ANTI-NMDA RECEPTOR ENCEPHALITIS:

Clinical Presentations and Pathophysiology

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□ No conflicts of interest to disclose
□ Will be discussing the off label use of immunotherapies
Anti-NMDA Receptor Encephalitis

- Recently identified, clinically important cause of autoimmune encephalitis
- Patients present with psychiatric symptoms, decreased level of consciousness, seizures, dyskinesias, and autonomic dysfunction
- Associated with ovarian teratomas in many patients
- Treated with immunosuppressive therapies
- 75% of patients have good recovery, but may take over two years
Anti-NMDA Receptor Encephalitis

Betrayed by the brain

Charlotte Wendel practices piano. She endured more than two years of minimal consciousness. (MICHAEL S. WIRTZ / Staff Photographer)

A tricky encephalitis that mimics mental illness can now be diagnosed and treated. But some don’t respond, and it’s not known why.

#1 NEW YORK TIMES BESTSELLER

“Stunningly brave . . . an unexpected gift of a book from one of America’s most courageous young journalists.” —NPR

BRAIN ON FIRE
— My Month of Madness —
Age of onset: non-tumor associated disease is more common in children

- **Under age 12:**
  - Female predominance is less
    - 39% boys / 61% girls
  - Tumor is rare (6%)

- **Tumors:**
  - 96% were teratoma
    - 94% ovarian
    - 2% extra-ovarian
  - Non-teratoma patients were adults

37% pediatric
Presenting symptoms

Children

Teenagers

Adults

Seizure

Movement disorder

Behavior change

Titulaer et al, 2013
Cumulative symptoms at one month

By one month only 1% of patients were monosymptomatic**

Titulaer et al, 2013
Treatment of anti-NDMAR encephalitis

- **First line therapies:**
  - IV solumedrol
  - IVIg
  - Plasmaphereis

- **Second line therapies:**
  - Rituximab
  - Cyclophosphamide
  - Steroid-sparing agents
Treatment of anti-NDMAR encephalitis

All patients

Responders (significant improvement by one month)

Non-responders
No 2^{nd} line rx

Non-responders + 2^{nd} line rx

Titulaer et al, 2013
NMDA Receptors

- ionotropic glutamate receptors
  - Co-ligand = glycine or D-serine
  - Magnesium blockade of channel pore
- two NR1 subunits, two NR2/3 subunits
- Role in long-term potentiation (LTP) – the synaptic correlate of learning
- Critical for learning and memory
- Hypofunction is implicated in schizophrenia
  - Acute psychosis with NMDAR antagonists (PCP, ketamine)
  - Agonists have a role in the treatment of schizophrenia
Anti-NDMAR antibodies

- Recognize a protein enriched in hippocampus
- Bind to synaptically localized puncta on the surface of cultured hippocampal neurons
- Colocalize with the NMDAR subunit NR1 in transfected cells

Dalmau et al., 2008
Antibodies crosslink surface NMDARs, leading to their internalization.

Hughes et al., 2010
Antibodies cause NMDARs to move out of synapses

Mikosova et al., 2012
Antibodies block LTP

Mikosova et al., 2012
Reduced NMDAR-mediated synaptic currents

• Impaired long term potentiation (LTP)

Synapse

Extra-synaptic

From pathophysiology to symptoms

Panzer et al., 2014

• LTP impairment → amnesia
• NMDAR hypofunction → psychosis, autonomic instability
• Network dysregulation → seizures, dyskinesias

Clinical symptoms


Isolated psychosis associated with anti-NMDAR antibodies

- NMDAR hypofunction is hypothesized to underlie schizophrenia
  - psychosis is a core feature of anti-NMDAR encephalitis, and NMDAR antagonists cause psychotic symptoms

- Can anti-NMDAR antibodies result in isolated psychosis or a schizophrenia-like illness in some individuals??
Anti-NMDAR encephalitis with isolated psychosis

- Subgroup analysis of Dalmau’s large anti-NMDAR cohort was published (Kayser et al., 2013).
  - Of the 571 patients in the original cohort, 23 (4%) developed isolated psychiatric episodes
  - five of these were at disease onset
  - 18 were during relapse

- Greater than 80% had full or substantial recovery after immunotherapy and tumor resection when appropriate.

- Therefore, there is a rare subtype of anti-NMDAR encephalitis consisting of isolated psychosis.
How often do patients with isolated psychosis or schizophrenia have anti-NMDAR antibodies?

- Multiple studies have attempted to address this question, but the results have been mixed.
  - 3 out of 46 patients with new onset isolated psychosis had detectable anti-NMDAR antibodies in their serum; one of these patients was treated with immunotherapy and had a positive response (Zandi et al., 2011).
  - 4 out of 51 patients with schizophrenia or schizophreniform disorders had anti-NMDAR antibodies (Tsutsui et al., 2012).
    - 3 of these antibody-positive patients had other features, such as seizures and/or ovarian teratoma (making a diagnosis of typical anti-NMDAR encephalitis more likely).
  - 15 out of 121 patients with schizophrenia had diverse anti-NMDAR antibodies (Steiner et al., 2013).
    - Only 2 had IgG antibodies specific to GluN1a, and these were subsequently re-classified as having typical anti-NMDAR encephalitis.
    - The other patients had IgA or IgM antibodies, or antibodies that were not specific to GluN1a alone.
  - 0 out of 7 patients with chronic schizophrenia were found to have antibodies to GluN1 (Rhoads et al., 2011).
  - 0 out of 80 patients with newly diagnosed schizophrenia, as defined by one year of symptoms, were also negative for IgG antibodies to GluN1 in serum collected at the onset of their symptoms (Masdeu et al., 2012).
- Seems unlikely that “typical” schizophrenia is caused by these antibodies.
Anti-NMDAR antibodies in patients with psychosis

- These conflicting results likely are due to:
  - variation how the psychotic syndromes were classified
  - differences in the timing of when samples were collected relative to onset of psychiatric symptoms
  - variations laboratory methodology
  - the inclusion of non-IgG antibodies
  - binding to NMDAR subunits other than GluN1
  - the study of serum rather than CSF

- A conclusive answer to this question may require specifically designed prospective studies examining CSF in patients with strictly defined new onset psychosis.


