SEIZURES AND THEIR TREATMENTS IN ANGELMAN SYNDROME – LOUISVILLE 2019

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Definitions

- Epilepsy is defined as 2 or more unprovoked seizures; recently modified to also include 1 unprovoked seizure with abnormal (epileptiform) EEG
- Seizure types – describe the individual seizures
- Epilepsy syndrome – constellation of seizure types, EEG findings and cognitive functioning
Seizure Types

■ Focal (Partial) Onset Seizures
  - Arise from a small area on one side of the brain

■ Generalized Seizures
  - Arise from large areas of cortex on both sides at the same time (“whole brain seizures”)
  - Secondarily generalized: begin as focal and then spread to the rest of the brain
Focal Seizure
Generalized Seizure
Generalized Seizures

- Epilepsies with or without developmental delays
  - Generalized Tonic-Clonic
  - Myoclonic
  - Absence (typical)

- Epilepsies with developmental delays
  - Atonic
  - Absence (atypical)
  - Tonic
  - Spasms
Epilepsy syndromes

- Epilepsy syndromes are a constellation of various seizures types along with other clinical criteria
  - Seizure types
  - EEG findings
  - Cognitive functioning

- 2 epilepsy syndromes associated with AS
  - Lennox-Gastaut syndrome (common)
  - Myoclonic status in non-progressive encephalopathies (not common)
Lennox-Gastaut syndrome (LGS)

- Difficult to treat seizures of mixed types
  - Atonic
  - Tonic
  - Atypical absence
  - Can also have myoclonic, GTC or focal
- EEG findings: generalized slow spike and wave (<3 Hz)
- Cognitive dysfunction
- Many children with AS meet criteria for LGS – Angelman syndrome is a genetic syndrome (UBE3A is the gene causing the symptoms; LGS is an epilepsy syndrome describing the epilepsy
Slow spike and wave in LGS
Myoclonic Status in Non-Progressive Encephalopathies

- Newer ILAE classification seizure syndrome
- Classified as an epileptic encephalopathy
- Characterized by sustained episodes of myoclonus with preserved consciousness but typically some regression
- Typically begins in early childhood
- Very rare but as many as 40% of reported cases are children with Angelman syndrome
STATUS EPILEPTICUS AND NON-CONVULSIVE STATUS EPILEPTICUS (NCSE)
Status Epilepticus

- **Definition:**
  - *Seizures lasting greater than 10-15 minutes or frequent seizures with no return to baseline between events (definitions for status range from 5-30 minutes)*
  - *Prevalence varied but not common in AS*
  - *If this does occur in AS, there is usually a trigger such as infection*
NCSE

Non-convulsive status epilepticus (NCSE)

- Occurs in 50-90% with AS (MGH clinic ~20%)
- Episodes of decreased alertness lasting days to weeks often with loss of skills
- Typical seizures usually lessen during NCSE
- AS not progressive so always consider NCSE first if any regression
- Most commonly absence status
- Frequent myoclonic jerks in this setting could be myoclonic status in non-progressive encephalopathies (MSNE) – rare but AS most common etiology
NCSE EEG
EPILEPSY IN ANGELMAN SYNDROME
Seizures in Angelman syndrome

- Epilepsy in Angelman syndrome is a generalized epilepsy
  - Generalized tonic-clonic
  - Atypical absence
  - Atonic
  - Myoclonic
  - Tonic (rare)
  - Spasms (rare if at all)
  - Focal seizures present in ~30%
ASF Seizure Survey

- Seizure survey performed in 2006-07
  - On-line questionnaire through ASF
- 461 responses
  - 391 (86%) had seizures
  - 60% had multiple seizure types
  - >90% had some combination of generalized seizure types with or without focal seizures
  - ~30% reported focal seizures

- Thibert et al., Epilepsia 2009
AS Seizure types

![Seizure Types Graph]

- GTC
- Atonic
- Absence
- Focal
- Myoclonic
- Tonic
- Spasms
AS Seizures by subtype

![Genetic Subtypes graph]

- Deletion
- UPD
- UBE3A
- Imprinting
Seizures in AS - Age

Seizures in AS relative to age:

- Average onset approximately 2-3 yrs of age, typically beginning in childhood; infrequent cases of seizures <1 year of age

- Seizures are usually most frequent and most intense in early childhood and tend to improve by puberty

- Seizures can then return and persist into adulthood but are typically much less frequent and less intense – our phone survey of 110 adults with AS showed ~1/3 had seizures recur in adulthood (Larson et al. AJMG 2015); a more recent case series from our clinic of 53 adults showed ~27% still with seizures in adulthood – ~2/3 of those with seizures had them monthly or yearly/sporadic
EEG IN ANGELMAN SYNDROME
EEG in AS

- Over 90-95% have abnormal EEG patterns with or without clinical seizures
- Normal EEG’s rare, but have been reported in some with imprinting center defects
- 3 common patterns
  - Bi-frontal predominant slow spike and wave with a “triphasic” appearance
  - Rhythmic 4-6 Hz centrotemporal activity
  - Posterior “notched” delta activity
Frontal slow spike and wave
Frontal triphasic spike and wave
Notched delta
NON-EPILEPTIC MYOCLONUS
Non-epileptic Myoclonus

- In Larson et al (conducted in 2010) there were reports of prolonged “myoclonic seizures” in adults which typically began in adulthood (many of those reporting seizures in adulthood)

- These same events were also being reported more frequently in our clinic
Non-epileptic Myoclonus

- **Myoclonic seizures**
  - *Common in Angelman syndrome (~15-40%) and are often the first seizure type reported; onset in early childhood*
  - *Events are usually brief in duration – typically seconds but can last up to a minute*
  - *Children with myoclonic seizures typically have generalized spike and wave activity on interictal EEG and seizures captured on EEG are associated with spike and wave activity*
  - *MGH clinic:*
    - 17/185 (15%) had myoclonic seizures
    - Age of onset ~1-8 years (78% had onset before 5 years)
Non-epileptic Myoclonus

- Non-epileptic myoclonus
  - Age of onset is at puberty or later
  - Events last seconds to hours and can occur multiple times per day
  - There is no significant alteration of consciousness during the events and no post-ictal period
  - There is no associated regression or loss of skills
  - Events captured on EEG show no EEG changes
    - 12 individuals had prolonged EEG capturing events
    - 5 has inpatient video (3 MGH); 7 ambulatory (2 MGH)
    - All captured events and none had EEG correlate
Non-epileptic Myoclonus (Pollack et al, 2018)

- 187 individuals seen in clinic at time of study – 87 were age 11+
- 35/87 (~40%) had non-epileptic myoclonus
- Prevalence increased with age, though most common age of onset was 11-20
- Longer events (>1 hour) were almost exclusively seen in those over age 20
Prevalence of NEM by age

Figure 1: Percent of patients in cohort with NEM by age group (n=185)
Age of onset of NEM

Figure 2: Age of NEM onset by age group (n=27)
SEIZURE TREATMENTS
Treat the Co-morbidities

- Epilepsy is associated with several medical, especially neurological and/or psychiatric symptoms (comorbid).
- Co-morbidities due to an underlying neuro-genetic syndrome are typically more frequent and severe.
- Common issues that can worsen seizures:
  - Poor sleep
  - Anxiety
  - Constipation
  - GI reflux
  - ADHD/impulsivity
Treatment options

■ Medications

■ Dietary Therapy
  - *Ketogenic diet*
  - *Low glycemic index treatment*

■ Surgical options
  - *VNS (not common)*
Seizure treatment in AS

Valproic acid
Clonazepam
Phenobarbital
Topiramate
Carbamazepine
Lamotrigine
Levetiracetam
Phenytoin
Zonisamide
Ethosuximide
Gabapentin
Felbamate
Oxcarbazepine
Tranxene
Clobazam
ACTH
Nitrazepam
Other
Broad spectrum meds (pre-2011)

- Ethosuximide (Zarontin)
- Benzodiazepines (Klonopin, others)
- Valproate (Depakote)
- Felbamate (Felbatol)
- Lamotrigine (Lamictal)
- Zonisamide (Zonegran)
- Topiramate (Topamax)
- Levetiracetam (Keppra)
Non-broad spectrum

■ Worsen seizures in Angelman syndrome
  - Phenobarbital – can be given IV for status
  - Phenytoin (Dilantin) – can be given IV for status
  - Carbamazapine (Tegretol)
  - Oxcarbazepine (Trileptal)

■ Likely do not worsen or improve seizures in AS
  - Gabapentin (Neurontin)
  - Pregabalin (Lyrica)
Newer Medications (since 2010)

- Clobazam (ONFI)
- Rufinamide (Banzel)
- Lacosimide (Vimpat)
- Ezogabine (Potiga) – off the market
- Perampanel (Fycompa)
- Eslicarbazepine (Aptiom) – likely not broad spectrum
- Brivaracetam (Briviact)
- CBD (Epidiolex)
## Seizure Medications (Shaaya et al 2016)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No change</th>
<th>&lt;50% improved</th>
<th>50-90% improved</th>
<th>&gt;90% improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>0</td>
<td>0</td>
<td>8 (38.1%)</td>
<td>13 (61.9%)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0</td>
<td>0</td>
<td>5 (14.3%)</td>
<td>30 (85.7%)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0</td>
<td>0</td>
<td>2 (11.8%)</td>
<td>15 (88.2%)</td>
</tr>
<tr>
<td>Clobazam</td>
<td>2 (7.1%)</td>
<td>0</td>
<td>2 (7.1%)</td>
<td>24 (85.7%)</td>
</tr>
<tr>
<td>LGIT</td>
<td>0</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
<td>7 (70%)</td>
</tr>
</tbody>
</table>
## Seizure Medications

(Shaaya et al, 2016)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average Dose (mg/kg/day)</th>
<th>Average course (months)</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>26.6 (8-60)</td>
<td>56</td>
<td>66.6%</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>60.4 (6-200)</td>
<td>36</td>
<td>20%</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>6.6 (2.5-12)</td>
<td>58</td>
<td>23.5%</td>
</tr>
<tr>
<td>Clobazam</td>
<td>1.0 (0.2-2.1)</td>
<td>13</td>
<td>32%</td>
</tr>
</tbody>
</table>
Summary - medications

- Best options from case series:
  - Keppra
  - ONFI
  - Lamictal

- Other broad spectrum options:
  - Topamax
  - Zonegran
  - Klonopin
  - Felbatol
  - Zarontin
Summary - medications

■ Broad spectrum with side effects
  - Depakote

■ Newer broad spectrum
  - ONFI
  - Banzel
  - Vimpat
  - Fycompa
  - Briviact
  - Epidiolex

■ Non-broad spectrum (OK for sleep and other purposes)
  - Neurontin/Lyrica
Summary - medications

- Non-broad spectrum
- Worsen seizures
  - Tegretol
  - Trileptal
  - Aptiom (may be more broad spectrum?)
- Worsen seizures but option for convulsive status
  - Dilantin
  - Phenobarbital
CBD

- Marijuana is divided into THC (psychoactive portion) and cannabinoids – CBD (non-psychoactive portion)
- CBD was recently shown to be effective for treating refractory seizures in children
- Side effects were minimal and included sedation and loose stool
- No specific studies have been performed in an Angelman syndrome population, but there is anecdotal evidence that it can be effective
- Some families have reported significant improvement in non-epileptic myoclonus; others have felt that it helped sleep and/or anxiety
Ketogenic Diet

- Used since 1920’s but evidence dates back much earlier
- Exact mechanism of action is not known
- High fat diet (90%) that allows <10 gm carbohydrate per day
- Typical ratio of fat to protein/carbs is 4:1 but can be less
- Initiate with a short hospital stay (fasting no longer used) with close laboratory monitoring
- Need to monitor for ketosis/acidosis and treat with poly-cytra if needed
- Carbonic anhydrase inhibitors (Topamax, Zonegran) can worsen acidosis and increase risk of renal stones
- Typically get hyperlipidemia and decreased bone density, supplement with Vitamin D, Calcium and multivitamins; also carnitine may be needed
Low Glycemic Index Treatment

- Based on the “glycemic index” foods (raises blood glucose)
- Allows for 40-60 g carbohydrates per day
  - 10% carbs; 20-30% protein; 60-70% fat
- No need for admission; monitoring less strict but still needed
- Meals based on percentages above and caloric needs
- Compliance better than ketogenic as less restrictive
- Efficacy not quite as good as ketogenic so can convert for better control
  - 1/3 not effective or not tolerated
  - 1/3 50-90% reduction in seizures
  - 1/3 >90% reduction in seizures or seizure free
  - Can take 2 weeks to 2-3 months to see effects
LGIT trial in AS

- LGIT prospective trial – 6 children with AS
- After 4 months:
  - 4 children >90% seizure-free
  - 1 child 50-90% seizure-free
  - 1 child <50% seizure free
- After 1 year (5 still on LGIT)
  - All 5 children >90% seizure-free
- Since trial have placed ~23 children on LGIT
  - Thibert et al. 2012
LGIT in AS (MGH – Grocott et al 2017 Ep and Behav)

- Overall – 23+ children/adults have been on the LGIT
  - Daily seizures (5) – all improved with 1 seizure-free except illness
  - Weekly seizures (3) – all improved with 1 seizure-free except illness
  - Monthly seizures (2) – both seizure-free, 1 except for illness
  - Seizures only when ill (3) – 2 were similar and 1 seizure-free
  - Only NCSE (1) – still had NCSE
  - Well controlled (1) – stayed well controlled and cut medications

- Overall themes
  - LGIT very effective in Angelman syndrome
  - Seizure control often achieved with >60 g per carbohydrates
  - Illness and NCSE are the 2 situations where diet is less effective
Surgical options

- **Resective surgery**
  - Removal of a portion of the brain causing the seizures
  - Not an option in Angelman syndrome

- **Vagal nerve stimulator (VNS)**
  - VNS generator implanted in chest wall and bipolar lead wrapped around left vagus nerve
  - Pulse sent to vagus nerve which transmits signals to the brain though exact mechanism is unknown
  - Generator can be reprogrammed to change current voltage, pulse width, signal frequency, on time and off time
  - Studies have shown 25-60% have experienced >50% seizure reduction with VNS
  - Typical side effects include altered voice, cough, paresthesia, dyspnea
  - Surgical complications and systemic effects rare
## Non-epileptic Myoclonus treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Worse or no change</th>
<th>&lt;50% improved</th>
<th>50-90% improved</th>
<th>&gt;90% improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam N=10</td>
<td>0</td>
<td>5 (50%)</td>
<td>2 (20%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Clobazam N=9</td>
<td>2 (22%) Fatigue</td>
<td>4 (44%)</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Clonazepam N=5</td>
<td>1 (20%) Fatigue</td>
<td>0</td>
<td>2 (40%)</td>
<td>2 (40%)</td>
</tr>
</tbody>
</table>
Non-epileptic Myoclonus treatment

■ Best treatment is to treat triggers!
  - Poor sleep
  - GI dysfunction (constipation/reflux)
  - Anxiety
  - Pain (GI or orthopedic)
Treatment of NCSE/LGS (Worden et al, 2018)

- 13 children (25 episodes of NCSE) treated outpatient with diazepam (Valium) 0.3-0.5 mg/kg/day divided into 2 doses – with doses decreased in half every 2-3 days

- Often an underlying cause is present, such as infection, poor sleep, etc. (14/25 episodes), so important to treat underlying cause as well

- Oral diazepam alone was effective in 20/25 (80%) of events

- If Valium fails, can use 6 week tapering course of prednisone (or prednisolone) +/- IV administration prior to oral medications

- Only 3/25 (12%) episodes required hospitalization

- No significant side effects (fatigue in 2 children)
Treatment summary

- Assess for seizure triggers and/or comorbidities and treat as needed
  - Especially in non-epileptic myoclonus

- Medications or dietary therapy first line if treatment needed
  - LGIT especially effective in AS, can be used first line

- If medication – use broad spectrum medication
  - Keppra, ONFI, Lamictal worked best in MGH study
  - Depakote is effective but has significant side effect rate in AS
MGH/LC Angelman Syndrome Clinic

- Neurology/Epilepsy – Ron Thibert
- Psychiatry – Chris Keary
- GI – Kriston Ganguli
- Dietary therapy – Heidi Pfeifer
- Neuropsychology – Amy Morgan
- Sleep medicine – Ken Sassower
- NP – Amanda Tourjee
- Nursing – Katrina Styles
- Behavioral therapy – Nicole Simon
- Clinic Coordinator – Kim Parkin
- Research Intern – Stephanie Yemane
MGH Angelman Syndrome Clinic