Anti-NMDA receptor encephalitis: A review of the data and an approach to testing
Agenda

• Case
• Background and Rationale
• Research Question
• Methods
• Results
• Take Home Points
26 F is brought into the ER by her boyfriend following a ?seizure where she was “shaking for 2 minutes”

- She is now stable with a temp of 37.6
- She appears to be post-ictal…

- **PMHx:** previous miscarriage
- **FHx:** NO history of epilepsy
- **SHx:** NO history of substance use

- **HPI:** boyfriend states she has “not been herself” for the last week – irritable, forgetful, twitching – thought it was stress related to an upcoming exam; also notes she had a viral illness 2 weeks ago but “seemed to get over it”
Background

- first described by Dr. Dalmau in 2007
- "auto-immune" encephalitis
  - Anti-bodies attack NMDA receptors
- More common in 30 and under
- Women (80%) > Men (20%)
- Often paraneoplastic
  - i.e. teratoma
  - more common in women

Brain on Fire
My Month of Madness
Susannah Cahalan
Pathophysiology

Dalmau et al. (Lancet 2008)
Patient Demographics

Titulaer et al. (Lancet 2013)
Clinical Presentation

Titulaer et al. (Lancet 2013)
...depends on stage of the disease

Dalmau et al. (Lancet 2008)
Diagnostic Work-up

- Lumbar Puncture
  - Lymphocytic pleocytosis (90%)
  - Oligoclonal bands (60%)
  - NMDA (NR1) receptor anti-bodies

- MRI
  - Non-specific abnormalities
  - 60% are normal

- EEG
  - Generalized or focal slow activity
  - Sometimes super-imposed epileptic activity
Treatment

• 1\textsuperscript{st} line: steroids, IVIG, plasmaphoresis +/- tumor removal

• 2\textsuperscript{nd} line: rituximab, cyclophosphamide
Rationale: Why do we care?

• Not as rare as you might think…
  – most common identified viral encephalitis in CEP database in 30 and under age group
  – More than 500 cases, exact prevalence unknown

Gable et al. (CID 2012)
Rationale: Why do we care?

• Morbidity & Mortality
  – 6% mortality during first 24-months
  – ONLY 15% get better within 1-month
  – 81% had a “good outcome” by 3 months
  – Relapse present in 12% (tend to be less severe)

*EARLY recognition and initiation of immunotherapy or tumor removal was predictor of good outcome

Titulaer et al. (Lancet 2013)
Research Questions:

1. How often are we sending cerebrospinal fluid to test for herpes simplex virus in the 30 and under age group?
   b) How often are we sending the anti-NMDAR antibody test in this population?

2. How many times have we sent the anti-NMDAR antibody test since 2013?

3. What are the logistical issues and costs associated with ordering the test?
Methods

HSV PCR sent between January 2013 - August 2015
*Age 30 and under
(n = 171)

Exclusion

Non-CSF samples:
 i.e. corneal, amniotic, blood

Infants <1 year

Outpatient clinic

ER or inpatient who had HSV
sent from “CSF” or “LP”
Results

1. Over 32 months, CSF testing for HSV was $n = 109$, in the 30 and under age group

b) Only $n = 1$ was sent for anti-NMDAR antibody
Results

2. How many times has the test been sent in all age groups? $n = 16$
Patient Demographics

Titulaer et al. (Lancet 2013)
3. What are the logistical issues and costs associated with ordering the test?

- ONLY one lab in Canada
- Results in 5-7 business days after sample received by lab
- Need approval of biochemist

- Cost: $130
  - Compare to HSV test: $22
**Autoantibody Test Requisition**

**Patient Information**

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**Ordering Physician Information**

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**Ordering Lab Information**

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**Required Information**

- **Medical Personnel:** Please mark ALL tests to be done.

**Encephalitis: NMDA (NR1) Receptor Antibodies**

- VGKC antibodies (Voltage gated potassium channel – LGI1 & Caspr2)
- Anti-GAD 65 antibodies
- Anti-AMPA antibodies

**Autoimmune Liver Disease Profile:**

- M2/M3, SEBPO, LKM, SLA, SP 100, gp210, PML, LC1, Ro 52.

**Antiphospholipase A2 receptor**

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<td>Anti-DPS 70 (Desfolded Polypeptides)</td>
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<tr>
<td>Anti-thrombinogens/thrombin complex</td>
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<tr>
<td>Anti-IgG, IgM (PS/PT)</td>
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<tr>
<td>Anti-p140/p155/TRIM28 (Research Use only)</td>
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<tr>
<td>Anti-alveolar proteinosis anti-GM/CSF (Research Use only)</td>
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<tr>
<td>Anti-elastase (Research Use only)</td>
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**Systemic Lupus ENA Profile:**

- Anti-Sm, RNP, Ro52/TRIM21, SSA/Ro60, SSB/La, Jo-1, PCNA

**Scleroderma Profile:**

- CENP A + B, Topo II, U1RNP, U1RNP, LM, SCL70, SCL70, Sm, Ku, POGF, Ro52/TRIM21, PM/Scl 75, PM/Scl 100.

**Anti-CCP**

- Cyclic Citrullinated Peptide Antibodies

**Autoimmune Neutrophil Antibodies:**

- MPO, PR3, NEU150, NEU140, NEU130.

**Miscellaneous:**

Probable anti-NMDA receptor encephalitis*

Diagnosis can be made when all three of the following criteria have been met:

1. Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
   - Abnormal (psychiatric) behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation

*Titulaer et al. (Lancet 2016)
Take home points

1. Anti-NMDAR encephalitis may be more common than HSV encephalitis in the 30 and under age group

2. More common in females and often related to ovarian teratoma… but not always

3. Clinical presentation may include: behavioural change, seizure, memory or cognitive impairment, abnormal movements, speech impairment
Take home points

4. Consider anti-NMDAR encephalitis in the “bizarre” psych patient, OR in the patient you are working up for HSV encephalitis

5. If you are sending CSF for HSV testing or covering with acyclovir, consider testing for NMDAR antibodies

6. You don’t know, what you don’t know…
References


• Chang et al. Anti-N-methyl-D-aspartate receptor encephalitis: Should psychiatrists shoulder the responsibility for a non-psychiatric disorder? J Neurol Sci 2015;353(1-2):189-90


• Gable et. al. The frequency of autoimmune N-Methyl-D-aspartate Receptor Encephalitis Surpasses that of Individual viral etiologies in young individuals enrolled in the California Encephalitis Project; CID 2012;54.
References


