Anti-NMDAR encephalitis or schizophrenia?

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Disclosures

Received a travel grant for lecturing in India from Sun Pharma

Will discuss unlabeled use of different immunotherapeutics
Anti-NMDA receptor encephalitis

Discovered in 2007

1) rat brain immunohistochemistry (IHC)
2) live rat hippocampal neurons
3) cell based assay (CBA)

Dalmau et al. Lancet Neurol 2008
Demographics

Median age 19 years

- < 18: 37%
- ≥ 45: 5%

81% female

- 12-45: 88%
- < 12 or ≥ 45: 60%

39% tumour

- 96% teratoma
- < 12 F or M: 4%
- ≥ 12 F: 54%
- ≥ 45 F or M: 23%

Titulaer et al. Lancet Neurol 2013
Titulaer et al. Neurology 2013
First symptom

- **Age < 12 yrs**
- **Age 12-18 yrs**
- **Age 18-45 yrs**
- **Age ≥ 45 yrs**

Legend:
- Behavior
- Cognition
- Memory
- Speech
- Level of consciousness
- Movement disorder
- Seizures

Source: Titulaer et al. Lancet Neurol 2013
Anti-NMDA receptor encephalitis

Clinical Worsening

agitation, psychosis, catatonia, memory deficit, speech reduction, abnormal movements +/- seizures

Clinical Improvement

coma, hypoventilation, +/- dysautonomia

prodrome

Dalmau et al. Lancet Neurol 2008
Irani et al. Brain 2010
Dalmau et al. Lancet Neurol 2011
Titulaer et al. Lancet Neurol 2013
Severity of disease

ICU stay
- <12 years: 75%
- 12-17 years: 73%
- ≥ 18 years: 78%
  \( p = \text{NS} \)

maximum modified Rankin Scale (mRS) of 5
- <12 years: 90%
- 12-17 years: 86%
- ≥ 18 years: 86%
  \( p = \text{NS} \)

**Number of major symptoms**

Titulaer et al. Lancet Neurol 2013
NMDAR antibodies in psychiatric patients? (1)

- 3 of 46 cases (6.5%) with 1st-episode schizophrenia (CBA serum)
  1/3 diagnosis doubtful; 2/3 had (mild) verbal dysfunction
  Zandi et al, J Neurol 2011

- 4 of 51 cases (7.8%) met 'schizophrenia'; 2/4 had seizures,
  1/4 orofacial dyskinesias (CBA serum)
  Tsutsui et al, BMC Psych 2012

- 0 of 207 patients with schizophrenia; 2 others were antibody-positive, but these had extensive anti-NMDAR encephalitis
  Steiner, JAMA Psych 2013; Masdeu, Am J Psych 2012; Rhoads J, Schizophr Res 2011

### Seropositive (IgG)

<table>
<thead>
<tr>
<th></th>
<th>CSF</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia (1081)</td>
<td>n.d.</td>
<td>7</td>
</tr>
<tr>
<td>Depression (148)</td>
<td>n.d.</td>
<td>5</td>
</tr>
<tr>
<td>Parkinson (263)</td>
<td>n.d.</td>
<td>1</td>
</tr>
<tr>
<td>Controls (1272)</td>
<td>n.d.</td>
<td>5</td>
</tr>
</tbody>
</table>

Hammer et al. Mol Psych 2013
NMDAR antibodies in psychiatric patients (2)

• 5 of 571 NMDAR patients had purely psychiatric symptoms during 1\textsuperscript{st} disease episode (retrospectively 2 mild orofacial dyskinesias)

Kayser \textit{et al}, JAMA Neur 2013

0 of 900 NMDAR patients developed schizophrenia

• Test in patients with new-onset psychosis, be cautious for (subtle) neurological symptoms; chance of NMDAR-antibodies will decrease sharply without additional symptoms < 4 weeks

Titulaer & Dalmau, Lancet Neur 2013
# Sensitivity en specificity

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>CSF</th>
<th>Serum</th>
<th>$p_{\text{McNemar's test}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>250</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Both tests positive</td>
<td>250</td>
<td>100.0%</td>
<td>214</td>
</tr>
<tr>
<td>95% CI</td>
<td>(98.5 – 100.0%)</td>
<td>(80.7 – 89.4%)</td>
<td></td>
</tr>
<tr>
<td>CBA negative</td>
<td>0</td>
<td>0.0%</td>
<td>33</td>
</tr>
</tbody>
</table>

- Specificity 100% (96.3 – 100.0%), in serum and CSF (n = 100)

- Serum positive in 0.4 - 3% healthy patients  
  CBA, not IHC

- Confirm positive serum test in CSF and/or by IHC

Gresa, Titulaer *et al*. Lancet Neurol 2014  
Viacozz *et al*. Neurology 2014  
Hammer *et al*. Mol Psych 2013
Diagnostics

CSF: 79% abnormal
- Lymphocytic pleocytosis
  WBC 32 (6-511) 75%
- Raised total protein 18%
- Oligoclonal bands 53%

EEG: 89% abnormal
- Extreme Delta Brushes 30%

MRI: 33% abnormal

Dalmau et al. Lancet Neurol 2008
Irani et al. Brain 2010
Titulaer et al. Lancet Neurol 2013
Schmitt et al. Neurology 2012
Armande et al. J Ped 2012
NMDA receptor hypofunction theory

Glutamate levels ↑↑ after intracerebral injections with patients’ antibodies

Gordon Nature Neurosci 2010

Manto et al. Orphanet J Rare Dis 2010
Antibodies diminish the number of NMDAR clusters

Hughes et al. J Neurosci 2010
Passive transfer leads to (reversible) encephalitis

Planaguma, Leypoldt, Mannara et al. Brain in press
Modified Rankin Scale (mRS)

0  No symptoms.
1  No significant disability. Able to carry out all usual activities.
2  Slight disability. Independent in activities of daily living (ADL).
3  Moderate disability. Needs some help, but able to walk unassisted.
4  Moderately severe disability. Requires assistance, and unable to walk unassisted.
5  Severe disability. Requires constant nursing care and attention, bedridden.
6  Dead.

Better outcome
- no ICU stay
- shorter time until treatment
- longer follow-up (until 18 months)

Follow-up (months)

Long-term outcome

All significant in multivariate analysis
Treatment-related outcome

NMDAR-encephalitis (n = 501)

- no treatment (n = 29; 6%)
  - 29% died / poor outcome

- immunosuppression tumour removal (n = 472)
  - no improvement / limited response (n = 221; 44%)
  - improvement (n = 251; 50%)

  - 1st-line IS (n = 96; 43%)
    - no additional treatment / repetition
  - 2nd-line immunotherapy (n = 125; 57%)

Follow-up (months): 0, 4, 8, 12, 18, 24

Erasmus MC
Efficacy of 2\textsuperscript{nd}-line treatment

\begin{figure}
\centering
\includegraphics[width=\textwidth]{efficacy_chart.png}
\caption{Efficacy of 2\textsuperscript{nd}-line treatment.
2\textsuperscript{nd}-line treatment
OR = 2.69 (1.24 – 5.80)
p = 0.012

Titulaer \textit{et al.} Lancet Neurol 2013}
\end{figure}
Plasma cells in PA brain of patients

CD20  CD3  CD4  CD8  CD138

CD138

Martinez-Hernandez et al. Neurology 2011
AMPAR: clinical symptoms (36 patients)

- Epidemiology: 67% female, median age ~60 (23-87)
- Symptoms:
  - 60% limbic encephalitis
  - 30% limbic encephalitis plus
  - 10% psychosis or rapid progressive dementia
  - 15% low sodium
- 60-65% SCLC, breast cancer, thymoma, ovarian teratoma
- Sensitivity serum 71% (10/14 paired samples)
- MRI: 80-85% temporal FLAIR hyperintensity
- Outcome: ~25% complete, ~50% partial recovery;
  However, outcome depends on additional onconeuronal abs

Graus et al. Neur 2010
Hoftberger et al. submitted
Conclusions

- Psychiatric symptoms are frequent in anti-NMDAR encephalitis
- Psychiatric symptoms are often the first symptoms
- Isolated psychiatric symptoms (> 4 weeks) are rare
- Beware of pitfalls in diagnosis, especially in serum; check CSF
- Outcome depends on treatment delay and severity of disease
- If 1\textsuperscript{st}-line immunotherapy (steroids, plasma exchange, IVIG) fails, 2\textsuperscript{nd}-line IT (rituximab, cyclophosphamide) is usually effective
- Overall, 80% have a good outcome
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