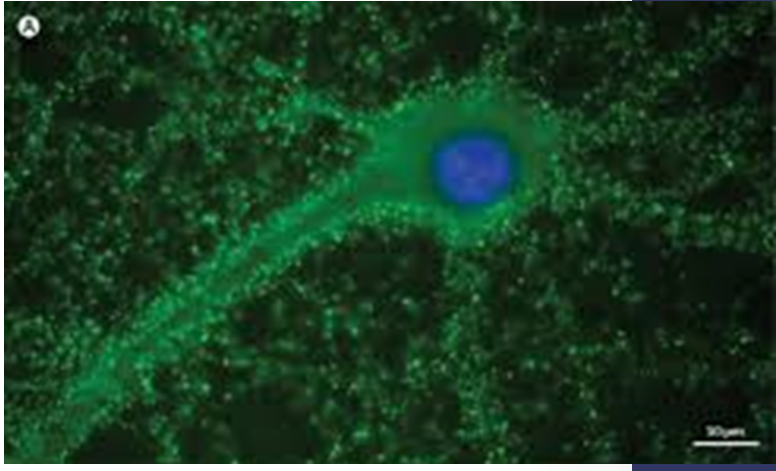

The Rationale Use of Immunotherapies in Children with Seizures

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Director of Pediatric Epilepsy
Mayo Clinic

Disclosures

- Consultant to Biocodex, Biomarin and Mallinckrodt

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?

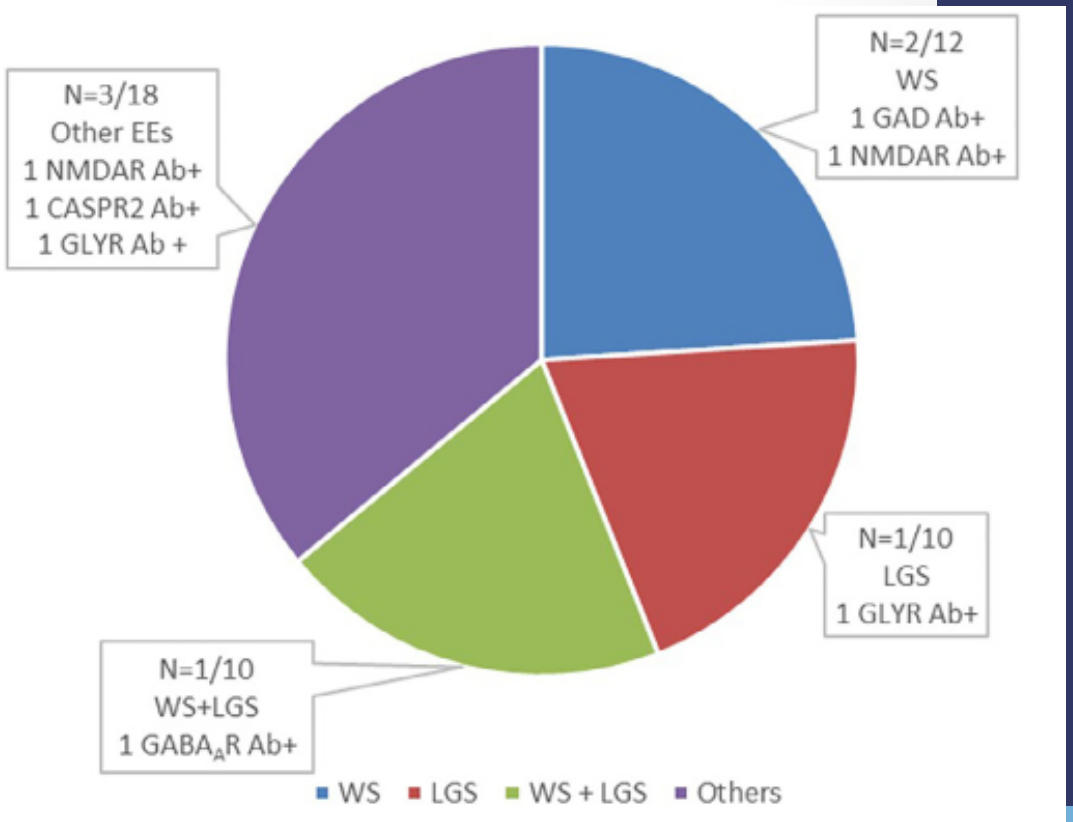
- **New-onset seizures:**
  - Non specific serum antibodies found in 5.8%-9.7% (*Garcia-Tarodo et al. 2018, Suleiman et al. 2013, Wright et al. 2016*)

- **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

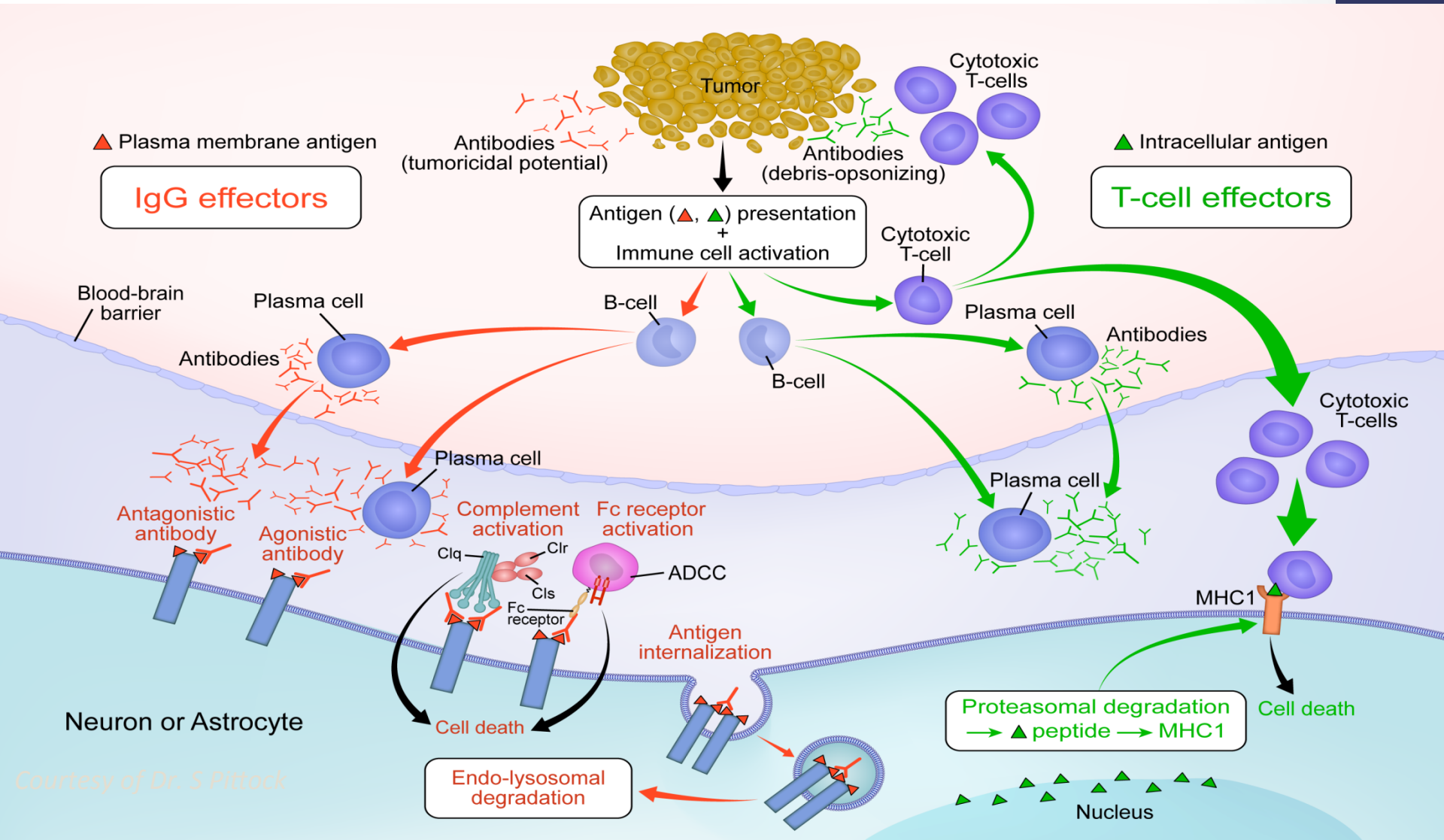
- Previously well child
- Seizures
  - Severe and drug resistant from onset
- Multifocal neurological symptoms/signs
  - Cognitive, behavioral, sleep, autonomic and **movement disorders**
- Personal or family history of autoimmunity

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)



	Cell Surface Ag	Intracellular Ag
Ages affected	Broad range, often children	Usually older
Tumor association	Much lower but depends on Ag	Higher risk
Pathogenicity of antibodies	Pathogenic	Not pathogenic – biomarker but does not correlate with disease severity
Response to immune therapy	Responsive	Usually nonresponsive

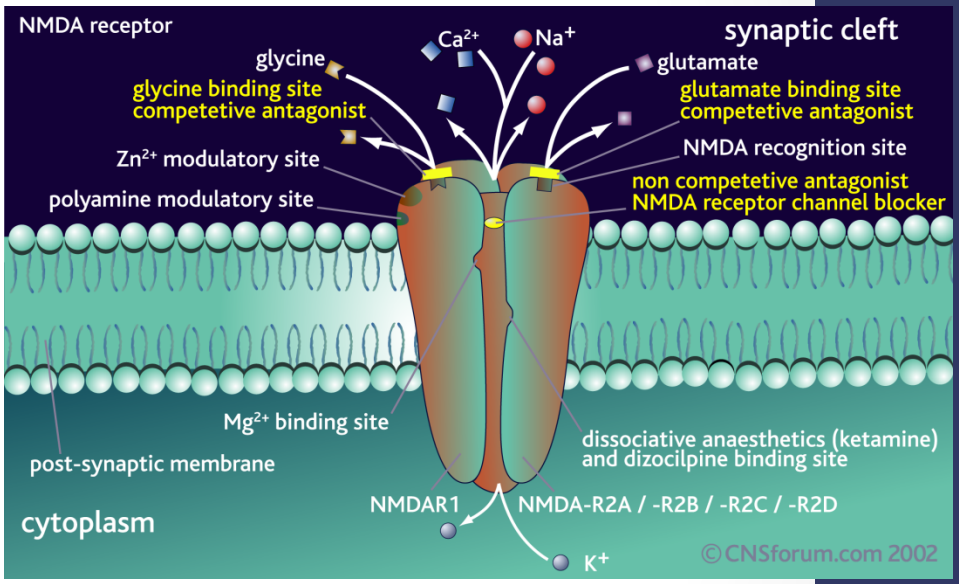
Specific Immune Epilepsies

Cell Surface Ag directed	Intracellular Ag directed
NMDA-R VGKC – LGI1, CASPR2 **$GABA_A$-R** $GABA_B$-R AMPA-R Glycine-R Folate-R DPPX **mGluR5**	**GAD65** Onconeural

Anti-NMDAR encephalitis

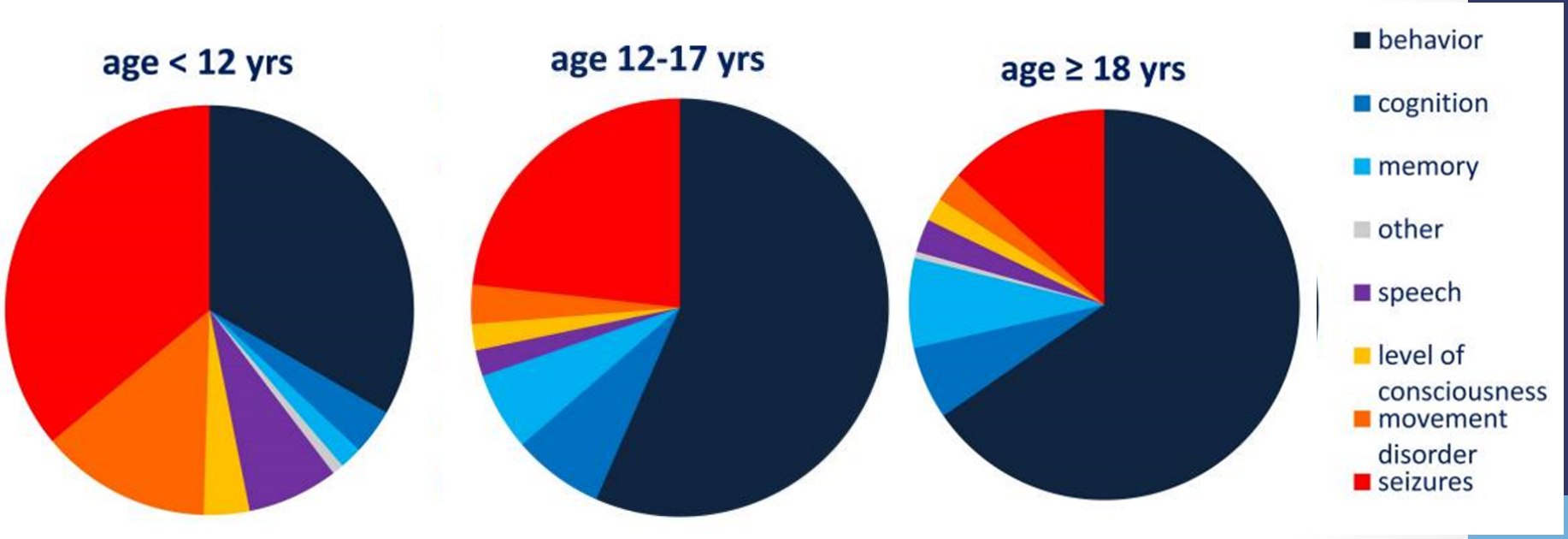
- Antibodies against NR1 subunit of NMDA receptor

- 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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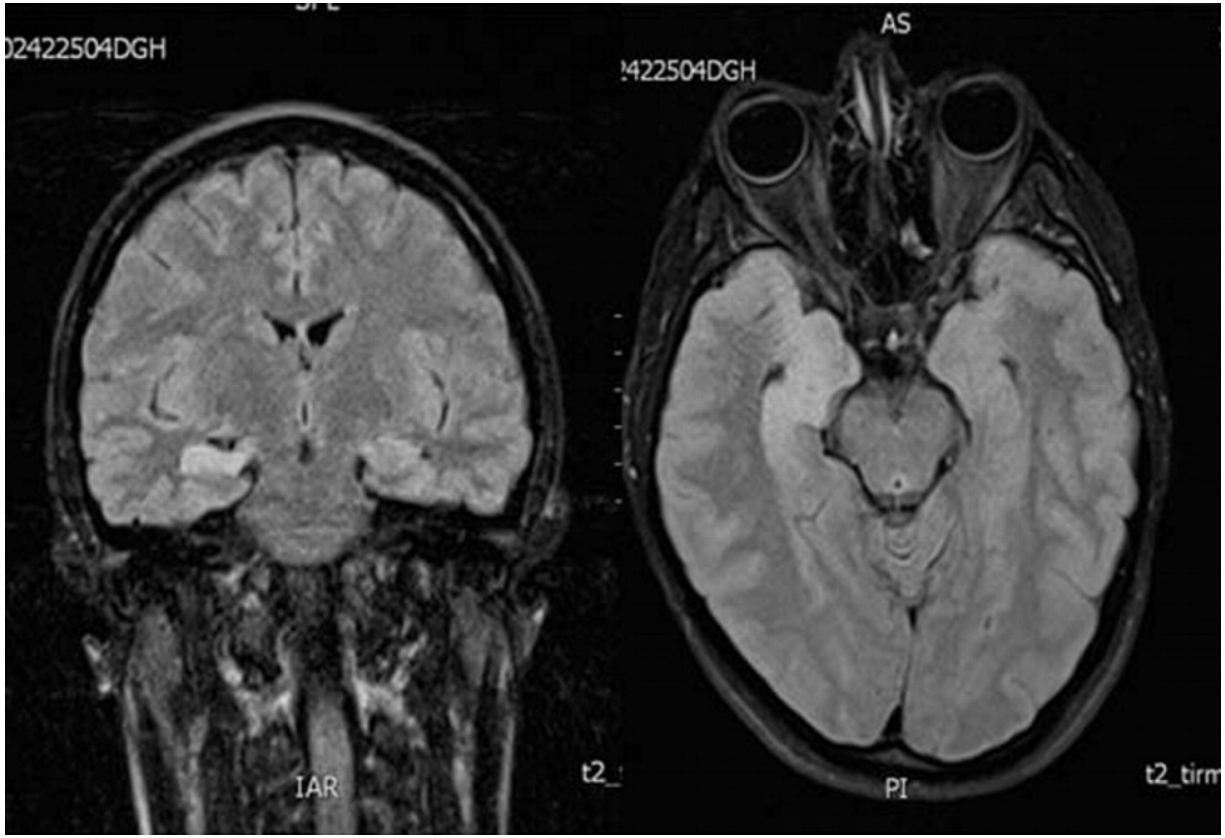
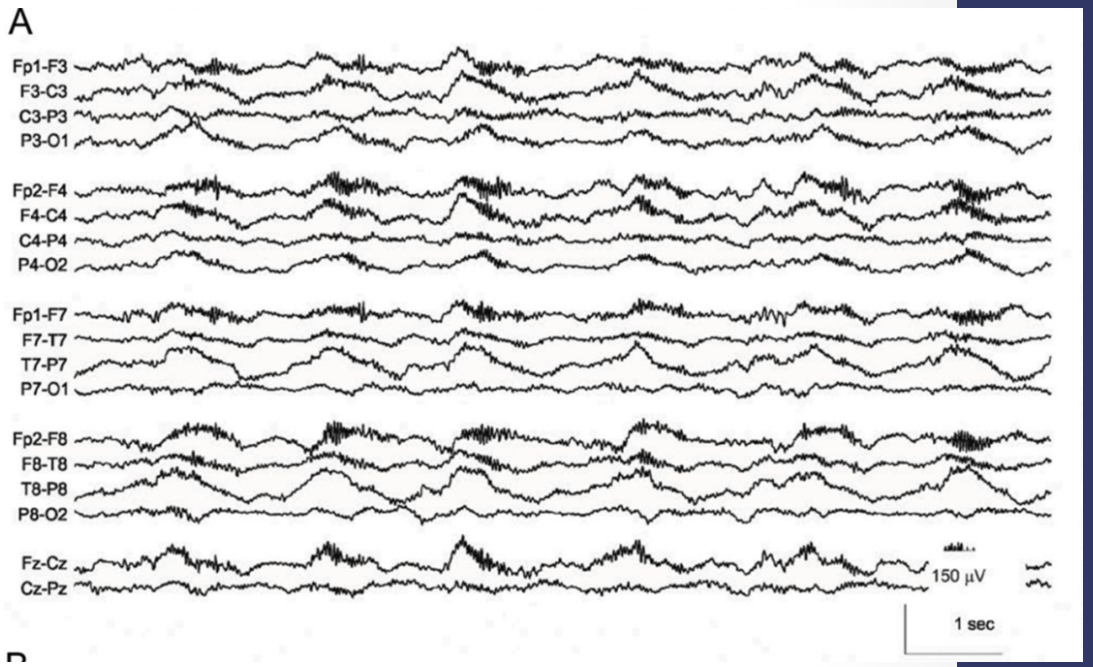
Investigations: MRI

- 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

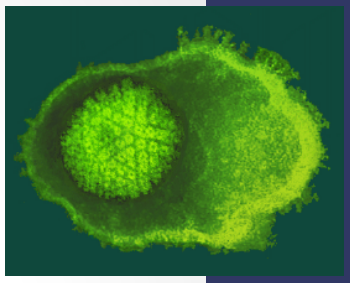
CSF

- 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

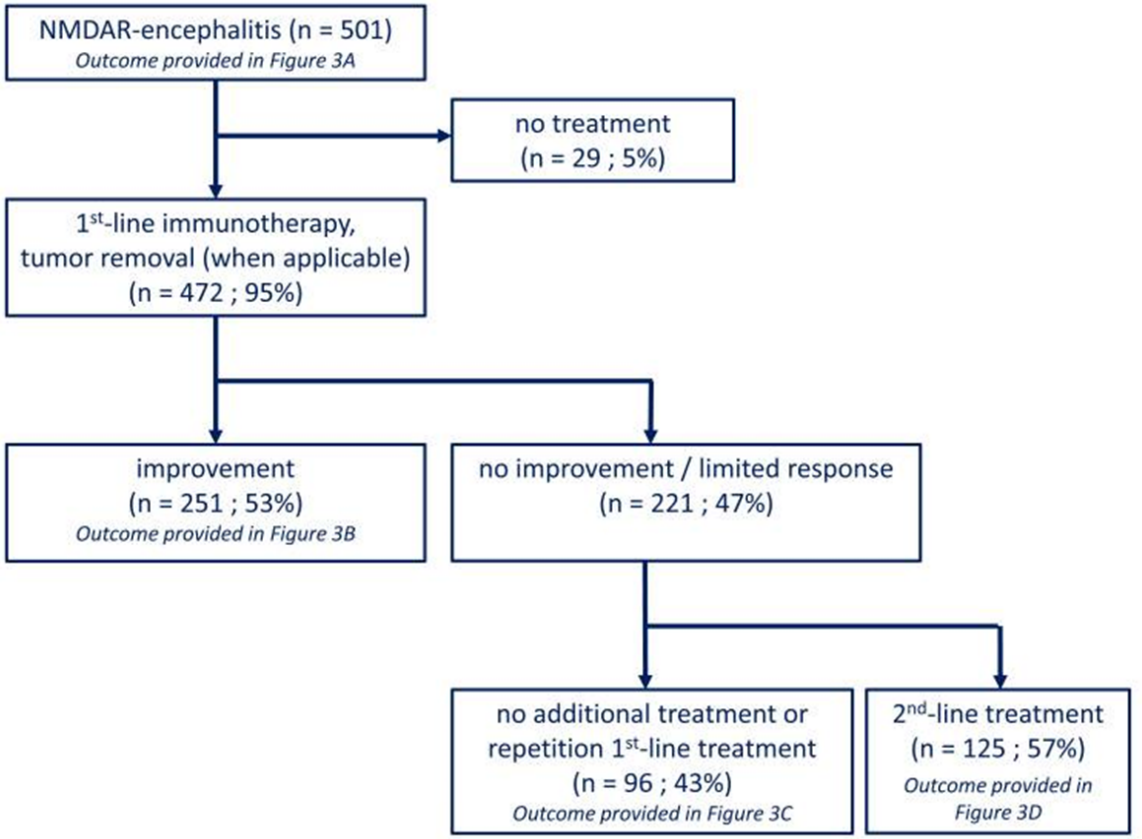
Anti-NMDAR encephalitis and HSV



- 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

Titulaer et al. Lancet Neurol 2013

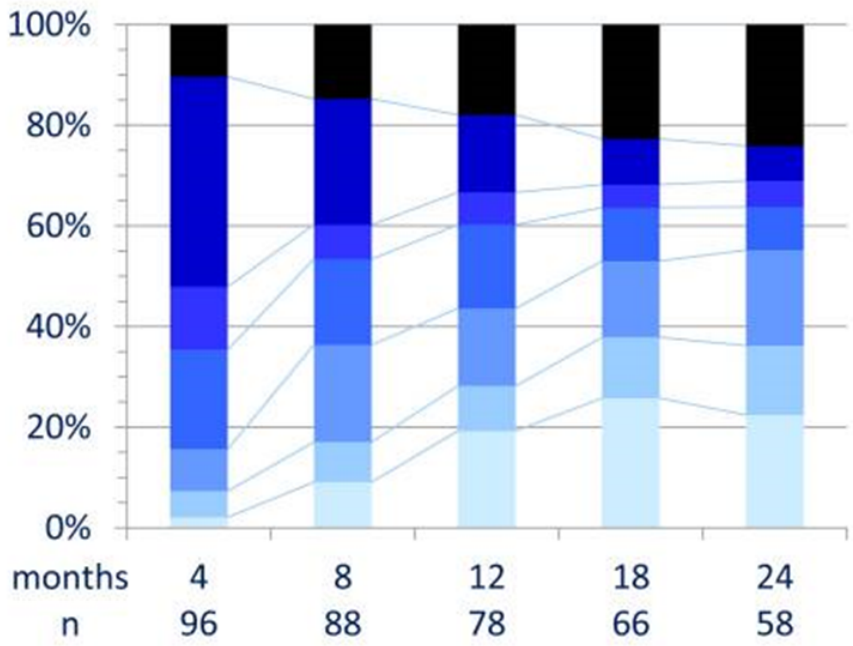
Predictors of outcome

- 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 ($p=0.011$)

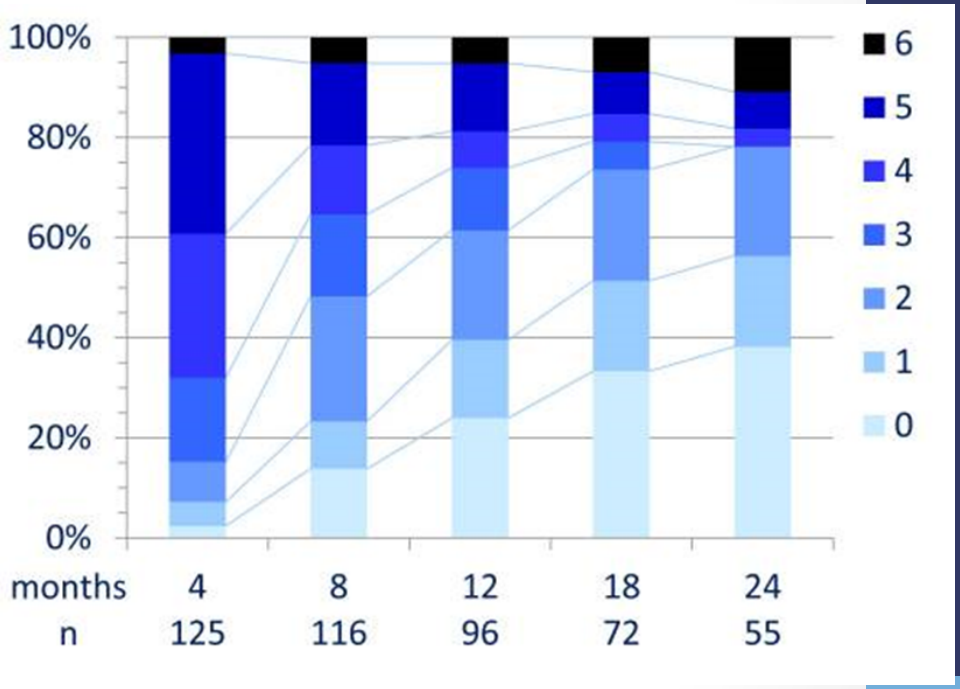
Titulaer et al. Lancet Neurol 2013

Anti-NMDA receptor encephalitis

Failed 1˚line, no 2˚line Tx



Failed 1˚line, received 2˚line Tx

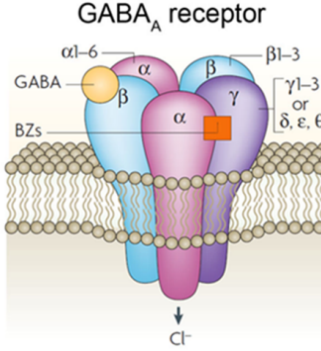


Titulaer et al. Lancet Neurol 2013

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-$GABA_AR$ Encephalitis

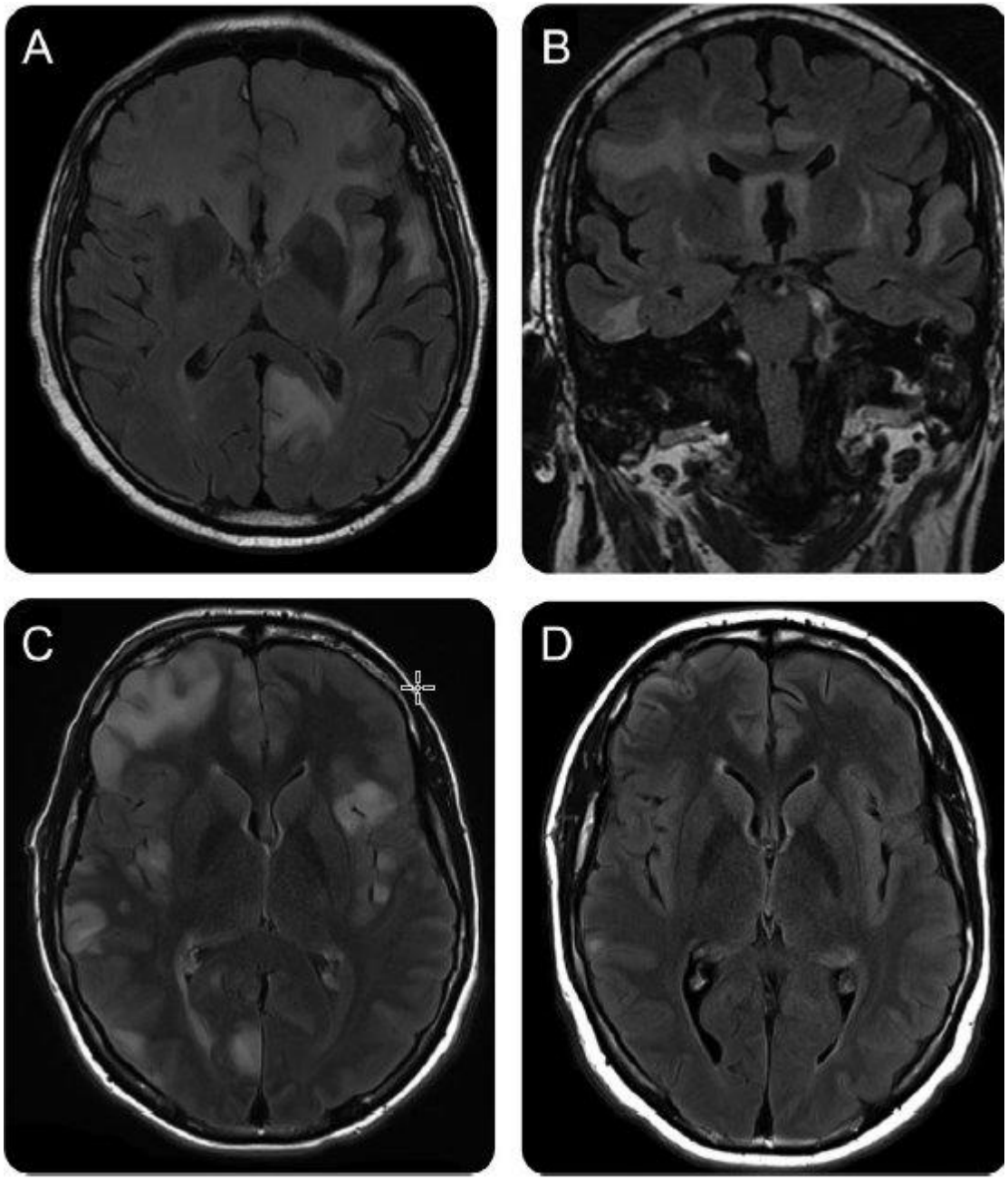


- 26 cases, 42% children/teens, youngest age 2.5 mos

- **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%

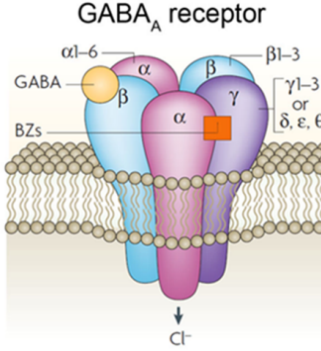
- **EEG**: abnormal in >80%
- **MRI**: multifocal abnormalities in 73%
- **CSF**: abnormal in 91%

Spatola et al. Neurology 2017



Spatola et al. Neurology 2017

Anti-$GABA_AR$ Encephalitis



- All had antibodies to $GABA_AR$, in serum and CSF
- 1/10 children had a tumor (Hodgkins lymphoma)

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

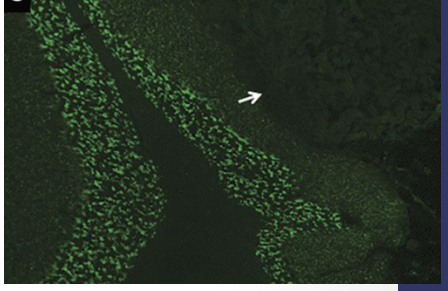
Spatola et al. Neurology 2017

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

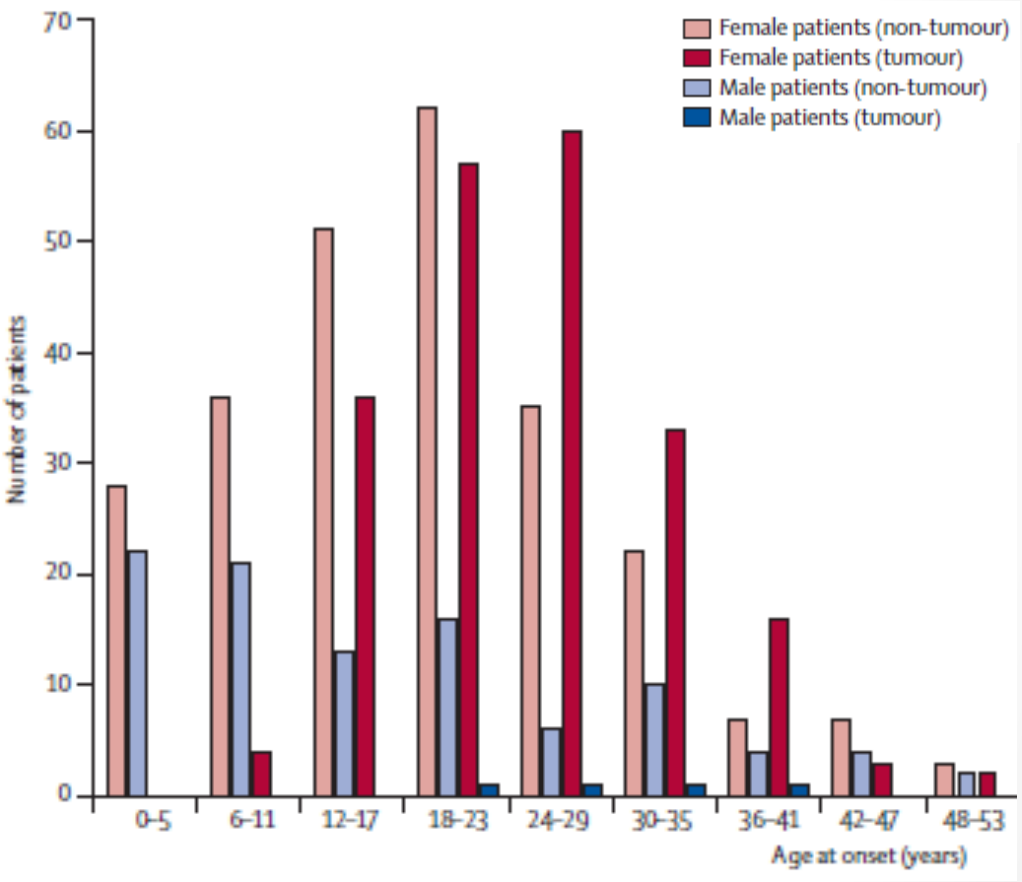


- Intractable, often temporal lobe foci, frequently with parenchymal atrophy or hyperintense changes in mesial temporal regions
- **Intracellular** synaptic antigen – only 50-60% improve and improvement is often only partial
- Low titres commonly seen with diabetes and thyroid disease but NOT pathogenic
- 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

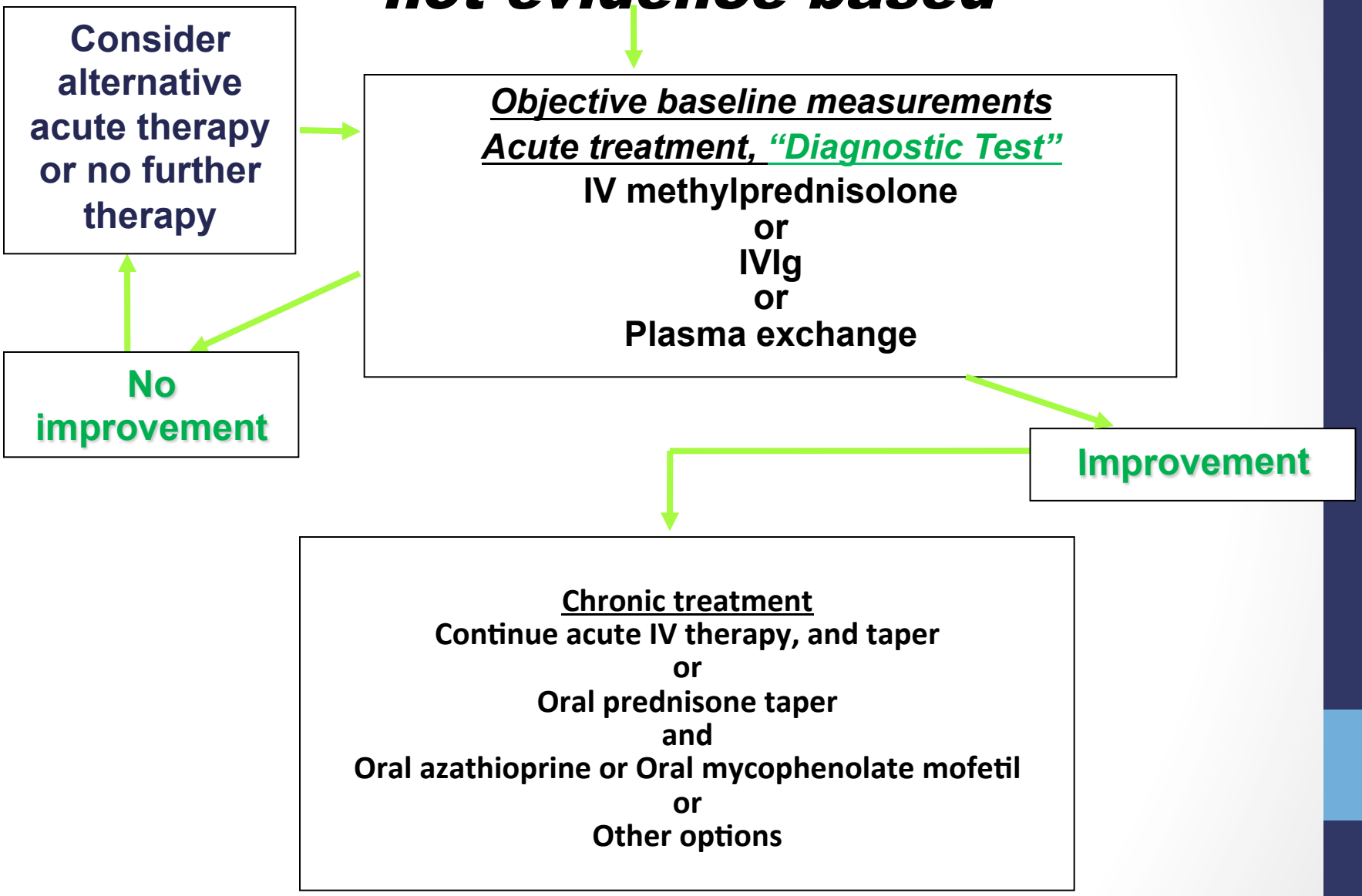
- **Steroids:**
  - IV Methyprednisolone: 30 mg/kg/d x 3-5 days (max 1 g/d) – often followed by oral prednisolone 1-2 mg/kg/d if benefit seen
  - Treatment duration not well studied – for anti-NMDAR encephalitis, durations from 5 days to 3 months are used
  - A prolonged course of steroids is often not 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 d

Immunotherapy Trial
not evidence based



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/m^2/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

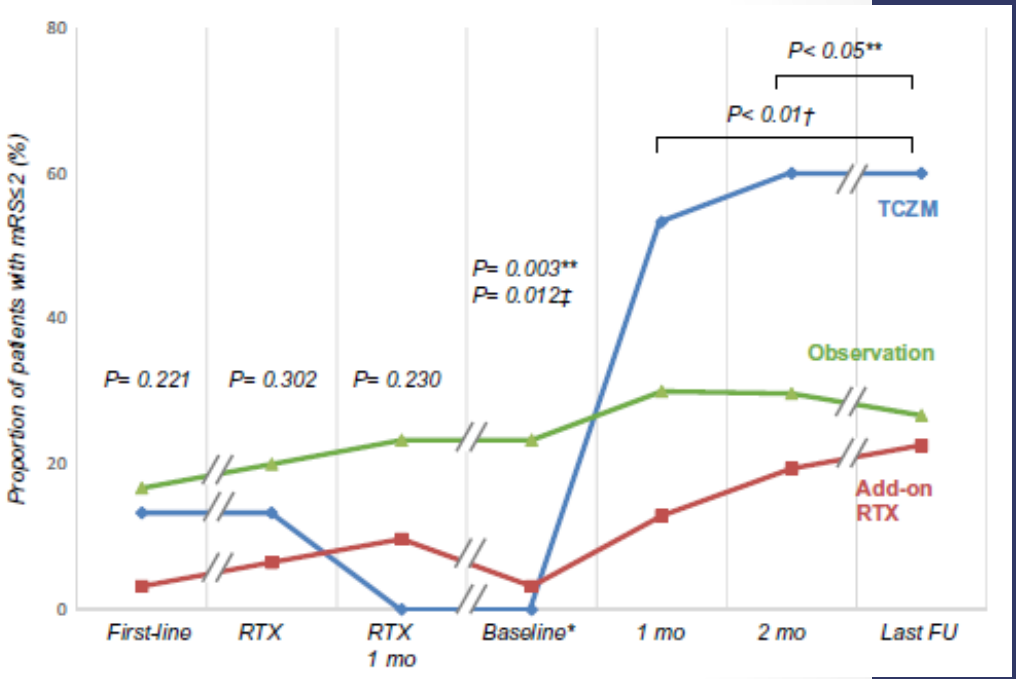
- *Randell et al 2018* – 3 children with refractory autoimmune encephalitis (1 GAD65, 1 Hashimoto, 1 elevated ASO Ab) and robust response

- 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