Seizures in Autism

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Seizures in Autism
• Prevalence of Seizures
• Age and Clinical Characteristics
• Common Seizure Types
• Seizures with Language Regression
  • Landau-Kleffner syndrome
  • Electrical Status Epilepticus during Slow Wave Sleep
• Subclinical Discharges
• Medical Causes of Seizures in Autism
• Treatment of Seizures in Autism

Prevalence of Epilepsy
Typically Developing Population 1-2%
Autism Spectrum Disorder up to 35%

Prevalence of an Abnormal EEG
Autism Spectrum Disorder up to 80%

Age and Gender Characteristics
Two Age Peaks:
Before age 5 years of age
Adolescents
Gender: Just as likely in Girls as Boys

Clinical Characteristics
More likely to have:
  • Another medical diagnosis
  • Lower Intelligence
  • More speech problems
Less likely to
  • be Aloof
  • have Poor Eye Contact

Long-term Studies
Adults diagnosed with Autism as Children
25%-38% had clinical seizures
If diagnosed with seizures as a child
  • Lower Intelligence
  • More maladaptive behaviors
  • Higher rate of psychotropic medications
Seizure Types

- Seizures
  - Partial
    - Complex Partial
  - Generalized
    - Secondary Generalization

Generalized (tonic-clonic) type Seizure

(from American Epilepsy Society)

Partial Seizure (Right temporal lobe)

Symptoms
- Focal motor seizures
- Staring Episodes
- Automatisms
- Auditory Agnosia
- Speech Arrest

Landau-Kleffner syndrome (model for autism)

- Frequent Spikes in the Temporal Region
- Language regression after 3 years of age
- Only Language skills affected
- Most have clinical seizures
- Controlling discharges on EEG sometimes results in return of language

(from Ballaban-Gill and Tuchman, 2000)

Electrical Status Epilepticus during Slow Wave Sleep (ESES)

- Generalized Discharges in 80% of slow wave sleep

(from Ballaban-Gill and Tuchman, 2000)

Subclinical Discharges

Specific Syndromes, such as Landau-Kleffner syndrome, are relatively rare.

Recent studies have shown that subclinical discharges are prevalent in children with Autism.

Other reports have suggested that the location of focal discharges correlate with specific symptoms.
Magnetoencephalography (MEG)

“Recording neuromagnetic signals is like listening for the footsteps of an ant in the middle of a rock concert”

Dewar filled with helium
Magnetically-shielded room

(From Lewine et al., Pediatrics, 1999)

Landau-Kleffner syndrome

(From Lewine et al., Pediatrics, 1999)

Example: Autism

Example: PDD-NOS

(From Lewine et al., Pediatrics, 1999)

Important Causes

Brain Malformations

Onset at Birth
Microcephally
Development Delay

Important Causes: Metabolic Disorders

Mitochondrial Disorders
1. Hypotonia, epilepsy, autism, and developmental delay (HEADD syndrome) 12 cases (Filano 2002). 42% large mtDNA deletions or multiple deletions 75% Complex III Deficiency
2. 15q11-13+ Complex III deficiency (Filipek, 2003)
3. Complex I+III deficiency (Poling, Frye et al., 2006)
4. ASD & Mito – 39% with seizures (Shoffner, 2009)
5. ASD & Mito – 20% with seizures (Weissman, 2009)

Relation to Complex III Deficiency?
**Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency** — Disorder of GABA Metabolism

**Symptoms**
- Developmental Delay from Early in Life
- Expressive Language Defects
- Hypotonia
- Ataxia
- Sleep Disturbances
- Movement Disorders
- Seizures

**Laboratories**
- 4-hydroxybutyric aciduria
- Elevated GHB (Gamma-hydroxybutyrate)

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**Important Causes: Metabolic Disorders**

**Adenylosuccinate lyase deficiency**

**Symptoms** — Disorder of Purine Metabolism
- Global Developmental Delay
- Very Happy disposition
- Excessive laughter
- Severe Speech Delay
- Seizure

**Laboratories**
- Urine Purines Elevation
- Succinylaminomimidazole carboxamide riboside (SAICAR)
- Succinyladenosine (S-Ado)

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**Important Causes: Metabolic Disorders**

**Cerebral folate deficiency**

**Antibody blocks folate from entering the brain**
- Early regression, decrease in head growth

**Testing**
- Antibody tests from Dr. Quados at SUNY Downstate
  Confirmation with Lumbar Puncture

**Treatment**
- Treat with Folinic Acid 1-2mg/kg/day
- Milk Free Diet

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**Important Causes: Metabolic Disorders**

**Cerebral folate deficiency**

- Pyridoxal deficiency
- Ataxia
- Instability
- Dyskinesias
- Retardation
- Action
**Important Causes: Genetic Disorders**

**Tuberous sclerosis complex: Multisystem disorder:**

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
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</thead>
<tbody>
<tr>
<td>Cerebral subependymomas</td>
<td>Multiple pils in dentinal enamel</td>
</tr>
<tr>
<td>Cortical tubers</td>
<td>Uncommon vascular malformations</td>
</tr>
<tr>
<td>Facial angiofibromas</td>
<td>Fine crenae</td>
</tr>
<tr>
<td>Hypomelanotic macules</td>
<td>Radial perigialat lines in</td>
</tr>
<tr>
<td>Hypomelanotic macules</td>
<td>Central white matter</td>
</tr>
<tr>
<td>Renal hamartomas</td>
<td>Cerebral hamartomas</td>
</tr>
<tr>
<td>Renal angiofibromas</td>
<td>Renal angiomyomatous patches</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>“Coffee bean” skin lesions</td>
</tr>
<tr>
<td>Subependymal</td>
<td>Multiple small cysts</td>
</tr>
<tr>
<td>Subependymal nodules</td>
<td></td>
</tr>
<tr>
<td>Digital TSC</td>
<td></td>
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</tbody>
</table>

**Definition:**
- TSC: Two major or one major plus two minor criteria.
- Probable TSC: One major plus one minor criteria.
- Possible TSC: One major or two minor features.

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**Important Causes: Genetic Disorders**

**Fragile X**

- **Males**
  - Distinct dysmorphism
  - Long coarse face
  - Big ears
  - Macroorchidism

- Increased CGG repeat on the FMR1 Gene
- X-linked
- Females with possible learning disabilities

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**Important Causes: Genetic Disorders**

**Rett Syndrome**

- **Females**
  - Developmental regression at 6-18 months
  - Acquired microcephaly
  - Periodic apnea / breath holding
  - Intermittent hyperventilation
  - Hand Stereotypies (wringing)

- Mutation in the MECP2 gene
- Possible mitochondrial disorder

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**Causes of subclinical discharges**

- **Metabolic and Mitochondrial Disorders**
- **Inflammatory**
  - Some children respond to steroids or IVIG
  - Specific antibodies (Endothelia) are sometimes found
- **Brain malformations**
  - Too small to see on clinical MRI but focal nature might suggest small cortical dysplasias exists
Endothelia Cell Antibody -- IgG
(Connolly et al., Bio Psych, 2006)

Endothelia Cell Antibody -- IgM
(Connolly et al., Bio Psych, 2006)

Seizures in Autism
Many Unanswered Questions
- Patient Characteristics
- Age of Onset
- Gender Ratio
- Associated Medical Conditions
- Types of seizures
- Relation to developmental regression
- Effect of Standard Antiepileptic Treatments
- Effect of Diet on Seizures
- Effect of Supplements on Seizures
- Effect of Alternative Treatments on Seizures

Treatments of Seizure
in Autism

- On-line web-based survey
  - Advertized on the ARI website
  - Average Completion Time 25 Minutes 26 Seconds
  - Total 737 Questions
  - Skip logic used to minimize questions.
- Asks about patient and seizure characteristics
- Asks about response to traditional and alternative treatments
- Each Treatment rated for effect on
  - Seizures
  - Sleep
  - Expressive Language
  - Receptive Language
  - Verbal Communication
  - Non-verbal Communication
  - Stereotypic and repetitive behavior
  - Rigidity, flexibility and adaptability
  - Hyperactivity
  - Attention
  - Mood
  - Side Effects and Frequency of Side Effects

Approximately 4:1 Boy to Girl ratio, similar to General Autism

Approximately Three-Quarters Diagnosed with Autism Disorder
Factors Associated with Regression

About one-third with Regression, Similar to the general autism population

Factors Associated with Regression:
- Seizures
- Fainting
- Head Trauma
- Vomiting

Routine EEG Most Prevalent Clinical Test
18% Diagnosed without a Clinical Test

Clinical Seizure Treatments

Antiepileptic Drugs (Cluster 1)
- Valproic Acid
- Lamotrigine
- Levetiracetam
- Ethosuxamide
- Phenytoin
- Clonazepam
- Carbamazepine
- Oxcarbazepine
- Topiramate
- Gabapentin
- Zonisamide
- Felbamate
- Phenobarbitol

Non-Antiepileptic Drugs (Cluster 2)

Antiepileptic Drugs (Cluster 1)
- AED Subcluster 1
- AED Subcluster 2
- AED Subcluster 3

AED Subcluster 1
- Valproic Acid
- Lamotrigine
- Levetiracetam
- Ethosuxamide

AED Subcluster 2
- Phenytoin
- Clonazepam
- Carbamazepine
- Oxcarbazepine
- Topiramate
- Gabapentin
- Zonisamide
- Felbamate

AED Subcluster 3
- Phenobarbitol

(Frye and Adams, submitted)
**Survey of Treatments for Seizures in Autism**

(Frye and Adams, submitted)

### Non-Antiepileptic Drugs (Cluster 2)

<table>
<thead>
<tr>
<th>Non-AED Subcluster 1</th>
<th>Non-AED Subcluster 2</th>
<th>Non-AED Subcluster 3</th>
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<tbody>
<tr>
<td>Ketogenic Diet</td>
<td>Ketogenic Diet / Atkin’s Diet</td>
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<tr>
<td>Atkins Diet</td>
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<tr>
<td>GFCF</td>
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<tr>
<td>HBOT</td>
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</tr>
<tr>
<td>Vitamin B6, IVIG</td>
<td>Steroids</td>
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<tr>
<td>L-Carnitine &amp; Acetyl-L-Carnitine</td>
<td>CoQ10, Vitamin B12</td>
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<tr>
<td>CoQ10, Vitamin B12</td>
<td>L-Carnosine, Chelation</td>
<td>Glutathione, SCD</td>
</tr>
<tr>
<td>Dimethylglycine</td>
<td>Magnesium, SHTP</td>
<td>Magnesium, SHTP</td>
</tr>
<tr>
<td>Taurine, GABA</td>
<td>L-Carnosine, Chelation</td>
<td>Glutathione, SCD</td>
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<td>Chelation, Glutathione</td>
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<tr>
<td>VNS</td>
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(Frye and Adams, submitted)

### Treatments for Subclinical Seizures

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<td>Oxcarbazepine</td>
<td>Taurine, Magnesium</td>
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<td>Chelation, Glutathione</td>
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<td>Lamotrigine</td>
<td>GFCF, Ketogenic Diet / Atkin’s Diet</td>
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(Frye and Adams, submitted)
Mood in Subclinical Seizures

- Chelation therapy
- GFCF
- Vitamin B6
- Taurine
- Glutathione
- Steroids
- Vitamin B12
- Lamotrigine
- Magnesium
- Ketogenic diet/Atkin's diet
- Coenzyme Q10
- Topiramate
- L-carnitine
- Oxcarbazepine
- Carbamazepine
- Valproic acid
- Levetiracetam

- Improvement
- No effect
- Worsening