients require hospitalisation for 3- 4months, followed by several months of physical and behavioural rehabilitation.

Mortality

- On the basis of data for 360 patients with clinical follow-up > 6 months, the estimated mortality for anti-NMDAR encephalitis is 4% (15 patients)
 - 1 died in nursing home of unknown cause
 - 14 died in ICU
 - 3 died of sepsis
 - 2 of sudden cardiac arrest
 - 2 of acute resp failure
 - 2 of refractory status epilepticus
 - 2 of tumour progression
 - 1 after withdrawal of medical support
 - 2 of unknown cause

Approach to Diagnosis and Proposal of a Treatment Strategy

- Anti-NMDAR encephalitis should be suspected in any patients, younger than 50 (esp. children/teenagers) who develop rapid change of behaviour or psychosis, abN postures or movements, seizures, autonomic instability, hypoventilation.
- Supportive findings Inc
 - CSF lymphocytic pleocytosis or oligoclonal bands
 - EEG with infrequent spikes, but frequent slow disorganised activity that does not relate with most abN movements
 - MRI that is often normal or shows transient FLAIR or contrast- enhancing abN
- Antibody studies should be done in both serum and CSF. This allows for comparison of antibody concentrations during the course of the disease. Periodic screening of serum and CSF is useful to assess the effectiveness of Tx.
- All patients should be lx for underlying tumour esp. ovarian teratoma and testicular germ-cell tumour

- Concurrent IVIg + methylprednisolone for 5/7
- Plasma exchange
- If no response in 10/7 → 2nd line therapy: rituximab (4wks) and monthly cyclophosphamide
- Tx is discontinued when patient has had substantial clinical recovery and is usually accompanied by decrease of CSF and serum antibody concentrations.
- Replaces occur in 20- 25% of patients, often in those without teratomas, thus continued immunosuppression (mycophenolate or azathioprine) is recommended for at least 1yr after immunotherapies are discontinued.