Young women with psychosis, seizures, and ovarian teratoma

A review on anti-NMDAR encephalitis

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MARCH 15, 2011
Objectives

- To review two cases of anti-NMDAR encephalitis
- To understand the clinical spectra of this syndrome
- To review the diagnosis, pathogenesis, and treatment of this entity
- To have this disease in mind in young women that present with acute psychosis and seizures
Case 1

- 26 year-old previously-healthy woman

- 2-4 weeks of flu-like symptoms, headaches and maybe once fever

- Had a syncope → ER:
  - Postural hypotension of non-cardiac etiology → echo and ECG normal

  - Mildly confused without fever → Routine labs normal including CBC, urine toxicology screen negative, CT head normal, chest XR normal
Case 1

- While at ER starts acting bizarre - laughing and crying - increasingly confused, agitated, disorganized, psychotic, with visual hallucinations
- Admitted to psychiatry - Increasingly getting more agitated and aggressive
- Had a first GTCS
Case 1

- EEG: diffuse slowing without epileptic focus
- Brain MRI: normal
- LP: CSF with ↑ proteins and ↑ lymphocytes
- Started to develop a progressive decrease in the level of consciousness to a GCS 5/15 and was moaning
- Then progressive hypoxia with more oxygen demand and had to be ventilated
Case 1

- New EEG with few frontal spikes with very slow background
- New MRI and MRV: both normal
- New CSF: Still high proteins and lymphocytes – gram stain, crypto, PCR for virus, flow cytometry and cytology all negative
- Started acyclovir (while waiting for PCR results)
- Had more seizures – received phenytoin, epival, propofol
- Progressive severe hypoxia and added fever: PE, started anticoagulation
Case 1

- Added continuous dyskinesias → choreiform movements in upper>lower limbs, and unusual paroxysms of facial grimacing

- Accompanied by severe hypersalivation

- She received empiric IV methylprednisolone 1gr daily for 5 days with no response at all
Case 1

- Brain biopsy: meningoencephalitis of unknown origin – non-vasculitic

- She later developed a septic shock from an acute cholecystitis and died (in less than 2 months since the arrival to the hospital)

- Autopsy showed a small ovarian teratoma

- Post-mortem testing for anti-NMDAR Abs: positive
Case 2

- 19 year old Nigerian woman

- Started with right ear ache and generalized headache

- The next day she was acting strange and “hearing music”

- On the following day she was found on the ground; Incontinent; GCS 8, confused & agitated

- Arrives to the ER with GCS 6 – she is intubated and transferred to ICU
Case 2

- 39.3 C, HR 120, BP 125/76
- Withdraws to pain x 4
- WBC 19.3 (ANC 17.8)
- CK 20 469
- CT head normal
Case 2

- Brain MRI and MRV: normal
- EEG: Left temporal slowing
- CSF: pleocytosis
- Covered with ceftriaxone/vancomycin/acyclovir
- Phenytoin load for suspected seizure
- CT chest abdomen and pelvis showed ovarian cysts
Case 2

- Wakes up and is transferred to the ward with diagnosis of possible viral encephalitis

- Starts having increased psychotic symptoms, with auditory hallucinations, paranoia and aggression

- Episodes of speech arrest and disconnection (non-epileptogenic as per video-EEG)

- Postural hypotension
Case 2

- Positive serum Ab against NMDA-R
- Received 5 days of IVIg and got clinically better
- In follow up one of the cysts appeared to be unchanged in ultrasound
- Had cystectomy: mature ovarian teratoma
- Doing well in life and school
Clinical synopsis cases 1 and 2

Young woman with flu-like prodrome

- Dysautonomic symptoms
- Acute psychosis
- Seizures
- Progressive decrease in LOC and progressive hypoxia
- Hyperkinetic state with dyskinesias and hypersalivation
- Death

Young woman with ear ache and mild headache

- Psychiatric symptoms
- Probable seizure
- Decrease in LOC
- Increased psychiatric symptoms and dysautonomic symptoms
- Recovery
Paraneoplastic Anti–N-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma

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Anti-NMDAR encephalitis

- Initially described in 2007 in healthy young females with ovarian teratoma

- Since then it has also been described in children and males, and in patients with no identified tumor

- 80% of the patients with this syndrome are women

- Incidence unknown but it seems to be more frequent than other paraneoplastic encephalitis
Anti-NMDAR encephalitis

- It is different from other types of paraneoplastic syndromes:
  - Highly characteristic syndrome
  - Mainly seen in young women
  - Treatment responsive
  - It is associated with benign tumors
Antibodies against the NR1 subunit of the NMDAR are associated with a characteristic syndrome.

It develops in several stages of illness and recovery:

- Prodromal
- Psychotic
- Convulsive
- Unresponsive
- Hyperkinetic
- Recovery or severe deficits/death
1. **Prodromal:**
   - In about 70% of the patients
   - Headache, fever, nausea, vomiting, diarrhea, or upper respiratory tract symptoms
   - Within a few days (less than 2 weeks) the next stage appears

2. **Psychotic:**
   - Patients are usually seen first by psychiatrists with anxiety, insomnia, fear, grandiose delusions, hyper-religiosity, mania, and/or paranoia
   - Social withdrawal and stereotypical behavior can be seen
   - Short term memory loss is common
   - Rapid disintegration of language up to mutism
   - In young children - hyperactivity, irritability, violent behavior
3. **Convulsive:**
   - Usually at the peak of the psychosis
   - Generalized or complex partial seizures
   - The frequency and intensity of the seizures decrease as the disease evolves
4. **Unresponsive:**

- Decrease responsiveness that can alternate between agitation, catatonia and coma
- In some cases odd reactions like resisting eye opening while not responding to pain (dissociative responses) with proposed diagnosis of malingering or psychogenic reactions
- Diffuse slow waves in EEG
- Then progressive hypoventilation, usually requiring mechanical ventilation
- In some cases the hypoventilation is noticed when the patient can not be weaned off the ventilator
5. **Hyperkinetic/autonomic instability:**
   - Oro-lingual-facial diskinesias are the most characteristic movements
   - Limb and trunk choreoathetosis, elaborate motions of arms and legs, oculogyric crisis, dystonia, rigidity, opisthotonic postures
   - The overlap of abnormal movements and epileptic seizures can lead to under-recognition of the seizures or unnecessary escalation of antiepileptics for dyskinesias that are interpreted as seizures
   - Video-EEG monitoring helps distinguishing both entities
Anti-NMDAR encephalitis - symptoms

- Autonomic manifestations include hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, orthostatic hypotension, urinary incontinence
- Two reported women were thought to have stress cardiomyopathy due to high blood pressure
- Some patients require temporary pacemakers for long-lasting cardiac pausing
- Three patients were thought to have rabies

6. Gradual recovery (75%) or death (25%)
**Brain MRI:**
- Normal in 50%
- In the other 50% T2 or FLAIR hyperintensity might be seen in hippocampi, cerebellar or cerebral cortex, frontobasal or insular regions, basal ganglia, brainstem, and, infrequently, in spinal cord
- Findings are usually mild and transitory and can be accompanied by subtle enhancement in the adjacent areas of meninges
- Follow up MRIs are normal or show minimum changes
Diagnostic tests

- **EEG:**
  - Abnormal in most patients
  - Non-specific, slow and disorganized activity, sometimes with electrographic seizures that are never associated with the dyskinetic movements
  - Slow, continuous, rhythmic activity predominates in the catatonic-like stage
  - Monitoring with video-EEG is important to diagnose and treat seizures appropriately (differential diagnosis with dyskinetic movements)
Diagnostic tests

- **CSF:**
  - Initially abnormal in 80% of the patients
  - Becomes abnormal later in most of the patients
  - Lymphocytic pleocytosis, normal or mildly increased proteins and in 60% of patients CSF-specific oligoclonal bands
  - Most patients have anti-NMDAR antibodies present in CSF
Diagnostic tests

- **Brain biopsy:**
  - Normal or non-specific findings like perivascular lymphocytic cuffing, sparse parenchymal T-cell infiltrates, or microglial activation
  - Doesn’t provide a diagnosis of anti-NMDAR encephalitis
Tumour association

- Detection of tumours other than teratoma is not common (2%)
- Whether tumours other than teratomas are true associations or unrelated coincident disorders is unknown
- The first concern in female patients should be screening for an ovarian teratoma
Tumour association

- The most useful screening tests include MRI, CT scan, and pelvic and transvaginal ultrasound (if appropriate).

- In some patients, exploratory laparoscopies and blind oophorectomies showed ovarian tumours, but in others no tumour was detected.
• This entity is secondary to the production of anti-NMDA receptor antibodies (Abs)

• These Abs react specifically with the NR1/NR2B heteromer of the receptor (cell membrane antigens)

• These Abs are pathogenic
NR1 and NR2 subunits of the receptor are expressed in all central nervous system.

But NR2B subunits are expressed preferentially in the forebrain and hippocampus.

- Structures that are involved in patients with this syndrome
- CSF of patients react with hippocampus and forebrain of rat
These data suggest an immune-mediated mechanism of NMDAR dysfunction.

NMDAR are the major mediators of excitotoxicity and their dysfunction has been associated with schizophrenia (NMDAR hypofunction), epilepsy, and dementia.

Also, drugs interacting with this receptor (Ketamine and phenylcyclidine) may result in paranoia, hallucinations, and dyskinesias.
It has been postulated that the ectopic expression of NR2 subunits in neural tissue contained in the teratoma may contribute to break immune tolerance.

The teratoma tissue reacts with the patient’s CSF (as the hippocampal tissue).

There could be an adjuvant effect of the prodromal viral-like illness to initiate the immune response.
The reversibility of the disorder, irrespective of the duration of symptoms, suggests an immune-mediated neuronal dysfunction rather than irreversible degeneration.

These features, coupled with the paucity of brain T-cell infiltrates, places this disorder in a category distinct from those that are mediated by complement or cytotoxic T-cell mechanisms (like anti-Hu syndrome).
Management of anti-NMDAR encephalitis should initially focus on:
- Detection and removal of a teratoma ASAP
- Immunotherapy

Most patients receive corticosteroids, intravenous immunoglobulins (IVIg) or plasma exchange as first-line of immunotherapy

These treatments have enhanced effectiveness and speed of action when patients have an underlying tumour that is removed
Treatment and outcome

- Patients whose tumor is identified and removed within the first 4 months have better outcome than the rest.
- In a study, median time to improvement was 8 weeks vs. 11 weeks for those patients with late removal or not removal at all.
In patients without a tumour or with delayed diagnosis, additional treatment with second-line immunotherapy is often needed:

- Rituximab
- Cyclophosphamide
- Or both
Treatment and outcome

- In one published series, second line immunotherapy resulted in substantial improvement in 15 of 23 (65%) patients.

- The final outcome was much the same in patients with or without tumour (84% vs 71%, p=0.16).

- But the five patients who died did not have a tumour and did not receive second-line immunotherapy.
Treatment and outcome

- About 75% of patients with NMDAR antibodies recover or have mild sequelae.
- 25% of patients remain severely disabled or die.
- There have been described several patients with spontaneous recovery (i.e. no removal of teratoma and no immunotherapy).
- In most patients that died, the diagnosis was made retrospectively.
Recovery is a multistage process

- In the reverse order of symptom presentation
- Patients slowly wake from coma, respiration recovers, and dyskinesias subside
- They are able to follow simple commands and can have appropriate interactions before they recover verbal functions.
- During this period patients can become psychotic and agitated again, calming as they recover further
Recovery

- Social behavior and executive function symptoms are usually the last to improve, and recovery can be incomplete or delayed by many months.

- For the acute stage of the disease, many patients need to be hospitalized for at least 3–4 months, followed by several months of physical and behavioral rehabilitation.
Mortality

- On the basis of data for 360 patients with clinical follow-up longer than 6 months, the estimated mortality for anti-NMDAR encephalitis is 4%.

- Median time from disease onset until death was 3.5 months.

- Causes of death: sepsis, cardiac arrest, acute respiratory distress, and refractory status epilepticus.
In summary...
Remember:

- Young women with psychiatric symptoms, seizures and pleocytosis in CSF: look for ovarian teratoma and remove it.

- This encephalitis is often paraneoplastic, treatable and can be diagnosed serologically!
Thank you