Objectives

- Describe the relatively common but only recently discovered entity: NMDA Receptor Antibody Encephalitis (NMDAR)
- Brief overview of other common pediatric autoimmune encephalitis antibodies: GAD, Voltage-gated K channel (VGKC), Anti-Thyroid Abs, anti-glycine, anti-dopamine
- Recognize clinically and medically the typical semiology of associated movement disorders of NMDAR: dystonia, chorea, myoclonus, ataxia, and stereotypies
- Detail long term prognosis and prolonged care needed for NMDAR (and perhaps other less prevalent autoimmune encephalitides)

Vignette #1

Previously healthy 13 mon Hispanic F
- Acute onset irritability
- Regression of speech and gait
- Jerky eye and body movements
- No seizures
Although semiology is distinctive no single antibody yet identified

- Strong association in children with neural crest tumors
- Ongoing surveillance for tumors
- Although movements improve there is guarded outcome developmentally and behaviorally

Previously healthy 8 yr old Hispanic male
- 3 days PTA had HA, developed intractable seizures and lapsed into prolonged coma
- T2 hyperintense bilateral temporal lobe signal changes (limbic)
- Marked dystonia, myoclonus, and seizures
- Developed severe “rage attacks” and regression that has persisted
2 major isotopes identified
- Rare association in children with malignancy
- Seizures are a major feature
- Although movements improve there is guarded outcome developmentally

Previously healthy 3 yr old Hispanic male
- 3 days PTA had myalagias, HA, N/V
- Given Abx for serum WBC 29, proteinuria

**Day of admit:** insomnia, confusion, hallucinations, slurred speech, ataxia, expressive aphasia
- IgM mycoplasma + (IgG neg)
- A few days later seizures and then chorea
- EEG: sz, slow background, & left post temp spikes
- Extensive autoimmune/infectious work up
- CSF - WNL
- NMDA IgG AB +
- Treatment: Steroids then IVIG
- Multiple Relapses
- BNZ, Tetrabenazine, and Keppra symptomatically

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- IgG to NMDA receptor
- Discovered in 2005 in women with ovarian teratomas
- Recognized as the most prevalent autoimmune encephalitis
- Prevalence of NMDAR surpassed viral encephalitides in one epidemiology study

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Gable MS et al. Clinical Infectious Diseases. 2012; 54: 899-904
MRI brain normal 67%  
(33% w/ nonspecific T2 changes)
- EEG abnormal 90%  
(slowing or epileptiform)
- CSF abnormal 79%  
(mild pleocytosis, elevated protein)
- CSF NMDAR + in 100%  
(Serum NMDAR +, only 85%)

AMS  Sz  Movements
- Time to onset of immuno-modulation is key to recovery.
- Usually requires intensive, first line therapy: steroids/IVIG and/or Pex
- 12% chance of relapse rate, less in those who had 2nd line therapy
- Prolonged recovery time up to 18 mo

Previously healthy 13 yr old AAF
- 7 days PTA c/o leg “heaviness”, “looked confused”, “laughing and singing hysterically”
- Went to ER x 2 and discharged
- Day of admit: neighbors called police because of hallucinations/agitation
- Given Geodon for agitation  →  obtunded
Most common movement disorder associated with NMDAR Encephalitis
- Stereotyped and purposeless
- Movement Fragment
- Semi-volitional?

Rhythmic
- Oscillatory
- Slower than tremor (< 1 Hertz)
- Purposeless
- Sometimes suppressible
- Does not carry the volitional connotation of stereotypy
MRI brain: subtle tempoparietal hyperintensity
EEG: slowing and sz
CSF: cell count/ protein/glucose WNL
Agitated, nonverbal, apneas  \(\rightarrow\) intubation and trach
Negative systemic autoimmune and infectious work up
NMDA IgG AB +
Steroids, IVIG, Pex, rituxan, then monthly cytoxan and IVIG (BNZ and Keppra symptomatically)
Stimulants for promoting wakefulness
- Hemiparesis and ataxia more common in pediatrics (often presenting symptom)
- Autonomic instability
- Symptoms improve in the reverse order, usually movements going away first.
- 80% improve with proper treatment but course prolonged
- ADHD-like symptoms may persist

Take Home Points from Vignette #4
Chorea

- Involuntary / insuppressable
- Non-rhythmic (random)
- Purposeless, Sudden
- Spreading/migrating (one body part to another)
- Motor-impersistence
- Hypotonia
- Hung-up Reflexes

Pediatrics
Age: 5 to 15 yrs
Gender: F > M
Typical 4 - 8 wks s/p Group A Strep
May be unilateral in up to 30%
Typically lasts 2 - 6 mos, almost always < 2 yrs
Comorbid Psych: OCD, ADHD, Anxiety, Depression
Exacerbations/Recurrences: 20 - 60%
Re-infection, OCPs, Pregnancy (ChoreaGravidarum)
Lab: +ANA, +/- ASO, +/- Anti-DNAase
MRI: Normal to BG Enlargement/T2 Changes
AMS, most have seizures then chorea vs. myorhythmia

In children most cancer associations are rare

Initial ovarian or testicular ultrasound as only screening

Recent discussion that older girls may need semi-annual MRI evaluations

Only 1 of 14 patients at TCH with a teratoma (11 yr old; pubertal)  

NMDA Encephalitis in the younger child

Involuntary / Insuppressable

Stereotyped (opposite of chorea)

Twisting (hyperextension)

Generalized or task specific

Exacerbated by movement or emotion

Hypertonia during movement

Reflexes range: normal to increased

Pediatrics
Dysmetria
- Finger to chin
- Heel to shin

Unsteady
- Wide-based gait

Impaired Dysdiadochokinesia

Scanning Speech

Unlike other “BG” movements, usually cerebellar in etiology

Sudden, “shock-like”

May be:

- Epileptic (cortical)
- Non-Epileptic (subcortical)
- Physiologic (e.g. sleep myoclonus)

Many Etiologies:

- Benign Myoclonic Syndromes
- Epileptic Myoclonic Encephalopathies
- Post Anoxic (Lance-Adams Syndrome)
- Myoclonic Dystonia (DYT-11)
- Opsoclonus Myoclonus

ADEM → 50
NMDAR → 14 patients
Hashimoto’s Encephalopathy → 5
Opsoclonus Myoclonus → 3
Anti-GAD → 3
Anti-VGKC → 2
Why Rheumatology?

- SLE-spectrum disorders?
- CNS vasculitides?
- Other systemic autoimmune dx?
- Immunosuppression anyone?

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CNS Deficit in a Child or Adolescent

- Change in behavior
- Seizures
- Movement disorder
- 100/400 in case series are pediatric
- Less than 40% of pedi cases have tumors

- 177/577 in case series are pediatric
- 40% of 12-17 yr old girls have tumors
What Did We Know in 2011?

- In 2011 most of outcome data was adult based

Education is a process, not a event
Treatment Algorithm: 2011

EBM: TCH 2012

AB-associated IBrainD

Immunosuppression
- IV immunoglobulin 10g
  - 2g/kg max, 7.5g q2 weeks x 2 months, then monthly x 4 months
  - Rituximab
  - 375mg/m2 q2, q4 weeks (2 doses)
- Prednisone 2mg/kg
- Redo T2 weekly x 6 months
- MMF - flare on steroid taper
- IVIG (Uldenovir)
- PLEX life-threatening disease

"EBM": TCH 2012

Clinical Guidelines for Pediatric Intensive Care Management in Suspected MELAS Syndrome/Encephalopathy
So How Are We Doing?

- Crunching data (n=8?)
- Diagnosis within 4 weeks (62%?)
- Max Follow up 2 years (most <1 yr)
- No Flares !!!!
- All back in school
- Deficits? Frontal? "ADAHD"
Dalmau 2013

48% flunk 1st line Tx!

At 24 mon f/u 81% had good outcome
(mRS 0-2)

Improvement continued at 18 mon

2nd line works when 1st line fails

dedi and adult pooled data

Dalmau 2013

Figure 1 Study profile

Dataset with titles

Fig 1: Study profile

Dalmau 2013

Dataset with titles

Fig 1: Study profile
Dalmau 2013: Predictors of Success

- No ICU stay
- Tx within first 4 weeks of onset
- 2nd line Tx (multi-variable analysis)

Predictors of effect and magnitude of 2nd line effect were similar in children.
<table>
<thead>
<tr>
<th>Gaps in Knowledge 2013</th>
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<tbody>
<tr>
<td>- True NP deficits at: 12, 18 and 24 months?</td>
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<tr>
<td>- Utility of psychotropic medications?</td>
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<tr>
<td>- Early roles of PM+R and psychiatry?</td>
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<td>- Utilization of decision tools in EMR?</td>
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<tr>
<td>- Are other autoimm. Encephalitides to be treated the same?</td>
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</tbody>
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References:

Clinical features, treatment, and outcome of 500 patients with Anti-NMDA Receptor Encephalitis.
March 14, 2012 Lecture AAN. Maarten Titulaer, MD, PhD

Auto-Immune Encephalopathies.
Feb 5, 2012 Lecture TNS Winter Cord. Amy Pruitt MD


Lippincott Williams & Wilkins, Hagerstown, MD.

