The Rationale Use of Immunotherapies in Children with Seizures

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Disclosures

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Outline

• What is the relationship between epilepsy and the immune system?

• Immune-mediated epilepsies in children:
  • Pathogenesis
  • Clinical clues
  • Specific syndromes
  • Management themes and therapies
Underlying Autoimmune Disorders Increase Risk of Epilepsy

• Examined relationship between epilepsy and 12 autoimmune disorders using data from National US Health Insurance Plan

• Risk of epilepsy was higher in those with autoimmune disorders (OR 3.8, 95%CI 3.6-4.0)

• This increased risk was particularly notable in children (OR 5.2, 95%CI 4.1-6.5)

Ong MS et al. JAMA Neurol 2014
How Frequent are Neuronal Antibodies in CWE?

- **New-onset seizures:**
  - Non specific serum antibodies found in 5.8%-9.7%
    (Garcia-Tarodo et al. 2018, Suleiman et al. 2013, Wright et al. 2016)

- **Focal epilepsy:**
  - 4% of children (Borusiak et al. 2016)

- **Significance** - many nonspecific VGKC, low titer GAD65, transient. In most cases, not treated and no impact on epilepsy course
Epileptic Encephalopathy of Unknown Cause

- 14% of 50 children
- 4% more showed nonspecific antibodies
- Clues: atypical progression of syndrome, associated movement disorder
- Response to immunotherapy varied

Tekturk et al. Brain Dev 2018
Clinical Clues Suggesting a Possible Immune Etiology

• Previously well child

• Seizures
  • Severe and drug resistant from onset

• Multifocal neurological symptoms/signs
  • Cognitive, behavioral, sleep, autonomic and movement disorders

• Personal or family history of autoimmunity
Laboratory Clues to the Diagnosis

- **EEG:**
  - NONSPECIFIC - slow background +/- multifocal (esp temporal) discharges

- **Imaging:**
  - Inflammatory FLAIR or T2 signal changes on MRI
    - Cortical (esp mesial temporal) or subcortical, cerebellar or basal ganglia

- **CSF:**
  - Inflammatory CSF with negative cultures
  - Increased IgG and IgG index, +/- oligoclonal bands
  - High CSF neopterin – indicates inflammation but not specific for autoimmune
Target of Antibody: Cell membrane vs Intracellular

(McKeon and Pittock, Acta Neuropathol 2011)

Courtesy of Dr. S Pilkoc
<table>
<thead>
<tr>
<th></th>
<th>Cell Surface Ag</th>
<th>Intracellular Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages affected</td>
<td>Broad range, often children</td>
<td>Usually older</td>
</tr>
<tr>
<td>Tumor association</td>
<td>Much lower but depends on Ag</td>
<td>Higher risk</td>
</tr>
<tr>
<td>Pathogenicity of antibodies</td>
<td>Pathogenic</td>
<td>Not pathogenic – biomarker but does not correlate with disease severity</td>
</tr>
<tr>
<td>Response to immune therapy</td>
<td>Responsive</td>
<td>Usually nonresponsive</td>
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Specific Immune Epilepsies

<table>
<thead>
<tr>
<th>Cell Surface Ag directed</th>
<th>Intracellular Ag directed</th>
</tr>
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<tbody>
<tr>
<td>NMDA-R</td>
<td>GAD65</td>
</tr>
<tr>
<td>VGKC – LGI1, CASPR2</td>
<td>Onconeural</td>
</tr>
<tr>
<td>$\text{GABA}_A$-R</td>
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<tr>
<td>$\text{GABA}_B$-R</td>
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<tr>
<td>AMPA-R</td>
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<td>Glycine-R</td>
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<td>Folate-R</td>
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<tr>
<td>DPPX</td>
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<td>mGluR5</td>
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Anti-NMDAR encephalitis

- Antibodies against NR1 subunit of NMDA receptor

- Binding of antibody leads to internalization of the NMDA receptors, thus reducing their density
NMDAR Encephalitis: Clinical Stages

- Viral prodrome,
- Clinical symptoms - 87% developing symptoms in >4 of the 8 categories

*Titulaer et al. Lancet Neurol 2013*
Investigations: MRI

- Often normal
- 1/3 show cortical/subcortical T2 hyperintensities
EEG

- Abnormal in 90%
- Extreme delta brush in approx 30% with severe seizures in ICU

Schmitt et al. Neurology 2012, Veciana et al. 2015
CSF

- Abnormal in 79%

- Detection of NMDAR antibodies
  - Positive in CSF in 100%
  - Positive in serum in 85% - false negatives and positives

*Titulaer et al. Lancet Neurol 2013*
Anti-NMDAR encephalitis and HSV

- Prospective study (Armangue et al. 2018):
  - autoimmune encephalitis develops in 27% after HSV (most within 2 months) and 2/3 were anti-NMDAR+
  - 30% without any clinical symptoms of autoimmune epilepsy have detectable anti-NMDA antibodies
Outcomes and Predictors

- 53% of treated pts significantly improved at 4 wks
- 12% relapsed
  - Most relapses less severe
- At 24 months:
  - 81% excellent/full recovery
  - 10% died

Titulaer et al. Lancet Neurol 2013
Predictors of outcome

- Univariable and multivariable predictors:
  - No need for admission to ICU (p<0.0001)
  - Shorter time to treatment initiation (p=0.009)
  - Longer time of follow-up (p<0.0001)
  - Lower severity of disease in first 4 wks (p=0.011)

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

Failed 1° line, no 2° line Tx

Failed 1° line, received 2° line Tx

Titulaer et al. Lancet Neurol 2013
VGKC Ab in Children are Common *Hacohen et al. 2015*

- Detected in 19% with inflammatory conditions vs 4.4% with noninflammatory conditions

- High titres (>400 pM) seen ONLY in inflammatory conditions (58% encephalopathy, 42% other – OMS, GBS)

- Most are not LGI1 or CASPR2

- Treatment with immunotherapy was not clearly beneficial

- VGKC Ab appear to be a nonspecific marker of inflammatory neurological disease
Anti-GABA$_A$R Encephalitis

- 26 cases, 42% children/teens, youngest age 2.5 mos

**Clinical presentation:**
- Seizures: 100%, generalized in kids, focal in adults, over half presented with status epilepticus
- Cognitive decline in 67%
- Behavior changes in 45%
- Movement disorder in 64%
- Dysautonomia in 30%

- **EEG:** abnormal in >80%
- **MRI:** multifocal abnormalities in 73%
- **CSF:** abnormal in 91%

_Spatola et al. Neurology 2017_
Anti-GABA$_{A}$R Encephalitis

• All had antibodies to GABA$_{A}$R, in serum and CSF
• 1/10 children had a tumor (Hodgkins lymphoma)

• Treatment andOutcome:
  • 90% received immunotherapy (40% first line, 50% first and second line)
  • 1 died of sepsis, 8 partial recovery and 1 complete recovery

Spatola et al. Neurology 2017
MGlur5 Ophelia syndrome

- Described by Dr. Carr in 1982 in his 15 yo daughter
- Demographics: all ages
- Clinical:
  - Limbic encephalitis – memory loss, seizures
  - Associated with Hodgkins lymphoma and symptoms typically precede the diagnosis
- CSF – lymphocytic pleocytosis
- MRI - T2 hyperintensities mesial temporal or other areas
- mGlur5 detected in serum and CSF
- Very responsive to treatment of tumor

*Lancaster et al. Neurology 2011*
GAD65

• Intractable, often temporal lobe foci, frequently with parenchymal atrophy or hyperintense changes in mesial temporal regions

• Intracellular synaptic antigen – only 50-60% improve and improvement is often only partial

• Low titres commonly seen with diabetes and thyroid disease but NOT pathogenic

• Very high titres (>20 nmol/L or >2000 U/ml) associated with variable neurological symptoms. Documentation of intrathecal synthesis may provide support of pathogenicity
MANAGEMENT OF AUTOIMMUNE EPILEPSIES
Tumor Screening in Kids

- Risk of tumors MUCH lower in children
- NMDA – ovarian teratoma
- Limbic encephalitis – Hodgkins lymphoma
- Other rarer antibodies – consider MRI/CT of chest/abdo/pelvis and urine for catecholamines

*Titulaer et al. Lancet Neurol 2013*
Treatment Themes

• No RCTs

• Symptomatic management is challenging!

• Earlier immunotherapy results in more complete recovery

• Be aggressive
  • If one first-line therapy fails, move quickly to the next
  • If first-line therapy suboptimal, start second-line agent
Symptomatic Management

• Very challenging!
  • Multiple symptoms requiring multidisciplinary team
    • Epilepsy
    • Movement disorders
    • Psychiatric symptoms
    • Sleep disorders
    • Dysautonomia

• Symptoms respond poorly to usual agents
  • Only 10% achieve seizure freedom with ASMs and only 15% have a >50% reduction (Quek AM et al. Arch Neurol 2012)
Other Considerations

- What is the likelihood of response to the specific antibody?
  - *Intracellular* or *Cell-surface* target?
  - Balance *risk of treatment* – effect on fertility, malignancy risk, infection, bone health – with *likely benefit*

- How sick is the patient?
  - Combine agents such as rituximab or cyclophosphamide as these can act very quickly
Immunotherapy: First Line

- **Steroids:**
  - IV Methyprednisolone: 30 mg/kg/d x 3-5 days (max 1 g/d) – often followed by oral prednisolone 1-2 mg/kg/d if benefit seen

- Treatment duration not well studied – for anti-NMDAR encephalitis, durations from 5 days to 3 months are used

- A prolonged course of steroids is often not needed. In rarer steroid-dependent cases, switch to steroid-sparing agents to avoid side effects
Immunotherapy: First Line

- **IVIG:**
  - 2 g/kg over 2-5 days
  - Need for recurrent treatments is not well studied.

- **Plasma Exchange:** 5-7 exchanges over 10-14 days
Immunotherapy Trial

not evidence based

Consider alternative acute therapy or no further therapy

No improvement

Objective baseline measurements

Acute treatment, “Diagnostic Test”

IV methylprednisolone

or

IVIg

or

Plasma exchange

Improvement

Chronic treatment

Continue acute IV therapy, and taper

or

Oral prednisone taper

and

Oral azathioprine or Oral mycophenolate mofetil

or

Other options
Treatments: Second Line

- **Rituximab**
  - Anti-CD20 monoclonal antibody that depletes circulating B-cells
  - Dose: 375 mg/m$^2$ weekly x 4
  - Safety - 144 children treated (*Dale RC et al. 2014*):
    - Infusion reactions in 12.5% (3 anaphylaxis)
    - Infection in 7.6% (2 deaths and 2 disabling)
    - No PML
    - 87% benefited from treatment

- **Cyclophosphamide**
  - Apoptosis of rapidly dividing cells (ie WBC)
  - Dose: 750-1000 mg/m$^2$ IV with prehydration monthly x 6 mos
  - AEs: emesis!!, alopecia, sterility, hemorrhagic cystitis
Treatment: Second Line Steroid-Sparing Agents

- **Mycophenolate mofetil**
  - Dose: 600 mg/m²/d (max 2000 mg)
  - Experience in autoimmune CNS diseases in kids (*Nosadini et al. 2018*)
    - 80% relapse-free – most relapses associated with suboptimal dose or weaning
    - Side effects in 18% - GI, movement disorder, infection

- **Azathioprine**
  - Dose: Start at 1-3 mg/kg/d po. Lower if mildly decreased thiopurine methyltransferase
  - Side effects: ~25% stop for nausea, hepatopathy or fatigue
Options for Very Refractory Cases: Tocilizumab

- Monoclonal Ab against IL-6
- Used to treat NMO in children

Randell et al 2018 – 3 children with refractory autoimmune encephalitis (1 GAD65, 1 Hashimoto, 1 elevated ASO Ab) and robust response

- Serious side effects 8.2 per 100 PY (infection, blood disorders, transaminitis)
Tocilizumab in Autoimmune Epilepsy refractory to Rituximab

- 91 patients divided into 3 groups (observational, not-randomized):
  - Tocilizumab treated (N=30)
  - Rituximab: (N=31)
  - No further therapy (N=30)

- Low rate of infectious or infusion-related complications in TOC cohort

Lee WJ et al. Neurotherapeutics 2016
Options for Very Refractory Cases: Bortezomib

- Proteosome inhibitor that targets plasma cells

- Small case series of refractory anti-NMDA encephalitis show benefit with acceptable safety (Scheibe et al. 2017, Schroeder et al. 2018)

- Shin YW et al. 2018:
  - 5 pts with anti-NMDAR encephalitis refractory to first-line immunotherapy, rituximab and tocilizumab in vegetative state
  - All treated with bortezomib
  - 3/5 improved to minimally conscious state but none achieved a functional recovery
Treatment of GAD65

• First-line:
  • IV steroid vs IVIG - swap after one month if suboptimal response

• Second-line:
  • If symptoms of recent onset (ie <1 year), consider a trial of cyclophosphamide
  • If long standing symptoms, without evidence of inflammation on CSF or MRI, response rates are low!
  • As pathogenesis involves cytotoxic T cells, rituximab is poorly efficacious in this syndrome
CONCLUSIONS

• **General Guidelines for Autoimmune Epilepsies**
  
  • High level of suspicion to allow early diagnosis
  
  • AB directed against cell-surface Ag are usually pathogenic and immunotherapy responsive – treat early and aggressively!
  
  • AB directed against intracellular Ag are usually not pathogenic and respond poorly to therapy
  
  • Symptomatic treatment is often challenging