SEIZURES AND THEIR TREATMENTS IN ANGELMAN SYNDROME – LOUISVILLE 2019

Ron Thibert DO, MsPH
Massachusetts General Hospital, Boston MA
Harvard Medical School

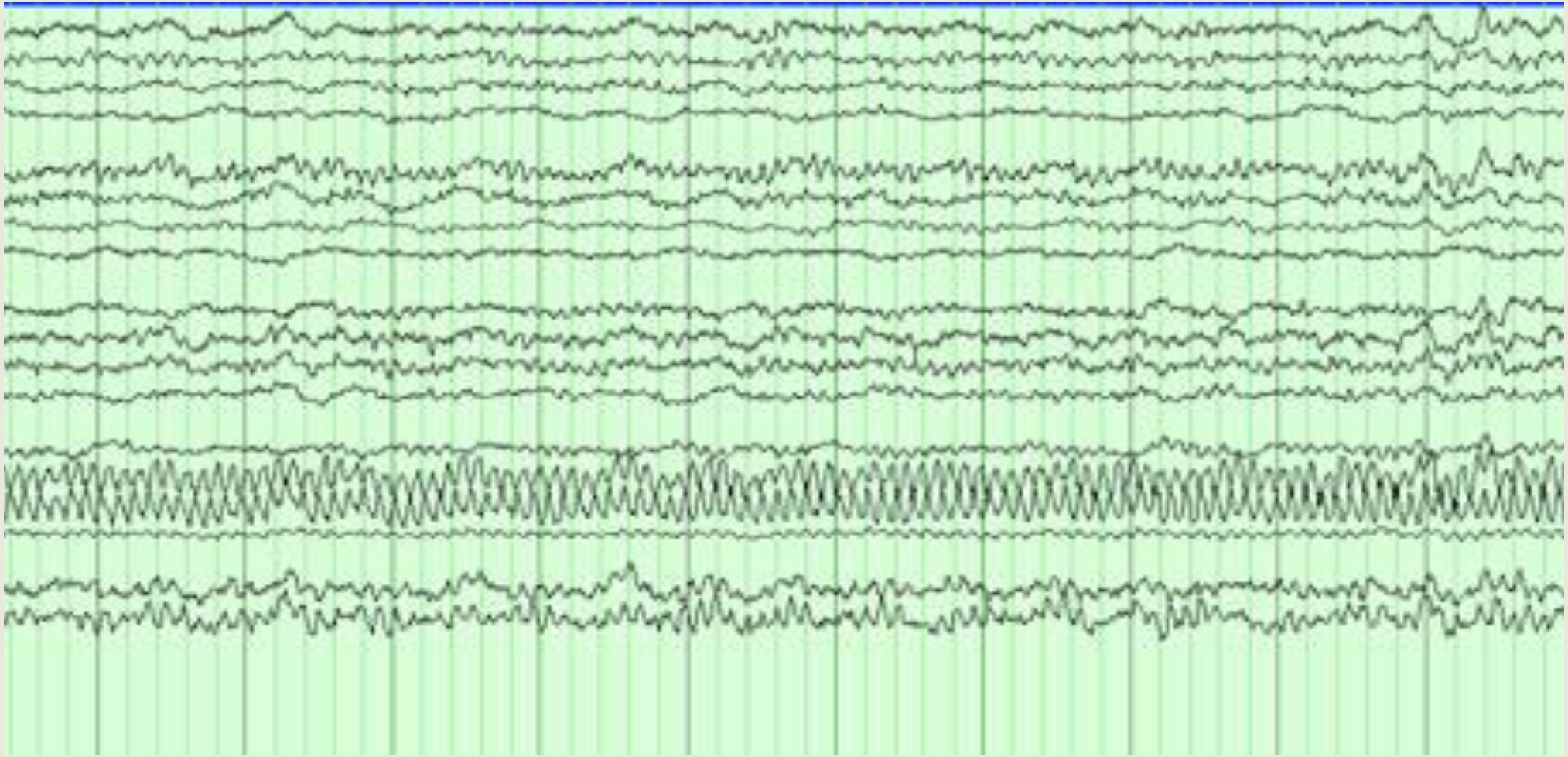
Definitions

- 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

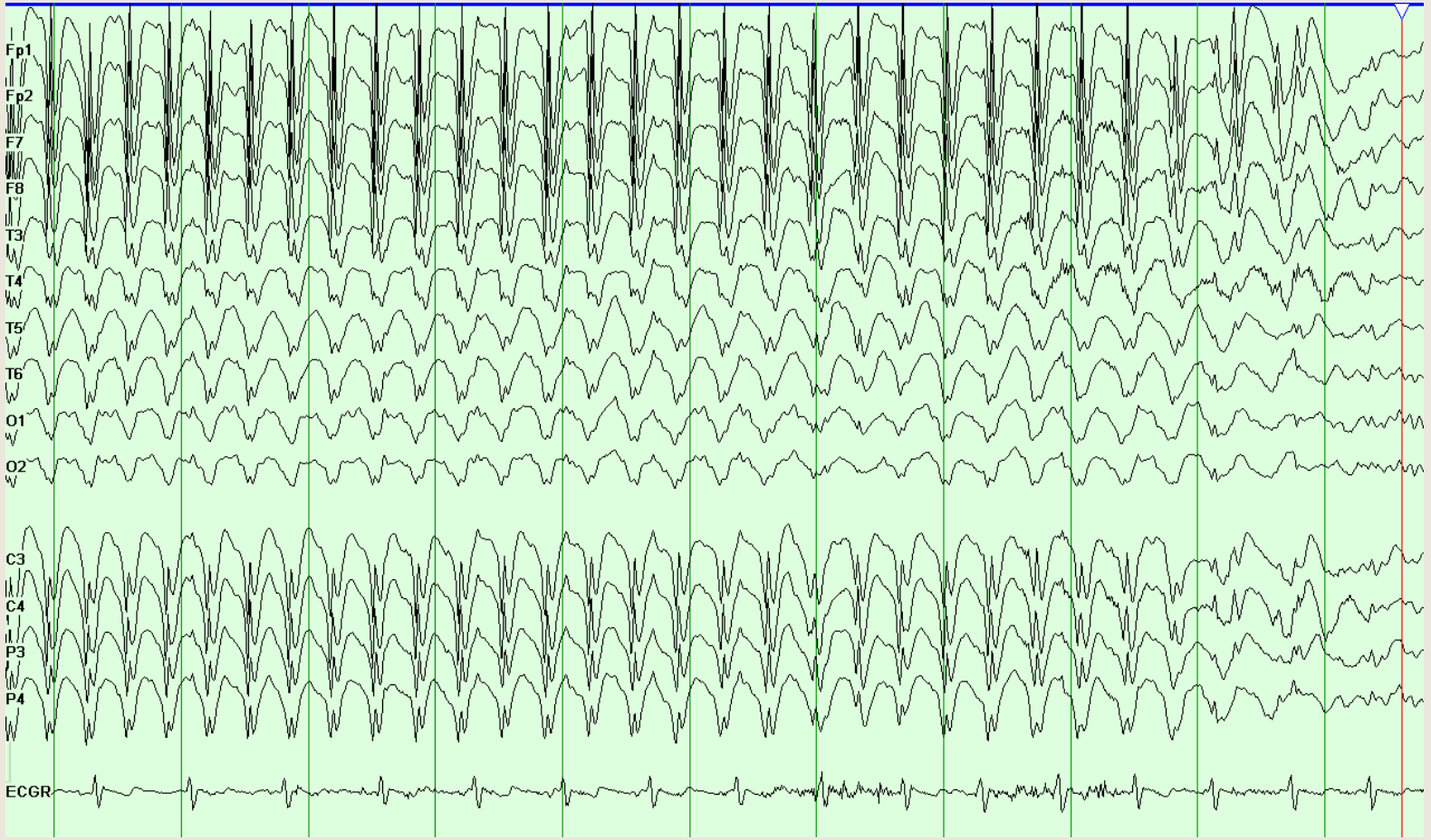
Seizure Types

- 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*

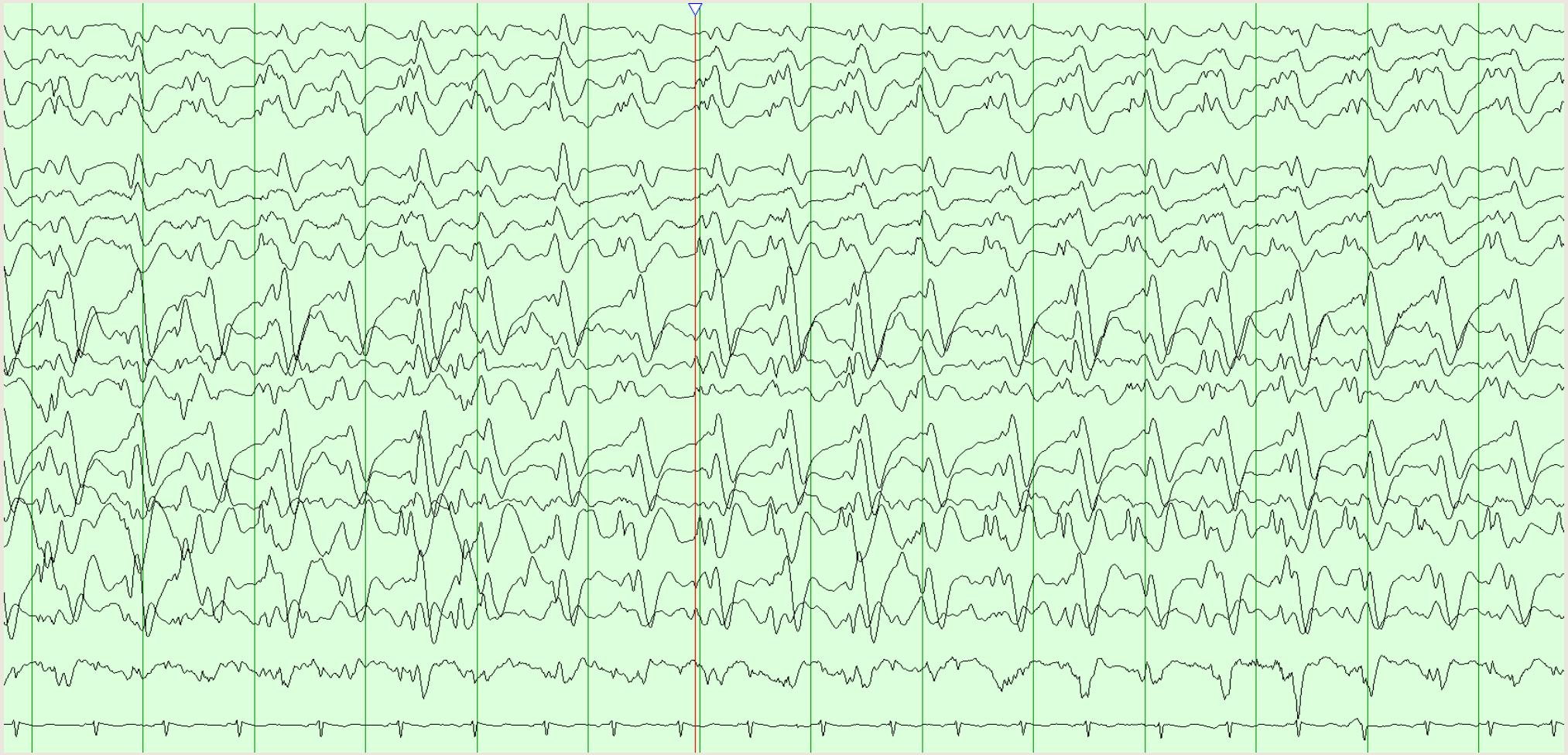
Epilepsy syndromes

- 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)

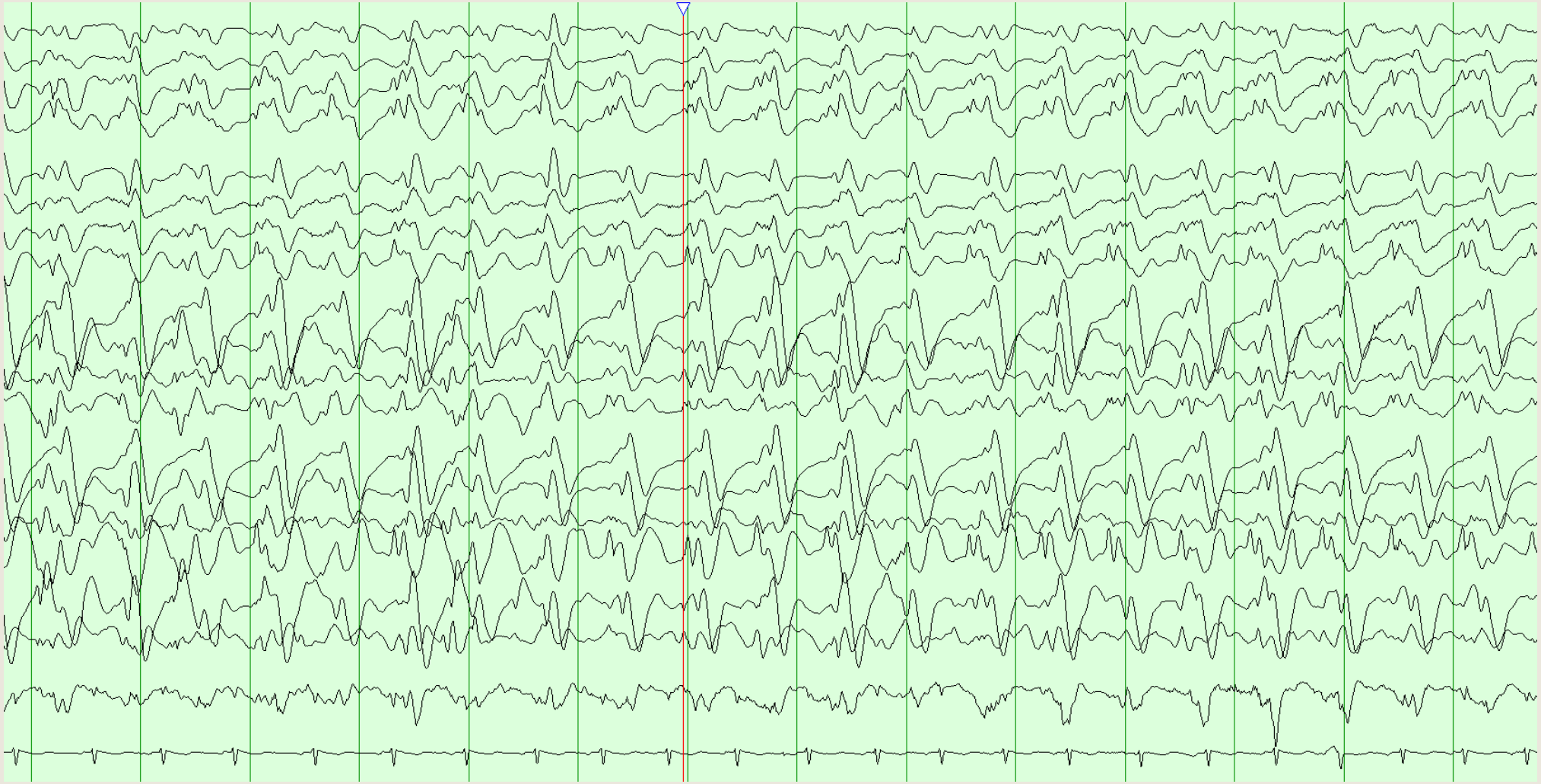
Status Epilepticus

- 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

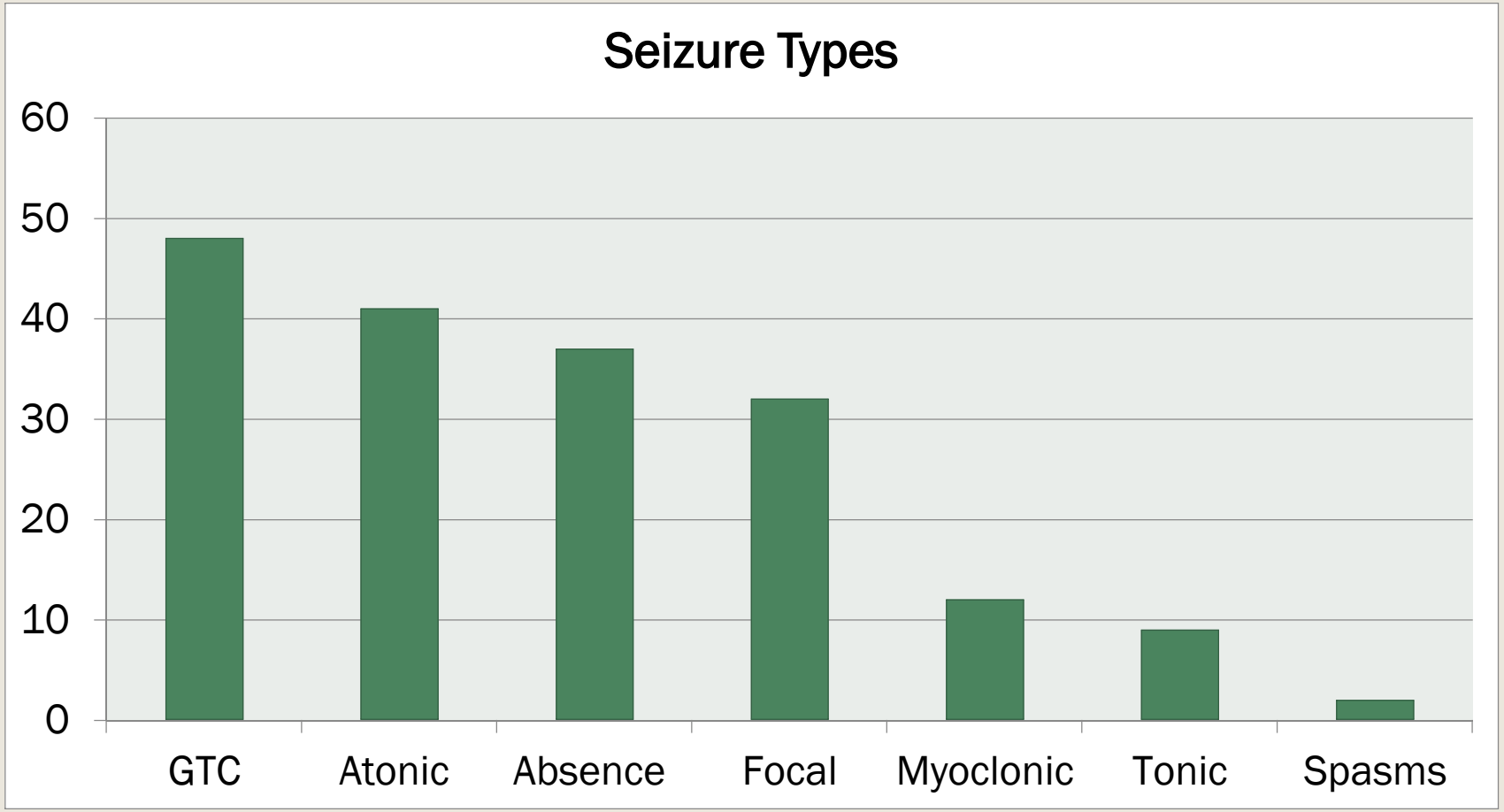
- Epilepsy in Angelman syndrome is a generalized epilepsy
  - *Generalized tonic-clonic*
  - *Atypical absence*
  - *Atonic*
  - *Myoclonic*
  - *Tonic (rare)*
  - *Spasms (rare if at all)*
  - *Focal seizures present in ~30%*

ASF Seizure Survey

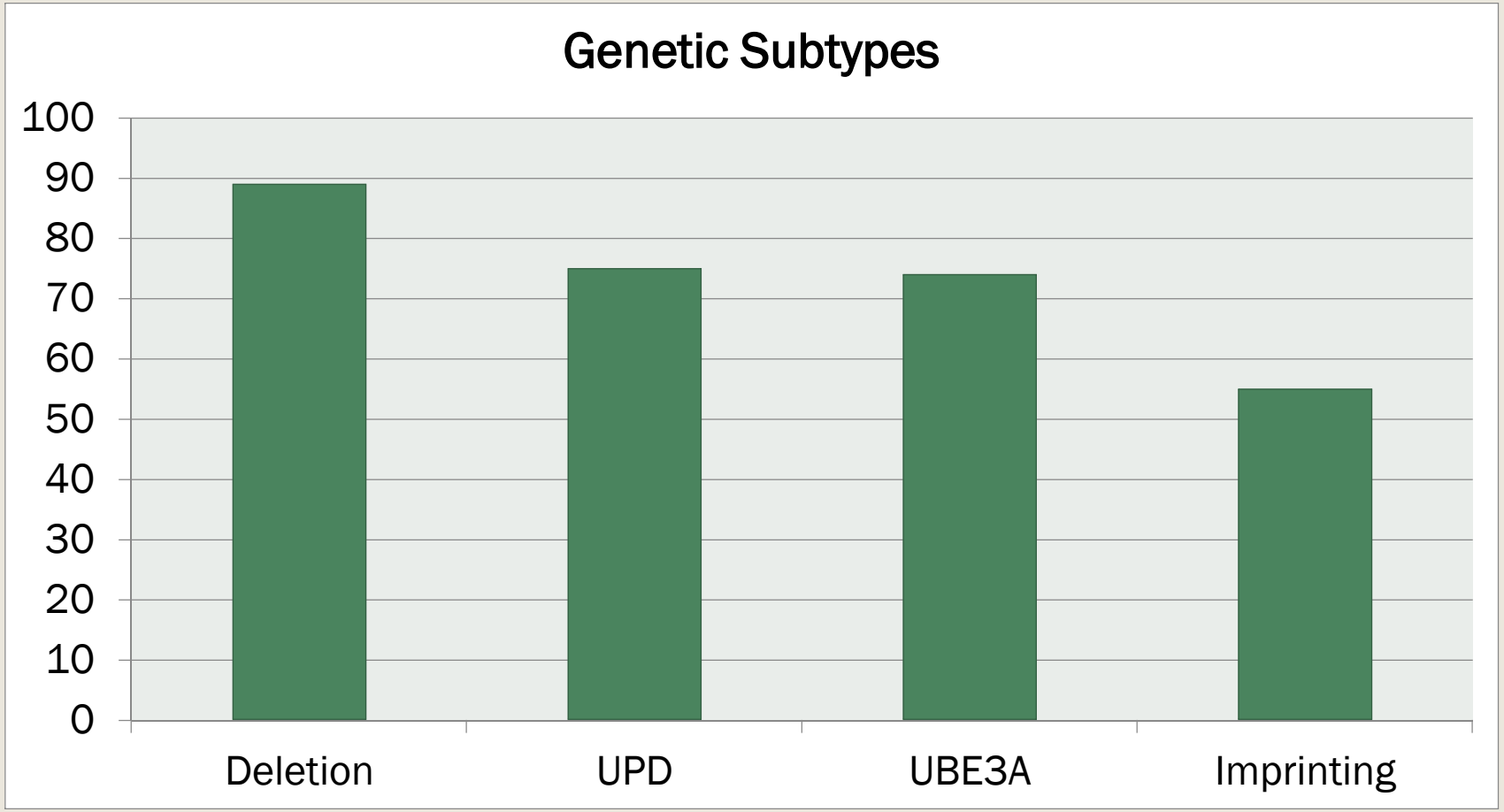
- Seizure survey performed in 2006-07
  - *On-line questionnaire through ASF*
- 461 responses
  - *391 (86%) had seizures*
  - *60% had multiple seizure types*
  - *>90% had some combination of generalized seizure types with or without focal seizures*
  - *~30% reported focal seizures*

    - Thibert et al., *Epilepsia* 2009

AS Seizure types



AS Seizures by subtype



Seizures in AS - Age

Seizures in AS relative to age:

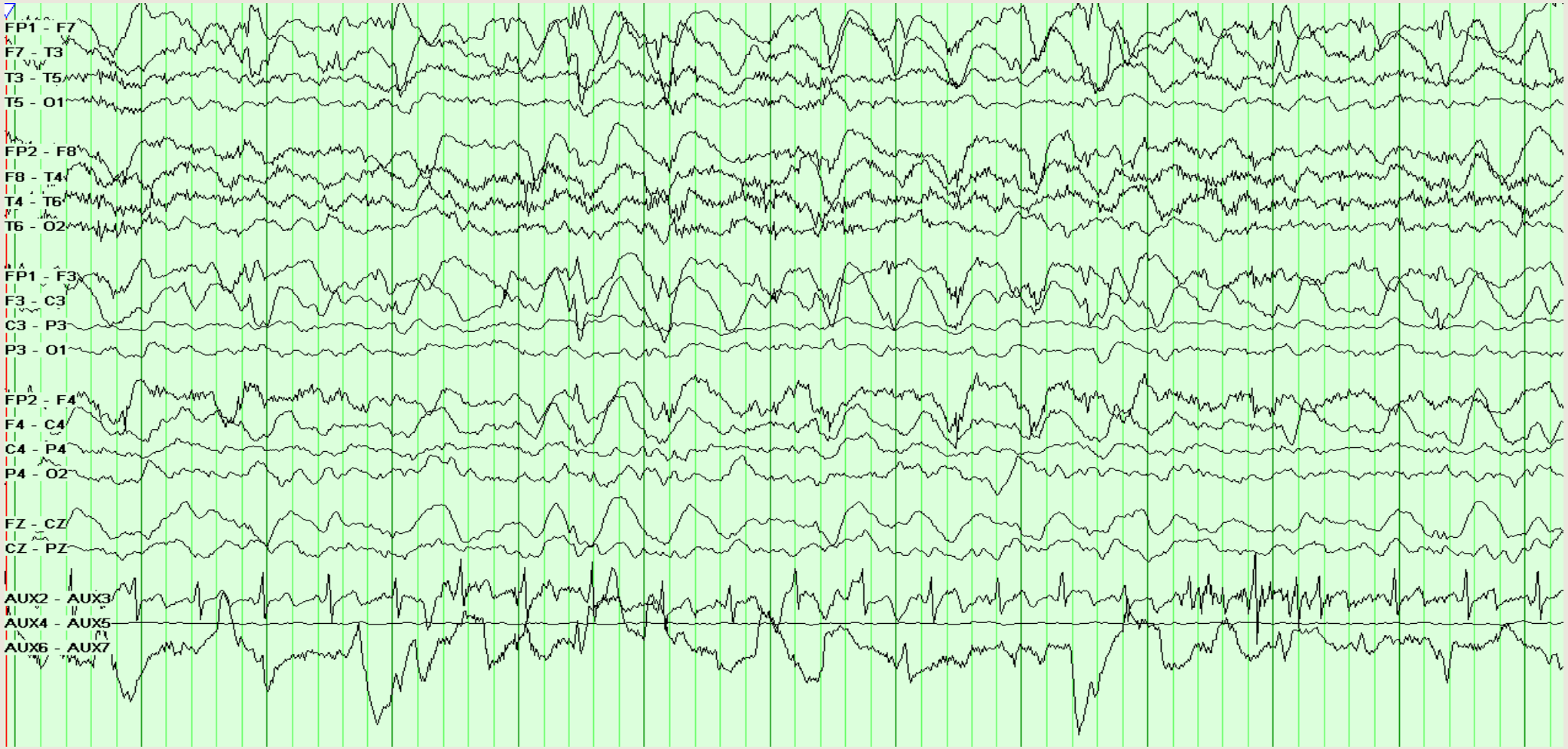
- Average onset approximately 2-3 yrs of age, typically beginning in childhood; infrequent cases of seizures <1 year of age
- Seizures are usually most frequent and most intense in early childhood and tend to improve by puberty
- Seizures can then return and persist into adulthood but are typically much 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

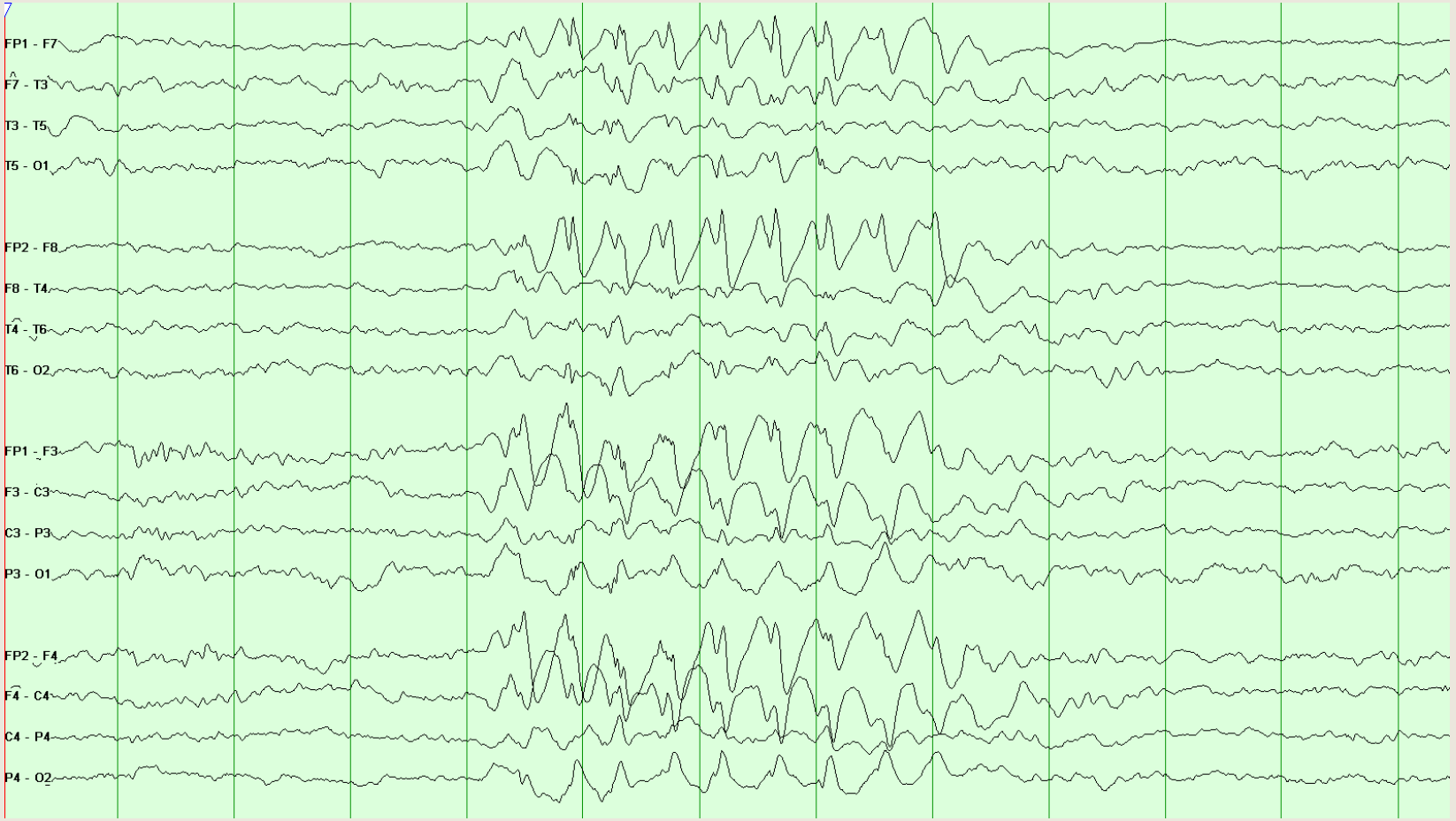
EEG in AS

- 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*

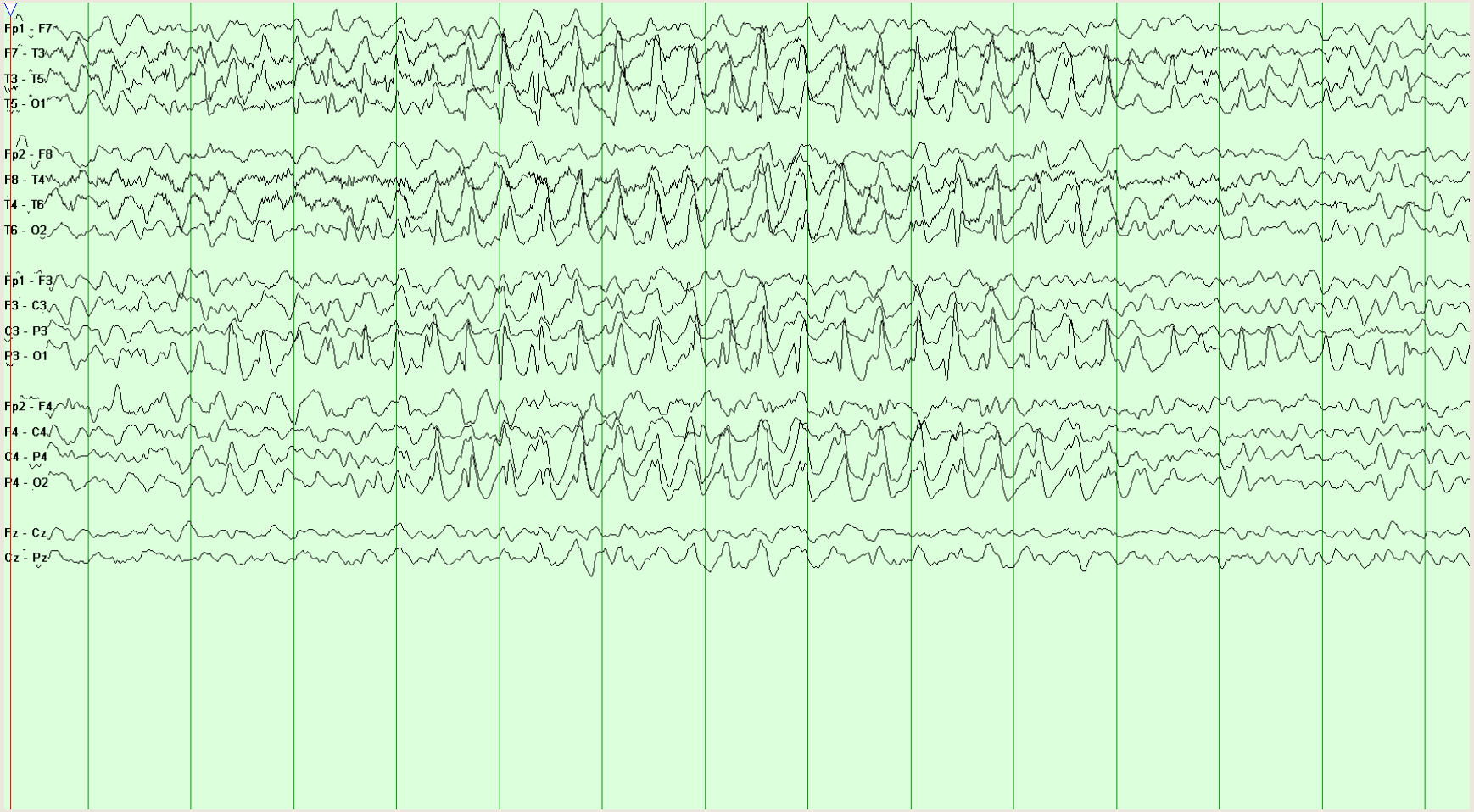
Frontal slow spike and wave



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)

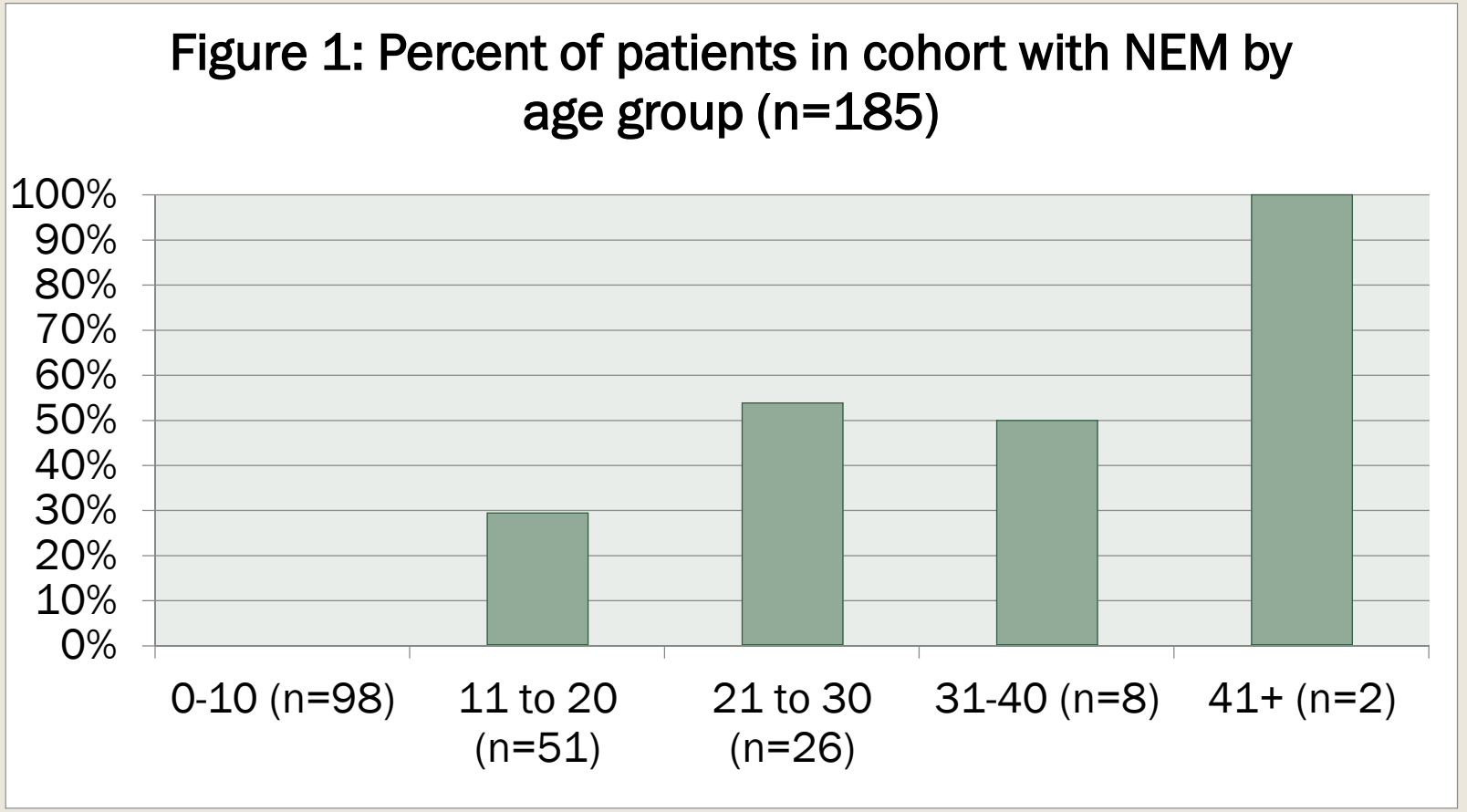
Non-epileptic Myoclonus

- 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

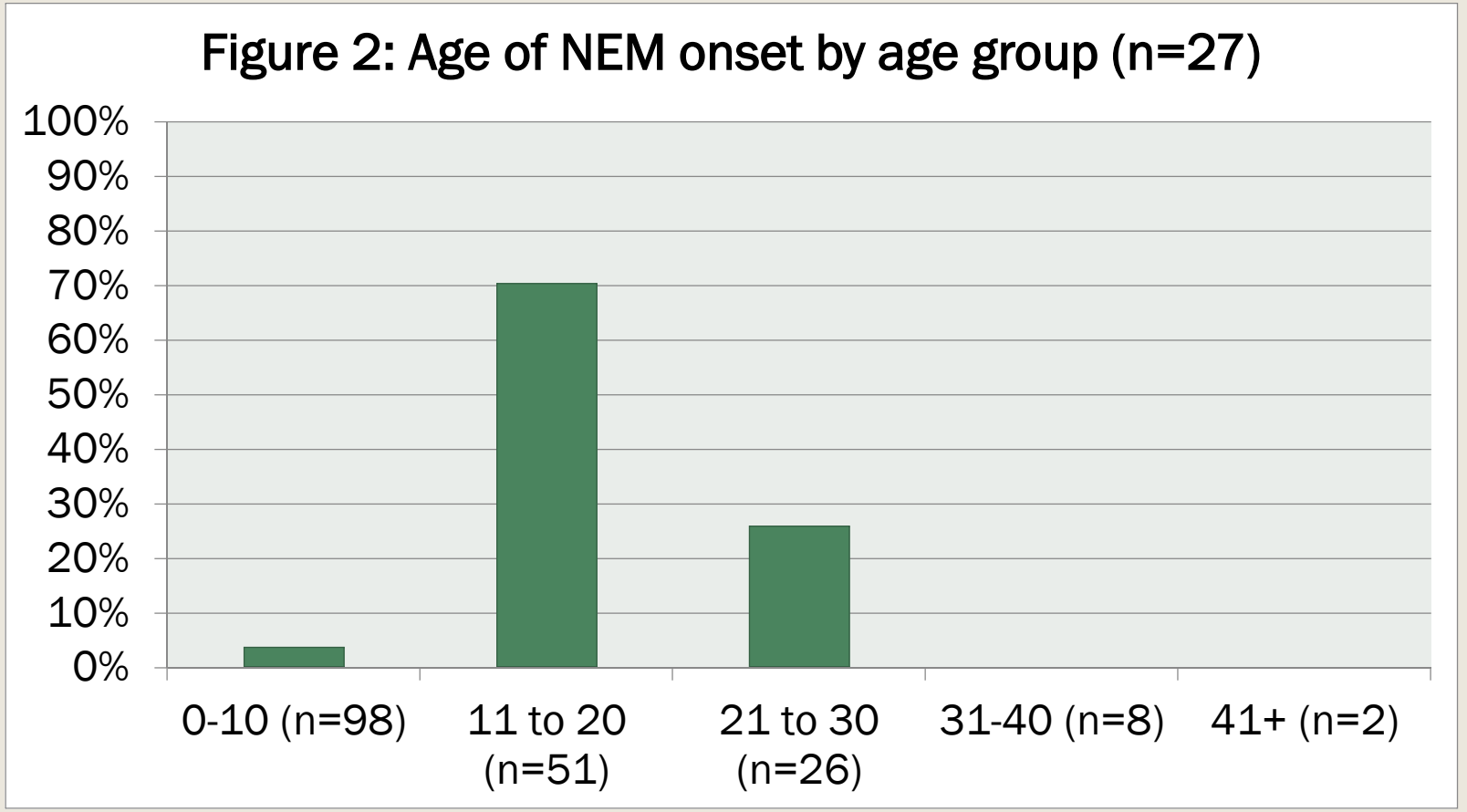
Non-epileptic Myoclonus (Pollack et al, 2018)

- 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



Age of onset of NEM



SEIZURE TREATMENTS

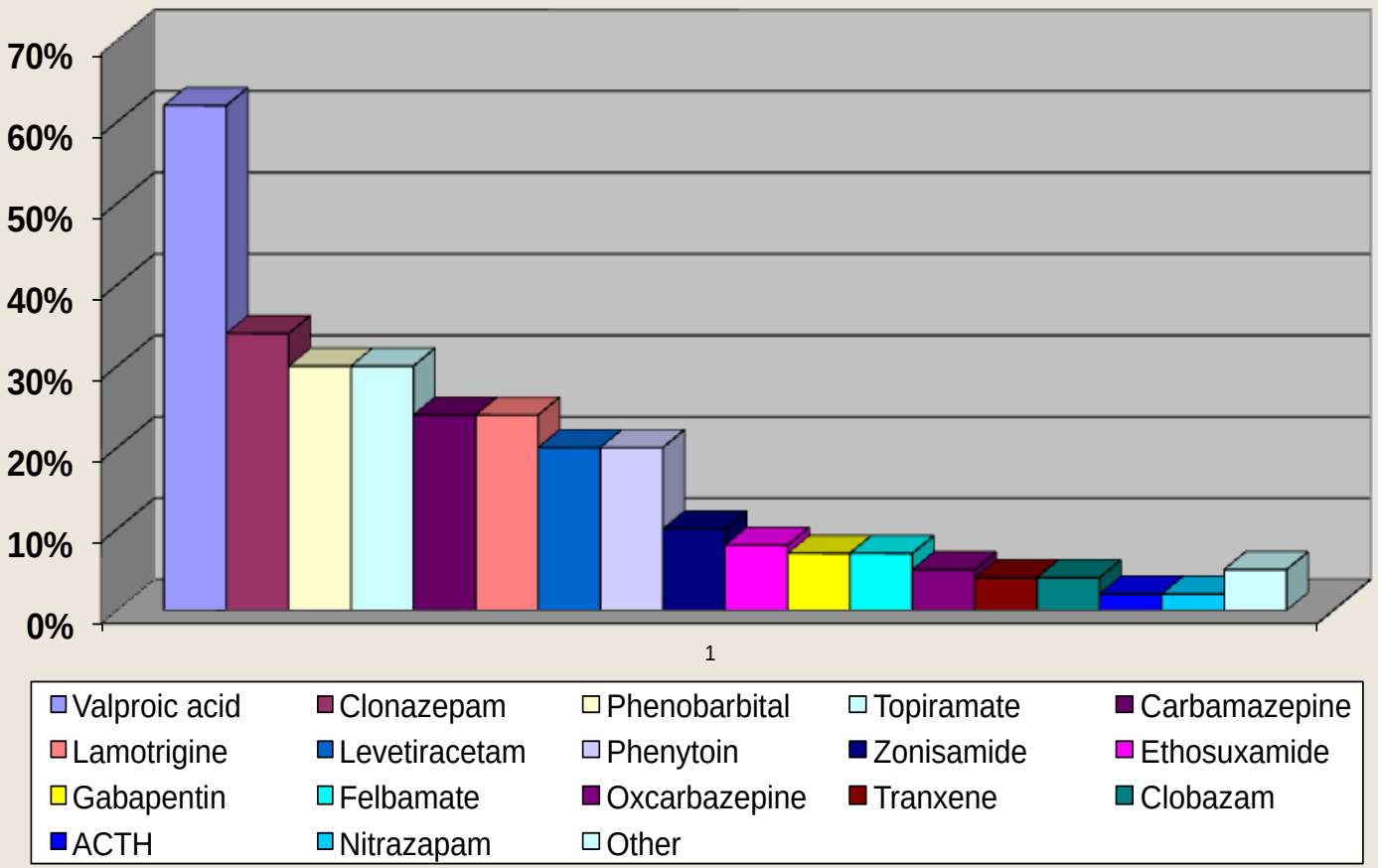
Treat the Co-morbidities

- 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



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)

Treatment	No change	<50% improved	50-90% improved	>90% improved
Valproic acid	0	0	8 (38.1%)	13 (61.9%)
Levetiracetam	0	0	5 (14.3%)	30 (85.7%)
Lamotrigine	0	0	2 (11.8%)	15 (88.2%)
Clobazam	2 (7.1%)	0	2 (7.1%)	24 (85.7%)
LGIT	0	1 (10%)	2 (20%)	7 (70%)

Seizure Medications (Shaaya et al, 2016)

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

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

Medication	Worse or no change	<50% improved	50-90% improved	>90% improved
Levetiracetam N=10	0	5 (50%)	2 (20%)	3 (30%)
Clobazam N=9	2 (22%) Fatigue	4 (44%)	1 (10%)	2 (20%)
Clonazepam N=5	1 (20%) Fatigue	0	2 (40%)	2 (40%)

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