Autoimmune Encephalitis
Autoimmunity and acute neuropsychiatric disorders: the clinical challenge of seronegative but probable autoimmune psychosis

Souhel Najjar, MD
Professor & Chairman, Department of Neurology
Donald AND BARBARA ZUCKER SCHOOL OF MEDICINE AT HOFSTRA/NORTHWELL

Common Threats: Post-Infectious Autoimmune Diseases of the Brain Conference
March, 2018

Conflicts of Interest: None to Disclose
**Linking Autoimmunity to Neuropsychiatric Syndromes**

- **Direct effects of autoantibodies: neuronal dysfunction**
  - Encephalitis related to antibodies against synaptic and neuronal surface antigens
    - Anti-NMDAR encephalitis (GluN1 subunit)
  - Neuro-psychiatric systemic lupus erythematosus
    - Anti-NMDAR (GlunN2A and B subunits)
    - Anti-ribosomal P antibodies and neuronal surface P antigen (NRSPA)

- **Neurovascular unit dysfunction with BBB hyperpermeability**
  - Primary vs. secondary?
  - Does BBB disruption predate or follow neuroinflammation?

- **Neuroinflammation: secondary?** Microglial activation
  - Astroglial activation
  - Recruitment of immune cells
  - Upregulation and release of inflammatory mediators (e.g., cytokines)
  - Upregulation of oxidative stress

- **Dysregulation of neurotransmitter systems**
**Increased IDO Activity and Elevated KYN/TRP Ratio in MDD**

**Tryptophan Metabolism Seesaw**

**Serotonin vs. Kynurenine**

**Tryptophan**

- **IDO** activates the Th1 response, resulting in increased KYN/TRP ratio.

- **KMO** and **Quinolinic acid** (NMDAR agonist) lead to hyperglutamatergia.

- **3-OH-KYN** and **Serotonin Degradation to 5HIAA** result in hyposerotonergia.

**IDO** = Indoleamine-2,3-dioxygenase

**KMO** = Kynurenine 3-monooxygenase

(Microglia, Astroglia)

---

**IDO** = Indoleamine-2,3-dioxygenase

(Microglia, Astroglia)

**KMO** = Kynurenine 3-monooxygenase

(Microglia)
Pro-inflammatory Cytokines and Dysregulation of Neurotransmitter Systems

- **Serotonergic hypofunction**
  - Reduce serotonin synthesis
  - Increase serotonin degradation

- **Glutamatergic hyperfunction**
  - Promote quinolinic acid (NMDAR agonist) synthesis
  - Attenuate astroglial glutamate reuptake
  - Promote astroglial glutamate release
  - Induce GABA$_A$R endocytosis
  - Decrease GABA$_A$R-mediated chloride (Cl$^-$) currents
Antibodies in the diagnosis of autoimmune encephalitis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Diagnostic assay</th>
<th>Frequency of cancer</th>
<th>Main type of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibodies against intracellular antigens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu (ANNA1)</td>
<td>Western blot</td>
<td>&gt;95%</td>
<td>Small-cell lung carcinoma</td>
</tr>
<tr>
<td>Ma2</td>
<td>Western blot</td>
<td>&gt;95%</td>
<td>Testicular seminoma</td>
</tr>
<tr>
<td>GAD</td>
<td>Radioimmunoassay</td>
<td>25%</td>
<td>Thymoma, small-cell lung carcinoma</td>
</tr>
<tr>
<td><strong>Antibodies against synaptic receptors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMDA receptor</td>
<td>Cell-based assay</td>
<td>Varies with age and sex</td>
<td>Ovarian teratoma</td>
</tr>
<tr>
<td>AMPA receptor</td>
<td>Cell-based assay</td>
<td>65%</td>
<td>Thymoma, small-cell lung carcinoma</td>
</tr>
<tr>
<td>GABAB receptor</td>
<td>Cell-based assay</td>
<td>50%</td>
<td>Small-cell lung carcinoma</td>
</tr>
<tr>
<td>GABA_A receptor</td>
<td>Cell-based assay</td>
<td>&lt;5%</td>
<td>Thymoma</td>
</tr>
<tr>
<td>mGluR5</td>
<td>Cell-based assay</td>
<td>70%</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Dopamine 2 receptor</td>
<td>Cell-based assay</td>
<td>0%</td>
<td>..</td>
</tr>
<tr>
<td><strong>Antibodies against ion channels and other cell-surface proteins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGI1</td>
<td>Cell-based assay</td>
<td>5–10%</td>
<td>Thymoma</td>
</tr>
<tr>
<td>CASPR2</td>
<td>Cell-based assay</td>
<td>20–50%</td>
<td>Thymoma**</td>
</tr>
<tr>
<td>DPPX</td>
<td>Cell-based assay</td>
<td>&lt;10%</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>MOG</td>
<td>Cell-based assay</td>
<td>0%</td>
<td>..</td>
</tr>
<tr>
<td>Aquaporin 4</td>
<td>Cell-based assay</td>
<td>0%</td>
<td>..</td>
</tr>
<tr>
<td>GQ1b</td>
<td>Cell-based assay</td>
<td>0%</td>
<td>..</td>
</tr>
</tbody>
</table>

*Graus et al., Lancet Neurol. 2016*
Anti-NMDAR Encephalitis

NMDAR Subunit Composition

Paoletti et al., *Nat Rev Neurosci* 2013
**Effects of IgG Antibodies Against GluN1 Subunit of NMDAR**

- Binding of IgG antibodies to NMDARs causes reversible, time- and dose-dependent internalization of the receptors (plateaued after 12 hours) from both synaptic and extra-synaptic spaces in hippocampal neuron cultures and rodent brain models.

- Internalization of NMDARs occurs through cross-linking of the receptors demonstrated by immunohistochemical staining.

- Reduced synaptic NMDAR clustering is associated with reduced NMDAR-mediated currents.

- No evidence of cytotoxic T-cell mediated mechanisms or complement activation.

- Anti-NMDAR antibodies:
  - affect both excitatory and inhibitory neurons
  - reduce inhibitory synapse density onto excitatory neuronal firing
  - do not induce compensatory upregulation of any of NMDAR subunit gene expression

Kayser et al., Schizophr. Res 2014
Leyboldt F et al., JAMA Neurol 2014
Moscato et al, ANN Neurol 2014
Hughes et al, J Neurosci 2010
<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Dalmau et al. 2008</th>
<th>Titulaer et al. 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size, n</td>
<td>99</td>
<td>577</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>23 (5–76)</td>
<td>21 (1.75–85)</td>
</tr>
<tr>
<td>Gender, female, %</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>Prodromal illness, %</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Psychiatric/cognitive, %</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>1st seen by a psychiatrist</td>
<td>77</td>
<td>...</td>
</tr>
<tr>
<td>Seizures, %</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>Dyskinesia/movement disorder, %</td>
<td>86</td>
<td>80</td>
</tr>
<tr>
<td>&lt; 12 years</td>
<td>...</td>
<td>95</td>
</tr>
<tr>
<td>12–18 years</td>
<td>...</td>
<td>82</td>
</tr>
<tr>
<td>≥ 18 years</td>
<td>...</td>
<td>70</td>
</tr>
<tr>
<td>Orofacial dyskinesia</td>
<td>55</td>
<td>...</td>
</tr>
<tr>
<td>Choreoathetosis</td>
<td>47</td>
<td>...</td>
</tr>
<tr>
<td>Dystonia</td>
<td>47</td>
<td>...</td>
</tr>
<tr>
<td>Catatonia, %</td>
<td>40</td>
<td>...</td>
</tr>
<tr>
<td>Decreased consciousness, %</td>
<td>...</td>
<td>65</td>
</tr>
<tr>
<td>Autonomic instability, %</td>
<td>69</td>
<td>50</td>
</tr>
<tr>
<td>Central hypoventilation, %</td>
<td>66</td>
<td>30</td>
</tr>
<tr>
<td>&lt; 12 years</td>
<td>...</td>
<td>12</td>
</tr>
<tr>
<td>12–18 years</td>
<td>...</td>
<td>28</td>
</tr>
<tr>
<td>≥ 18 years</td>
<td>...</td>
<td>40</td>
</tr>
<tr>
<td>Neoplasm, %</td>
<td>59</td>
<td>38</td>
</tr>
<tr>
<td>Female, all ages</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Female, ≥ 12 years</td>
<td>...</td>
<td>94</td>
</tr>
<tr>
<td>Male, all ages</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Male, ≥ 18 years</td>
<td>...</td>
<td>94</td>
</tr>
<tr>
<td>Ovarian teratoma</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Asian</td>
<td>...</td>
<td>45</td>
</tr>
<tr>
<td>Black</td>
<td>...</td>
<td>48</td>
</tr>
</tbody>
</table>
Anti-NMDAR Encephalitis
Role of Infections and BBB disruption

- About 70% of patients exhibit prodromal illness
- Temporal evolution of CSF abnormalities; first lymphocytic pleocytosis within 4-6 weeks, frequently followed by resolution of cellular response and evolution of OCBs
- Infections-induced BBB disruption hypothesis
- Synaptic and neuronal antibodies-induced neuronal injury can in turn trigger neuroinflammation
- HSV encephalitis as a trigger for anti-NMDAR encephalitis
Autoimmune Psychosis

- Inflammatory-immunological abnormalities can cause acute drug-resistant neuropsychiatric disorders including psychosis

- Autoimmune Psychosis (AP)
  - **Types:**
    1. *Psychosis associated with well-characterized synaptic and neuronal surface autoantibodies*
      - Incomplete form or forme fruste of AE
    2. *Psychosis associated with systemic or isolated CNS autoinflammatory disorders, Hashimoto’s encephalopathy, or paraneoplastic Syndromes*
    3. *Seronegative but Probable Autoimmune Psychosis (SPAP)*
      - Absence of well-characterized antibodies to synaptic and neuronal cell surface proteins
      - Absence of serum and imaging biomarkers for classical systemic or isolated CNS autoinflammatory disorders, Hashimoto’s encephalopathy, or paraneoplastic syndromes
      - Caused by autoantibodies still undiscovered or present only in the CSF at low titers, innate immunity, or T cell autoimmunity
      - **Core pathology:** BBB disruption and neuroinflammation

_Najjar et al., Front Psychiatry. 2017
Najjar et al., J Neuroinflammation 2018_
Seronegative but Probable Autoimmune Psychosis

“SPAP”

Diagnostic challenges in identifying this subpopulation of patients:
- Frequent absence of CNS hyperexcitability (e.g., hyperekplexia, tremors, myoclonus), abnormal movements, seizures, or autonomic instability
- Frequent absence of focal neurological deficits
- Frequent absence of diagnostic findings on conventional MRI studies
- May not be associated with CSF pleocytosis or OCBs

Core pathology:
- Immunologically-mediated neuroinflammation associated with BBB disruption
Case illustration

History and examination

- A 26-year-old woman presented at 21 years of age with a cyclic encephalopathy with superimposed psychosis that started acutely at age 15 years.

- Symptoms:
  - Monthly episodes of encephalopathy associated with overt psychosis (prominent auditory hallucinations) and severe insomnia recurring within days of menstruation and lasting < 15 days.
  - Progressive cognitive decline

- Full scale IQ was 77 (6th percentile)

- Non focal segmental neurological examination

- No family history of psychiatric illness

Work-up

- Extensive diagnostic workup was negative, including brain MRIs, serologic and CSF analyses for inflammatory, autoimmune, infectious, metabolic, and genetic causes

- Slightly elevated CSF albumin
Onset of a cyclic encephalopathic-neuropsychiatric disorder required a 3-4 week psychiatric admission in 2001; neuropsychiatric symptoms improved with hormonal therapy (2002-05), with more dramatic and sustainable responses during 2002-04.

Progression from cyclic to continuous neuropsychiatric disorder
Elevated pro-inflammatory cytokines during the cyclic neuropsychiatric episodes:

- IL-6
- TNF-α

Immunotherapy:

- IV Methylprednisolone
- IVIG pulse therapy
Onset of a cyclic encephalopathic-neuropsychiatric disorder

First initiation of immune therapy:
Pulse methylprednisolone 1gm/d x 3 d, followed by IVIG 1 gm/kg q mo for 6 mo and q 2 mo for subsequent 4 mo; every IVIG treatment was followed by a 12-day tapering course of oral prednisone.

Brain MRI (Oct., 07): Normal

Brain MRI: normal (Oct. 2006) (Fig. 2)

2001

15-year-old

2007

21-year-old

Full clinical recovery sustained for 10 mo.

Progression from cyclic to continuous neuropsychiatric disorder
Onset of a cyclic encephalopathic-neuropsychiatric disorder

First initiation of immune therapy:
Pulse methylprednisolone 1gm/d x 3 d, followed by IVIG 1 gm/kg q mo for 6 mo and q 2 mo for subsequent 4 mo; every IVIG treatment was followed by a 12-day tapering course of oral prednisone.

Brain MRI: Normal (Oct. 2006) (Fig. 2)

2007

2008

2009

2010

2011

26-year-old

2001

15-year-old

Onset of a cyclic encephalopathic-neuropsychiatric disorder

IV methylprednisolone 500mg/d x 4 d, followed by IV methylprednisolone 250 mg/wk x 4, followed by rituximab x 2 infusions; limited improvement

Full clinical recovery sustained for 10 mo.

Plasma exchange x 20 and a 4-day tapering course of oral steroids following every 5 consecutive plasma exchanges (Nov., 08 – Jan., 09)

Severe relapse (Aug., 08); Brain MRI (Sept., 08) showing extensive bi-hemispheric abnormalities Fig. 3); brain biopsy performed (Sept., 08) (Fig. 4)

2007

Brain MRI (Oct., 07): Normal (Fig. 2)

2008

IVIG 0.4gm/kg/d x 3 d q mo for 12 mo.

Complete resolution of MRI abnormalities (Feb., 09) (Fig. 5) despite only limited clinical response

Plasma exchanges x 5, followed by IV methylprednisolone 1 gm/d x 3 d, followed by oral prednisone 30 mg tapered over 4 mo and IVIG 0.5 gm/kg/2 wk for 4 mo., azathioprine 50 mg/d; limited improvement; Re-initiation of IV methylprednisolone 500 mg/d x 2 d/wk x 10 weeks; marked clinical improvement for approximately 1 week after each treatment.

Progression from cyclic to continuous neuropsychiatric disorder
23-year-old woman presented with acute-onset refractory psychosis and catatonia
Serology and CSF analysis are negative        EEG is normal
Family history notable for sibling with MS
21 year old right handed man presented with subacute-onset refractory psychiatric symptoms (depression, anxiety, psychosis) associated with cognitive impairment about 2 weeks following viral illness

No prior personal or family history of psychiatric illness

**DIAGNOSTIC FINDINGS:**
- EEG: Intermittent frontotemporal slowing, L>R
- BRAIN MRI: normal
- Serology and CSF: normal
18-year-old right handed young man presented with acute-onset refractory neuropsychiatric symptoms including OCD, Tics, depression, and progressive cognitive impairment.

PMHx: POTS, adrenal insufficiency, venous thrombosis

FHx: Hashimoto’s thyroiditis

Non-focal neurological examination

No prior personal or family history of psychiatric illness

Serologic assays notable for slightly low C3 and C4 levels

Brain MRI and CSF analysis are normal
CT PET brain: Frontotemporal-Occipital Gradient (frontotemporal hypermetabolism /relative occipital hypometabolism)
Conclusions

1. SPAP is an acute neuropsychiatric syndrome dominated by atypical acute psychotic symptoms associated with cognitive impairment related to autoimmune dysregulation

1. SPAP can masquerade as drug-resistant primary psychotic disorders such as recent-onset schizophrenia or first-episode psychosis?

1. Core pathology: BBB breakdown and neuroinflammation

1. Does BBB breakdown predate or follow neuroinflammation associated with psychosis in SPAP?

1. We propose multimodal diagnostic approach to address the challenges inherent to early diagnosis of SPAP
Future Directions

Is there better way to diagnose and treat ISPAP?

- Integrating more advanced neuroimaging modalities such as:
  - PET imaging of microglial activation utilizing translocator protein (TSPO)
  - High-resolution whole-brain dynamic contrast-enhanced MRI to assess BBB integrity
  - Resting-state functional MRI to detect aberrant connectivity or disconnectivity

- Incorporating CSF studies in the evaluation of individuals with first-episode psychosis

- Designing randomized clinical trials aimed at assessing the efficacy of targeted immune therapies in carefully selected subgroups of patients with drug-resistant atypical new-onset psychosis suspected to have SPAP
Thank You!

Questions/Comments