AIR-P Presents:
Epilepsy in Autism

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Objectives

• Definition of seizures
• Definition of epilepsy
• Prevalence of epilepsy in autism
• Pathophysiology of epilepsy in autism
• Treatment strategies unique to epilepsy in autism
Disclosures

• Clinical trial support: Biogen, Novartis, Eisai, UCB, SK Life Sciences
• Discussion of off-label use of medications
Seizures

• Seizures are a common occurrence, affecting an estimated 8 to 10 percent of the population over a lifetime

• Seizures account for 1 to 2 percent of all emergency department visits, and approximately one-quarter of these will be a first seizure

• What is a seizure?
  • Sustained, abnormal electrical activity arising from the cerebral cortex with discrete beginning and end
  • Evolution in amplitude, frequency, morphology
  • Clinical presentation depends on origin, generalized versus focal
Seizure versus Epilepsy

- A seizure is the event
- Epilepsy is the disease associated with spontaneously recurring seizures
Epilepsy is a disorder characterized by two or more unprovoked seizures occurring more than 24 hours apart.

**Traditional Epilepsy Definition**

Concise, easy to apply, known to many, but . . .

- Some people now are treated as if they have epilepsy after 1 seizure
- A person can never outgrow epilepsy
- Can have an epilepsy syndrome (e.g., BRE), but not epilepsy
- Those with photic or reflex seizures are not defined as having epilepsy
These are not Epilepsy because there is small risk of a seizure in the absence of a precipitating factor

- Febrile seizures in children age 0.5 – 6 years old
- Alcohol-withdrawal seizures
- Metabolic seizures (sodium, calcium, magnesium, glucose, oxygen)
- Toxic seizures (drug reactions or withdrawal, renal failure)
- Convulsive syncope
- Acute concussive convulsion
- Seizures within first week after brain trauma, infection or stroke
Epilepsy is a disease of the brain defined by any of the following conditions:

1. A least two unprovoked (or reflex) seizures occurring >24 h apart

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.
Conceptual Definition of Epilepsy

_Epilepsia, 46_(4):470-472, 2005
Blackwell Publishing, Inc.  © 2005 International League Against Epilepsy

Epileptic Seizures and Epilepsy: Definitions Proposed By the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE).


Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.
After two unprovoked seizures, the risk of a 3rd by 60 months is 73% (59-87%, 95% confidence intervals).

- So adopt 59 (~ 60%) as the lower end of the confidence interval for the recurrence risk we all agree is epilepsy.

Epilepsy in autism

• Prevalence of epilepsy in general population is 0.5-1%
• In individuals with autism, the prevalence of seizures is 5-40%
  • recent meta-analysis (Jette et al 2019): overall median period prevalence 12.1%, excluding those with syndromic epilepsy 11.2%, generally higher in females
• Link between epilepsy and autism first described in 1970s
  • Gubbay et al 1970 – 30% with seizures, 80% with abnormal EEG
  • Small 1975 – 64% with abnormal EEG
Epilepsy in autism – role of ID and CP

• Without ID or CP, risk of epilepsy 2% by 5 years and 8% at 10 years
• With ID, 7% at 1 year, 16% at 5 years, 27% at 10 years
• With both ID and CP, 20% at 1 year, 35% by 5 years, 67% at 10 years

(Tuchman and Rapin 2002)

• Most of the time epilepsy does not resolve with age
  • Remission in only 16% of adults

(Danielsson 2005)
When does epilepsy develop?

• Bimodal: infancy to age 5, second peak in adolescence
• Higher risk with concurrent intellectual disability, with suggestion of increasing risk with more severe impairment
  • 21.5% of patients with ID v 8% without (Cohen 2008)
• Can be any form of seizure (generalized, focal)
• No specific epilepsy type is more associated with ASD
• Children with ASD and a single non-febrile seizure have higher recurrence risk
Why does epilepsy develop?

• Epileptic encephalopathy can cause autism phenotype
  • Lennox-Gastaut, Dravet, ESES
    • Often lack the social impairment
  • Treatment of seizures and interictal discharges can sometimes lead to improvement in autism phenotype
    • Speaks to the impact of epileptiform discharges and seizures on social/cognitive functioning
• Epilepsy itself is a risk factor for autism
  • In children with TSC, having epilepsy increases risk of ASD
Family history of ASD and/or epilepsy

• In families with ASD, epilepsy rate of 12.8% in children with ASD and 2.3% in siblings without ASD
• Suggests a genetic link between epilepsy and ASD
• Another study showed epilepsy was independently associated with broader autism phenotype (autistic traits) in relatives
• Family history of epilepsy associated with an increase risk of epilepsy in those with ASD
Genetic syndromes with ASD and epilepsy

- Downs syndrome
  - Epilepsy in 8-13%, ASD in about 5-9%
- Phelan-McDermid syndrome (SHANK3)
  - Epilepsy prevalence unknown
  - Seizures more common if maternally inherited mutation on chromosome 22
- Fragile X
  - Epilepsy in 10-20%
- Tuberous sclerosis complex
  - Epilepsy in 80-90%, ASD in 20-60%
Genetic syndromes with ASD and epilepsy

- **PTEN**
  - Associated with macrocephaly and ASD
  - Can be associated with focal cortical dysplasias
- **MECP2** (Rett syndrome)
  - 50-90% with seizures
- **CDKL5** (atypical Rett)
  - Early onset epilepsy, usually infantile spasms
- **FOXG1**
  - Frequently present with infantile spasms
  - Can develop ASD even with successful treatment
- **SCN2A**
  - Varying spectrum of epilepsy from benign infantile epilepsy to Ohtahara syndrome
Why does epilepsy develop?

• Prenatal exposure to VPA increases risk of ASD
  • Role of modulation of excitation during fetal development

• Symptomatic infantile spasms, even when treated early, are more likely to be associated with later diagnosis of autism

• Suggests pathophysiologic role of epilepsy in development of autism
Why does epilepsy develop?

• Individuals with epilepsy more likely to have sibling or first-degree relative with ASD (Sundelin 2016)

• Role of maternal inflammation
  • Animal models: higher risk of ASD and epilepsy with prenatal infection (Mazarati)

• Aberrant neuronal networks
  • Overconnectivity or hyperconnectivity
  • Frontal location might be more predictive (Kanemura 2012)
Why does epilepsy develop?

- SPECT studies
  - used for seizure localization in children with refractory epilepsy
  - Can also reveal areas of hypometabolism
- May also identify areas of neuronal dysfunction in individuals with ASD
  - Temporal hypometabolism on PET
Why does epilepsy develop?

- Evidence from incidence of ASD in epilepsy
- Children with epilepsy underwent neuropsych testing
  - 21% met criteria for autism
  - 61% with ID, 28% were severe
- 26% had features of autism without meeting criteria for ASD
- ID was a significant predictor of ASD
  - Epilepsy may play a role in ID, thereby impacting ASD, not direct impact
- High rates of other neurobehavioral comorbidities
  - OCD, tics, ADHD

Reilly 2014
EEG in autism

• Routinely obtaining EEG is not considered standard of care in ASD
  • Only indicated if clinical suspicion for seizures
  • Some will also consider if history of regression
EEG in autism

- May be challenging to acquire recordings
  - difficulty with having head touched or being restrained
  - medical trauma/fear

- Routine versus overnight?
  - Longer studies more likely to find abnormalities

- Low utility of sedated EEGs
  - If sedating, might as well get longer study
Abnormal EEG in autism

• May be useful to guide treatment
  • Certain psychiatric medications can lower seizure threshold
  • Use of ASMs for behavior

• To treat the EEG or treat the patient?

• Some suggestion of higher association of interictal discharges with severity of behavior, presence of autistic regression (Baird 2006, Trauner 2014)
  • Studies have been difficult to replicate
Abnormal EEG in autism

• EEG abnormalities can be found in 6-61% without clinical seizures
  • In early studies, definition of “abnormality” was broader

• Can find focal discharges in about 17-20%, including spikes similar to those found in benign focal epilepsies of childhood
  • No association between localization of discharges (centrotemporal) and presence of language regression (Tuchman and Rapin 2002)

• Children with electrical status epilepticus in slow wave sleep (ESES) can present with autistic-like regression
  • May be misdiagnosed as autism and then “cured” with treatment
ESES and autism

- Regression reported in about 30% of patients with autism
  - Associated with abnormal EEG in about 20% (autistic regression with epileptiform EEG = AREE) but not ESES

- Some studies suggest higher rates of epilepsy in children with autism and regression, others with no correlation
  - Seizures more likely in those who have language regression after age 3
  - McVicar et al 2005: all patients with regression admitted for overnight vEEG over a 10-year period, only 10 children with ESES identified, only one had autism
Treatment considerations

• Medications with potential “beneficial” behavioral side effects:
  • Valproic acid – mood stabilization, migraine prophylaxis
  • Lamotrigine – mood stabilization
  • Topiramate – mood stabilization, OCD
  • Carbamazepine – mood neutral or stabilizing
  • Clobazam – anti-anxiety

• Other medications for specific epilepsy syndromes:
  • Ethosuximide (absence) – mood neutral
  • Vigabatrin (infantile spasms) - may be protective in TSC
  • Everolimus (TSC) – some trend to improving ASD
Treatment considerations

• Medications with potential “adverse” side effects:
  • Levetiracetam/brivaracetam – agitation/irritability*
    • Only develops in 15-20%
    • May actually reduce agitation if associated with epileptic encephalopathy
    • Also works as a spike suppressant
  • Valproic acid – easy bruising/bleeding
    • Also spike suppressant
  • Lamotrigine – activation
  • Perampanel – agitation/aggression
  • Clobazam – disinhibition
Other considerations

- ASD found to be a common comorbidity in patients with non-epileptic seizures in one study. Found high rate of concurrent neuropsychiatric disorders.

- May be related to alexithymia:
  - Difficulty in recognizing internal emotional states
  - Difficulty with social participation may lead to decompensation at times of social and academic pressure

- Clinicians working with NES should also screen for ASD

<table>
<thead>
<tr>
<th>Features of patients with and without ASD</th>
<th>Total (n=59)</th>
<th>ASD (n=10)</th>
<th>No ASD (n=49)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex female</td>
<td>37 (62.7%)</td>
<td>6 (60.0%)</td>
<td>31 (63.3%)</td>
<td>0.557</td>
</tr>
<tr>
<td>epilepsy</td>
<td>22 (37.3%)</td>
<td>3 (30.0%)</td>
<td>19 (38.8%)</td>
<td>0.406</td>
</tr>
<tr>
<td>age of first non-epileptic seizure</td>
<td>12.5 (5.4-17.5, 2.6)</td>
<td>11.8 (7.2-15.0, 2.7)</td>
<td>12.7 (5.4-17.5, 2.5)</td>
<td>0.291</td>
</tr>
<tr>
<td>co-morbid psychiatric illness (any)</td>
<td>30 (50.1%)</td>
<td>7 (70.0%)</td>
<td>23 (46.9%)</td>
<td>0.184</td>
</tr>
<tr>
<td>ADHD</td>
<td>5 (8.5%)</td>
<td>3 (30.0%)</td>
<td>2 (4.1%)</td>
<td>0.030*</td>
</tr>
<tr>
<td>tic disorder (any)</td>
<td>3 (5.1%)</td>
<td>3 (30.0%)</td>
<td>0</td>
<td>0.004*</td>
</tr>
<tr>
<td>intellectual disability</td>
<td>4 (6.8%)</td>
<td>2 (20.0%)</td>
<td>2 (4.1%)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

*except age, where n=45  *statistically significant
Conclusions

• Children with ASD are at higher risk for developing epilepsy than the general population

• No clear role for treatment of interictal discharges

• Regression does not necessarily equate underlying epileptic process, but epilepsy can be a risk factor for developmental regression

• Treatment can be specific for epilepsy type but also keeping in mind side effect profiles
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Thank you for attending!
A link to view the recording will be emailed to all registrants. We hope to see you next month!

Tuesday November 30
4:00 pm – 5:00 pm ET

AIR-P Presents: Utilizing a cross-system framework to guide research on autism and criminal justice intersections: implications for physical health outcomes

By Lindsay Shea, DrPH, MS; Dylan Cooper; Amy Blank Wilson, PhD, MSW