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: myorhythmia, dystonia, chorea, myoclonus, ataxia, and stereotypes
- 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 main antigens identified (LG11, CASPR2)
- Rare (15% in adults) association with malignancy
- Refractory seizures a major feature
- “Limbic” changes especially agitation, cognitive impairment, and insomnia

Previously healthy 3 yr old Hispanic male
- 3 days PTA had myalgia, 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 AEDs symptomatically

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

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.

12% chance of relapse rate, less in those who had 2nd line therapy

Prolonged recovery time up to 18 mo

Being hopeful with family is realistic.
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 (may vary slightly in rate)
Oscillatory but slower than tremor (<3 Hertz)
Purposeless
Sometimes suppressible
Associated with brainstem involvement
Does not carry the volitional connotation of stereotypy

MRI brain: subtle temporoparietal hyperintensity
EEG: slowing and sz
CSF: cell count/protein/glucose WNL
Agitated, nonverbal, apneas→ intubation and trach
Negative systemic autoimmune and infectious work up
NMDA IgG AB +
Aggressive immunosuppression
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
Early identification and rapid escalation of immunomodulation with better outcome

Psychiatric presentations easily missed

Reasonable optimism with the family

Early involvement of multi-disciplinary care team

Pediatrics
Chorea

- Involuntary / insuppressible
- Non-rhythmic (random)
- Purposeless, Sudden
- Spreading/migrating (one body part to another)
- Motor-impersistence
- Hypotonia
- Hung-up Reflexes
- Hypometric Saccades
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 months, almost always < 2 yrs
Comorbid Psych: OCD, ADHD, Anxiety, Depression
Exacerbations/Recurrences: 20 - 60%
Re-infection, OCPs, Pregnancy (Chorea Gravidarum)
Lab: +ANA, +/- ASO, +/- Anti-DNAase
MRI: Normal to BG Enlargement/T2 Changes
- AMS, most have seizures then chorea vs. myorythemia
- 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) *Pediatrics*

- Involuntary / Insuppressible
- 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 *Pediatrics*
- 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
- Opsoclonus Myoclonus → 12
- Hashimoto’s Encephalopathy → 5
- Anti-GAD → 3
- Anti-VGKC → 2
Why Rheumatology?

- SLE-spectrum disorders?
- CNS vasculitides?
- Other systemic autoimmune dx?
- Immunosuppression anyone?
- 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 an event
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? “ADHD”
- 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 - pedi and adult pooled data

Dalmau 2013
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

Relapse Lower with 2nd Line Tx?
Gaps in Knowledge 2013

- True NP deficits at: 12, 18 and 24 months?
- Utility of psychotropic medications?
- Early roles of PM+R and psychiatry?
- Utilization of decision tools in EMR?
- Are other autoimmune encephalitides to be treated the same?

References


