When Autism and Epilepsy Overlap: What does it mean?
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Disclosures

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- Member of DSM 5 Neurodevelopmental Disabilities workgroup.
- Current Co-Investigator in Roche trial for ASD (not epilepsy)
- Previous consultant to Yamo pharmaceuticals for new compound (not epilepsy)
National Epilepsy Awareness Month

NATIONAL EPILEPSY AWARENESS MONTH 2020

1 in 26
3.4 Million

WARRIOR
STAY SAFE SIDE

EPILEPSY FOUNDATION
END EPILEPSY TOGETHER
Overview

- The concept
- The definitions
- The numbers
- The risk factors
- The meaning
- The practicalities
- The science
THE CONCEPT
Association is frequent
Major impact on patient quality of life
Could represent common neural mechanisms
Overlapping symptoms

EPILEPSY

Behavior

Communication

Cognition

ASD

Is there any causal relationship or is this epiphenomenon?
Challenges to research

- Heterogeneity
- Fields of investigation
- Diagnostic differences
THE DEFINITIONS
What is a seizure anyway?

Seizure

Definition: a sudden disruption of the brain's normal electrical activity accompanied by altered consciousness and/or other neurological and behavioral manifestations.

Can be provoked or unprovoked

Lots of different kinds

- Febrile – when you only have a seizure with fevers
- Grand Mal – Generalized tonic clonic (GTC)
- Petit Mal – Absence
- Focal (with or without impaired awareness)

Also: Infantile Spasms, Myoclonic, Atonic, Tonic, Status Epilepticus
What is epilepsy?

- Not a bad word!
- Epilepsy (aka seizure disorder) is a condition characterized by recurrent seizures (more than one unprovoked).
- Lots of different kinds
  - Temporal lobe epilepsy
  - Childhood absence epilepsy
  - Rolandoic (BECTS)
  - Lennox Gastaut syndrome
How do we diagnose epilepsy?

- Good history
  - What exactly did the child do?
    - What happened before
    - What happened during
    - What happened after

- EEG
  - Measurement of the brain waves to look for changes that may be associated with epilepsy
    - Abnormal (epileptiform) discharges
EEG
THE NUMBERS
Epilepsy is increased in ASD

- But - rates very variable (5-45%)
- Probably dependent on sample characteristics:
  - SAMPLE ASCERTAINMENT
    - Population based samples have lower rates than clinic based
  - AGE
    - bimodal age of onset (early childhood & adolescence).
    - Bolton (2011) found >50% had seizure onset after age 10
  - NON-IDIOPATHIC AUTISM
    - Neurogenetic syndromes or brain injury have more epilepsy.
  - IQ and LANGUAGE skills
    - Most studies show that lower IQ associated with epilepsy.
    - Some studies show language regression and poorer language skills predict epilepsy.
<table>
<thead>
<tr>
<th>Citation</th>
<th>Sample size</th>
<th>Age</th>
<th>Ascertainment</th>
<th>Diagnosis</th>
<th>Syndrome</th>
<th>Epilepsy rate</th>
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<tbody>
<tr>
<td>Amiet 2008</td>
<td>2112</td>
<td>Mixed</td>
<td>Autism, PDD</td>
<td>yes</td>
<td>With intellectual disability: 21.4 % Without intellectual disability: 8%</td>
<td></td>
</tr>
<tr>
<td>Miles et al. 2005</td>
<td>233</td>
<td>Clinic based</td>
<td>Autism, Asperger’s</td>
<td>yes</td>
<td>17% “essential” 39% “complex”</td>
<td></td>
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<tr>
<td>Canitano 2005</td>
<td>46</td>
<td>Mean 7.8 yrs</td>
<td>Clinic based</td>
<td>Autism, PDD</td>
<td>no</td>
<td>13%</td>
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<tr>
<td>Danielson 2005</td>
<td>108</td>
<td>Mean 25.5 yrs</td>
<td>Population Based</td>
<td>Autistic or “Autistic Like”</td>
<td>yes</td>
<td>38%</td>
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<tr>
<td>Hughes 2005</td>
<td>59</td>
<td>0.5-21 yrs</td>
<td>Clinic based</td>
<td>Autism</td>
<td>yes</td>
<td>46%</td>
</tr>
<tr>
<td>Gianotti 2008</td>
<td>104</td>
<td>30mo. -8 yrs</td>
<td>Clinic based</td>
<td>Autism or ASD</td>
<td>yes</td>
<td>19.4%</td>
</tr>
<tr>
<td>Hara 2007</td>
<td>130</td>
<td>18-35 yrs</td>
<td>Clinic based</td>
<td>Autism, PDD</td>
<td>no</td>
<td>17% (25% when 1 seizure included)</td>
</tr>
<tr>
<td>Bolton 2011</td>
<td>150</td>
<td>All adult</td>
<td>Prospective research cohort</td>
<td>ASD</td>
<td>yes</td>
<td>22%</td>
</tr>
<tr>
<td>Mouridsen 2011</td>
<td>118</td>
<td>All adult</td>
<td>Clinic/ population</td>
<td>ASD</td>
<td>no</td>
<td>25%</td>
</tr>
<tr>
<td>Kohane 2012</td>
<td>14,381</td>
<td>0-35 yrs</td>
<td>Hospital EMR</td>
<td>ASD</td>
<td>yes</td>
<td>19.4%</td>
</tr>
<tr>
<td>Suren 2012</td>
<td>1726</td>
<td>0-11 yrs</td>
<td>Population based</td>
<td>ASD</td>
<td>yes</td>
<td>11.2%</td>
</tr>
</tbody>
</table>
## Overlap between epilepsy syndromes and autism

<table>
<thead>
<tr>
<th><strong>Infantile Spasms</strong></th>
<th><strong>Tuberous Sclerosis Complex</strong></th>
<th><strong>Landau Kleffner Syndrome</strong></th>
</tr>
</thead>
</table>
| • High rates of intellectual disability with social communication deficits >> expected for IQ  
• 10-15% of kids develop autism  
• IS history in 6% of all ASD and up to 30% of ASD patients with epilepsy | • Very high rates of epilepsy and high rates of ASD (~40%)  
• ASD higher in those with intellectual disability | • Language and behavioral regression  
• EEG abnormalities |
No single epilepsy syndrome

Seizure types

- Generalized convulsive seizure
- Partial/focal seizure
- Absence

Seizure Behavior

- Unresponsiveness
- Eye deviation
- Repetitive behavior (automatisms)

Autism Behavior

- Not responding to name
- Peering from the corner of eyes
- Stereotypies

INVOLUNTARY

VOLUNTARY

Sometimes hard for even expert epileptologists to tell the difference between seizure and behavior
THE RISK FACTORS
## Risk factors

| Intellectual disability | Most (but not all) show epilepsy associated with intellectual disability  
| Meta-analysis of 10 studies epilepsy in 21% with ID vs 8% without (Amiet et al., 2008) |
| Co-morbid conditions: syndromic or non-idiopathic autism | 2-5 x increased risk (Pavone et al., 2004; Miles et al., 2005; Parmegianni et al., 2010) |
| Female gender | Most studies (but not all) show higher epilepsy in females  
| Meta-analysis epilepsy in 34% of females vs 18% of males (Amiet et al., 2008) |
| Developmental regression | Several studies suggest an association (Kobayashi & Murita, 1998; Hrdlicka et al., 2004; Giannotti et al., 2004; Parmegianni et al., 2010)  
| Other studies show no association (Tuchman & Rapin, 1997; Canitano et al., 2005; Hara, 2007) |
| Pre and perinatal factors | Finish birth cohort study n=4705  
| Prematurity, birth weight, low APGARS (Jokiranta et al., 2014) |
THE MEANING
Epilepsy in ASD

- Treatment refractory epilepsy may be common (Sansa et al., 2011)
  - 34% treatment refractory
    - significantly earlier age of seizure onset
  - 39% with infrequent or difficult to categorize
  - 27% seizure free

- Epilepsy may increase mortality in ASD (Pickett et al., 2011)
  - data from California DDS
  - 5-6x higher mortality in those with ASD plus epilepsy than ASD alone

- Epilepsy may impact outcome of early intervention (Eriksson et al, 2013)
  - Epilepsy (among other medical problems) associated with lower adaptive function scores
SUDEP: Sudden Unexplained Death in Epilepsy

- Important BUT RARE complication to know about.
- VERY rare in children (1/4,500 or 0.002%)
  - Increases with age (1/1,000 or 0.1% in adults)
- Cause still unknown
- Risk increases with
  - Generalized tonic clonic seizures
  - Not taking medication as prescribed
- Talk to your provider for more information
Relationship between epilepsy and ASD clinical profile

- Less is known
  - Retrospective clinical review (Hara 2007)
    - lower social scores and more medication use
  - Age, IQ matched groups of ASD + EPI & ASD alone (Turk et al 2009)
    - Increased motor & adaptive behavior deficits
    - One item in nonverbal communication: “stares too long and too hard”
    - Several items on social interaction scale: difficulties with peers, psychological barriers, and socially shocking behaviors.
But are these associations independent?

- Viscidi et al., 2013 PLOS-ONE
  - Large study designed to examine the clinical characteristics of epilepsy and ASD
  - Sample of convenience
    - Large data sets available from genetic studies
      - AGRE, Boston Autism Consortium, Simons Simplex Collection
    - Strengths
      - Good ASD diagnostic data
      - Detailed ASD and related behavioral phenotyping data
    - Weaknesses
      - Turns out mediocre epilepsy data
  - Initial analysis showed significant effects of:
    - Regression, Language, IQ, Adaptive function, ASD severity
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model 1: Unadjusted</th>
<th></th>
<th>Model 2: Adjusted for FSIQ</th>
<th></th>
<th>Model 3: Fully Adjusted</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>9 years and younger</td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
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<td>1.00 [Reference]</td>
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<tr>
<td>10 years and older</td>
<td>3.05 (2.29–4.06)</td>
<td>&lt;.001</td>
<td>2.40 (1.51–3.82)</td>
<td>&lt;.001</td>
<td>2.35 (1.42–3.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
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<tr>
<td>Female</td>
<td>1.86 (1.35–2.56)</td>
<td>&lt;.001</td>
<td>1.43 (0.82–2.49)</td>
<td>0.21</td>
<td>1.36 (0.77–2.43)</td>
<td>0.29</td>
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<tr>
<td>Cognitive Ability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Full Scale IQ Score</td>
<td>0.51 (0.41–0.63)</td>
<td>&lt;.001</td>
<td>0.51 (0.41–0.63)</td>
<td>&lt;.001</td>
<td>0.53 (0.39–0.73)</td>
<td>&lt;.001</td>
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<tr>
<td>Adaptive Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adaptive Behavior Composite Score</td>
<td>0.52 (0.45–0.61)</td>
<td>&lt;.001</td>
<td>0.80 (0.58–1.10)</td>
<td>0.17</td>
<td>0.98 (0.70–1.37)</td>
<td>0.89</td>
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<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Meaningful Use of Single Words, Two-</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Word Phrases, or Three-Word Phrases</td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Fewer than 5 Words</td>
<td>2.00 (1.39–2.87)</td>
<td>&lt;.001</td>
<td>0.75 (0.27–2.05)</td>
<td>0.57</td>
<td>0.75 (0.27–2.13)</td>
<td>0.59</td>
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<tr>
<td>Developmental Regression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No Loss of Language or Skills</td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
<td>1.00 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Loss of any Language or Skills</td>
<td>1.93 (1.45–2.57)</td>
<td>&lt;.001</td>
<td>1.05 (0.64–1.72)</td>
<td>0.86</td>
<td>1.14 (0.69–1.89)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval; FSIQ, full scale IQ score.

*Genetic Collaborative Samples (AGRE, SSC, and AC) combined.
Model 1: Individual models for each variable.
Model 2: Individual models for each variable, adjusted for full scale IQ score only.
Model 3: Single model adjusted for all variables.
Odds ratios for full scale IQ score and adaptive behavior composite score represent the odds of epilepsy for a one standard deviation increase.
doi:10.1371/journal.pone.0067797.t006
In reality: Probably multiple kinds of epilepsy in autism

When early onset seizures actually contribute to autism

• infantile spasms

When other disorders co-exist

• neurogenetic syndromes (eg Tuberous Sclerosis, Fragile X, 15q duplication)
• neurologic injury (eg CNS malformation or stroke)
• severe intellectual disability

True idiopathic autism

• whatever that means…
Epileptiform EEG Abnormalities reported even without clinical seizures
EEG abnormalities in ASD: Rates variable

- Tuchman & Rapin (1997)
  - 585 pts with sleep EEGs
  - 14% had epileptiform EEG
    - 8% if they never had a seizure

- Later studies
  - Higher rates
    - 25-30%

- Higher yield with 24 hour EEGs
  - Chez et al (2006) 60%
  - Kim et al (2006) 60%
  - Mulligan et al (2014) 50%
Treatment

- Anti-Seizure drugs dependent on:
  - seizure type
  - side effect profile
  - practicalities
    - formulation, dosing schedule, need for blood draws in monitoring, etc

- All seizure medications can have behavioral and cognitive effects … so practitioners need to be careful in children who already have challenges.

- New cannabis data is sparking a lot of interest
  - GWPharma Epidiolex trial in severe epilepsy (Devinsky et al. 2017)
    - Lots of interest in using CBD in autism for behavior
    - Safety and Tolerability of GWT42006 (cannabidivarin) in subjects with drug resistant epilepsy and autism (U of Louisville, G Barnes PI)
      - Measuring both behavioral and seizure outcomes
Treatment

- Treating EEGs is CONTROVERSIAL
  - Child neurologists are taught to “treat the child not the EEG”
  - The only time we focus on EEG is LKS and IS
  - Almost no data in autism … but some clinicians do it:
    - typical anti-convulsants (valproate (Depakote), lamotrigine (Lamictal), benzodiazepines)
    - atypical treatments such as steroids used in spasms and LKS
    - epilepsy surgery
      - Only case reports, not recommended
Getting an EEG

What are the challenges?

- Before: sleep deprivation
- During: lots of head touching, need to stay still, smells and sounds ... then you have to go to sleep!
Helps to prepare

- Know what will happen
- Tour the lab
- Practice with the materials
Using “Social Stories”

Outpatient EEG Visit
Boy Version
My Hospital Story

http://www.childrenshospital.org/patient-resources/child-life-specialists/preparing-your-child-and-family-for-a-visit/my-hospital-story
The technologist is the person that will help with the EEG. He/she will explain how the EEG works and then we can start!
First, the technologist will measure my head with a tape measure. I will keep my body very still.
Next, the technologist will draw dots on my head with a soft crayon to mark where the electrodes will go.
The technologist will use a Q-tip and soap to rub off the crayon dots. The soap will feel sandy.
Next, the technologist will place electrodes (small gold discs with colorful wires) on my head.
The technologist will use special tape to help the electrodes stay in place.
THE SCIENCE
Translational Research: Are there common mechanisms?

- A disconnection syndrome with overconnectivity in local regions and underconnectivity in long range.
- A disorder of the synapse.
- Excitatory/inhibitory imbalance during critical period of brain development
- Many overlapping genes and regions
Shared neurobiology of ASD and epilepsy

- Both occurring in critical period
- Both disorders largely involving the synapse (connection between neurons)
- Both disorders of activity dependent pathways
- Evidence for epilepsy in human autism syndromes and animal models
- Seizures can dysregulate autism-related protein cascades

Slide courtesy of Frances Jenson
Epilepsy and autism converge at the synapse

Shared molecular targets?

Modified from Lamprecht and LeDoux, Nature Neurosci Rev, 2004

Slide courtesy of Frances Jenson
Common Mechanisms?

- Focus on specific syndromes could allow more detailed mechanistic investigation
  - mechanisms are likely relevant beyond that syndrome

- Single genes
  - TSC, CDKL5, reelin, FMR1, MECP2
  - CNTNAP2, PTEN, SCN1A, PCDH19

- CNVs
  - 15q del or dup
  - 16p11 del or dup
Translational Research: Data from animal models

- Early treatment may reduce risk of developing epilepsy in Tuberous Sclerosis
  - Could prevention of epilepsy reduce risk of ASD as well?
Translational Research: Data from animal models

**TSC Alert**

**PREVeNT Trial Enrolling Participants**

The Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) trial, led by Martina Bebin at the University of Alabama Birmingham, is continuing to enroll participants at seven sites across the country.

The central hypothesis of this Phase IIb trial, supported by a $7 million grant from NINDS, is that early identification of electroencephalography (EEG) biomarkers and early treatment versus delayed treatment with vigabatrin in infants with tuberous sclerosis complex (TSC) will have a positive impact on developmental outcomes at 24 months of age. It would also prevent or lower the risk of developing infantile spasms and refractory seizures. This preventative approach would be expected to result in more favorable long-term cognitive, behavioral, developmental and psychiatric outcomes and significantly improve overall quality of life.
Translational Research: Data from animal models

- Altered excitatory-inhibitory balance pattern seen in many of the mouse models of ASD.
  - Can this be altered with intervention?
  - If so, when?
Clinical Research Questions

- What are the effects of:
  - Severity (of the autism, the epilepsy, the EEG abnormalities)
  - Development (which comes first – the autism or the epilepsy?)

- EEG abnormalities
  - What are the risk factors for EEG abnormalities in ASD?
  - What is the relationship specifically to ASD symptoms?
    - Is there a causal relationship or is this epiphenomenon?
    - What is the role for intervention?
Autism and Epilepsy: Moving forward

Genetics, Basic molecular mechanisms, Pathway analysis

Prevalence, Symptom descriptions

Development of targeted treatments
Take Home Messages

- Epilepsy is increased in individuals with ASD
  - Best estimate are population based studies 10-20%
- Any seizure type is possible (and some are hard to tell from autistic behaviors)
  - Usually not severe
- Risk factors include ID, female sex, other syndromes
- There is overlapping biology
  - This may lead us to targeted treatments
THANK YOU