Objectives:

- Background
- Pathophysiology of ASD in Epileptic patients
- Association between Epilepsy and ASD
- EEG changes in ASD
- Treatment of epilepsy in ASD patients
Epilepsy is a common childhood disorder.

The prevalence is estimated to be 2-3% in general population.

Epilepsy in children with autistic spectrum disorders (ASD) is more common and range from 8-38%.
Historical Background

- Autism was tied to epilepsy in Kanner’s initial description of autism over 60 years ago.
- The initial studies on the relationship of autism to epilepsy and to electroencephalogram (EEG) abnormalities in the 1960s.
- In 1960, epilepsy was classified as a neurological versus mental disorder in the WHO classification system for epilepsy.
Historical Background

- Early efforts to classify autism were led by Lorna Wing who introduced the concept of the “autism triad” and highlighted common impairments in social, language and repetitive behaviors among children with cognitive deficits

Definitions

- Epilepsy: is a chronic disorder characterized by the tendency for spontaneous, recurrent seizures and requires at least two unprovoked seizures to be considered as a diagnosis.

- The DSM-IV-TR has 3 key criteria for the diagnosis of autistic disorder:
  - Impairments in social interaction
  - Impairments in communication
  - A restricted, repetitive range of interests, behaviors, and activities
Why are seizures so common in children with ASD?

The heterogeneous etiologies of ASD and epilepsy make it unlikely that a single common mechanism explains seizure predisposition in both disorders.

Recent genetic studies point to numerous, diverse gene mutations that have autism and epilepsy as joint sequelae.

Pathophysiology of ASD in Epileptic patients

- A common neurobiological antecedent
  - structural or developmental lesions
  - genetic susceptibilities
  - environmental insults
- Abnormal brain circuitry underlying ASD could predispose the brain to seizures
### Pathophysiology of ASD in Epileptic patients

- **Neuropathological Studies from Post-mortem patients of with autism showed cortical malformation, Polymicrogyria and megalencephaly.** A. Bailey et al Brain (1998), 121, 889–905

<table>
<thead>
<tr>
<th>Case</th>
<th>Cortical dysgenesis</th>
<th>White matter</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slightly irregular laminar pattern in superior frontal gyrus with clusters of abnormally orientated pyramidal cells. White matter/layer 6 boundary poorly defined.</td>
<td>Numerous patches of ectopic grey matter and increased numbers of single neurons</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Thickened cortex and increased neuronal density. Increased numbers of neurons in lamina 1 of frontal cortex, including inverted pyramidal cells.</td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Increased neuronal density and mild focal disturbance of laminar pattern in frontal cortex</td>
<td>Patch of nerve cells deep in the deep white matter of anterior frontal cortex. Increased number of single neurons.</td>
<td>Small shallow focus of gliosis in frontal cortex. Larger area of gliosis involving full cortical thickness in one occipital lobe.</td>
</tr>
<tr>
<td>4</td>
<td>Thickened cortices and increased neuronal density in frontal cortex and cingulate gyri. Laminar pattern of superior temporal gyrus disorganised.</td>
<td>Subpial gliosis.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Increased number of single neurons in superior temporal gyrus.</td>
<td>Numerous corpora amylacea within subpial zone and molecular layer of insular cortex.</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Increased number of white matter neurons.</td>
<td></td>
</tr>
</tbody>
</table>
Pathophysiology of ASD in Epileptic patients

- Independent Epilepsy
  - ASD
- Common Pathway Epilepsy
  - ASD
- Epilepsy Causation
  - Epilepsy
  - Epileptiform discharges
- Developmental ASD
  - Epilepsy
  - Autistic Regression

Genetic
Lesional
Multifactorial
The Association between Epilepsy and ASD

- The frequency of epilepsy in ASD range from 5-38%.
- The age peak from 1-5 years and > 10 years and adolescent
- All seizure types can be associated with autism like complex partial, atypical absence, myoclonic, and tonic-clonic seizures

Examples for seizure types:
Be careful ....

Not all the abnormal movements are seizures
• The prevalence of autism in children with epilepsy around 27% and it increased in patients with mental retardation.

• The developing brain is well known to be more susceptible to seizures than the mature brain. Holmes GL. Epilepsia 1997; 38: 12–30.

• Epileptiform discharges on electroencephalography (EEG) without clinical seizures can cause behavioural and cognitive impairment.

The Association between Epilepsy and ASD

Autistic spectrum disorder subtypes and risk of epilepsy

Autistic disorder (AD)
Classic autism with incapacitating deficits in all three behavioural domains: (1) sociability, (2) language and imagination, (3) cognitive and behavioural flexibility. Symptoms are present from infancy or the toddler years (< 3 years). Early unexplained regression of language and sociability is reported by about a third of parents. Clinical epilepsy develops by adolescence in more than a third of children, its risk is tied to the severity of the underlying brain dysfunction.6

Asperger’s syndrome
Autism without mental retardation or delayed language development. There are no specific studies on risk of epilepsy but extrapolation from the studies on risk factors for autism2 suggest that the likelihood for developing epilepsy is 5–10% in early childhood.

Pervasive developmental disorder not otherwise specified
Generally milder autism that does not fit criteria for any other subtype. The risk of epilepsy is probably linked to the severity of the underlying brain dysfunction.6

Disintegrative disorder
Severe autism acquired between ages 2 and 10 years after entirely normal early development of language, sociability, and cognition. The risk of epilepsy may be as high as 70%.10

Rett’s syndrome
Specific X-linked genetic defect strongly associated with mutations of the MeCP2 gene. It affects postnatal brain growth, resulting in severe mental retardation, motor deficits, and other features. The risk of epilepsy is more than 90%.11

Roberto Tuchman and Isabelle Rapin
The Association between Epilepsy and ASD

- Autism
- Epilepsy
- Disintegrative Disorder
- ESES
- BRET
- Developmental Language Disorder
- LKS
Landau-Kleffner Syndrome (LKS)

- Acquired aphasia, seizures, and an epileptic electroencephalogram
- A language regression between the age of 2-8 years. Peak age is 4-5 years
- Progressive loss of speech in a previously well child
- Patients tend to have partial onset seizures, atypical absence
- Epileptiform EEG abnormalities and/or clinical seizures
EEG changes:
EEG changes:
Psychiatric symptoms in LKS

- Hyperactivity, inattentiveness, impulsivity and aggression
- Abnormal social behaviors resembling autistic symptoms.
- Psychiatrist described it as "the symptom of autism" secondary to a medical condition, or a depressive adjustment disorder.
The differences Between ASD & LKS:

<table>
<thead>
<tr>
<th></th>
<th>ASD</th>
<th>LKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of regression</td>
<td>18-24 months</td>
<td>3 years</td>
</tr>
<tr>
<td>Regression affect</td>
<td>behavioral</td>
<td>Only language</td>
</tr>
<tr>
<td>Epileptiform activity</td>
<td>Centro-temporal, Infrequent</td>
<td>Fronto-temporo-parietal, Frequent</td>
</tr>
</tbody>
</table>
Treatment:

- Anti–Epileptic Drugs:
  - IV Ig
  - Steroid
  - Surgery
Outcome

- Epilepsy usually well controlled
- Language deficits usually persist; sometimes correlated with the epileptiform EEG
Electrical Status Epilepticus in Sleep (CSWS)

- An epileptic disorder characterized by specific EEG abnormalities which is associated with language, cognitive and behavioral regression in children

- Global regression in cognitive and/or motor skills

- Age 3 - 14 years with a peak age of 5 - 7 years

- Up to one third of children with CSWS have a preceding neurologic condition, such as meningitis or neonatal encephalopathy
EEG changes:
EEG criteria

- Various SWI criteria are proposed by different authors for ESES.
- The commonly used definition in clinical studies is "bilateral secondarily generalized 1.5 to 4.5 Hz spike-waves occurring during greater than 85% of slow wave sleep.
- Focal, multifocal, unilateral, asymmetric/symmetric bilateral, diffuse, or more restricted.
- The ESES/CSWS pattern may be continuous, fragmented, or periodic.
Psychiatric symptoms in CSWS

- Severe decline in IQ, short term memory deficits and poor reasoning
- The language impairment includes an expressive aphasia as well as difficulties with lexical and syntactic skills
- Reduced attention, hyperactivity, disinhibition and aggression
- Motor deficits and apraxia, ataxia, dystonia, dyspraxia
Seizure type in CSWS:

- Seizures can present in many types; partial onset or secondarily generalized, typical or atypical absence
- Focal MRI abnormalities have been reported
Treatment

- Anti-Epileptic Drugs: Valproic Acid, Levetiracetam, and Clobazam
- IV Ig
- Steroid
- Surgery
Benign Childhood Epilepsy with Centrotemporal Spikes (Rolandic epilepsy)

- Age: 5-9 years
- Remission: By 16 years of age
- Nocturnal seizures with sensory motor symptoms involving the face and oropharynx
- EEG:
- Treatment:
EEG in ASD

- Normal EEGs are frequently seen
- Paroxysmal epileptiform activity (spike, spike-wave, polyspikes, and polyspikes and waves)
- Rossi et al. studied EEG finding in 106 patients with ASD found:
  - 57.5% had no seizure and no paroxysmal activity
  - 18.9% had central, temporal and parietal spikes as seen in benign epilepsy of childhood with centro-temporal spikes (BRECT) *Epilepsia, 48*(Suppl. 9):33–35, 2007
EEG in ASD
EEG in ASD

- Occipital spikes similar to those seen in benign occipital epilepsy of childhood were seen on video-EEG monitoring in 17% \( \text{Nass et al., 1998} \)
• Some studies suggest that epileptiform discharges on EEG without clinical seizures can cause behavioural and cognitive impairment


• It is very important to do EEG in patients with ASD in order to exclude possibility of some epileptic encephalopathy
We can divide the cases as following:

- ASD patient who has clinical seizure and EEG abnormalities
- ASD patient who has no clinical seizure but EEG abnormalities
Treatment of epilepsy in ASD patients

- ASD patient who has clinical seizure and EEG abnormalities:
  - The treatment of epilepsy in ASD children is not different from the treatment of other children with epilepsy
  - The choices of Anti-Epileptic Drugs (AED) depend on clinical semiology of seizure as well as EEG abnormalities
Treatment:

- Choices of anti-epileptic medications
- Start with small dose and build up slowly
- Explain to the parents possible side effects
- Educate the parent about how to manage the attack of seizure
What to do during a convulsion:

**First Aid for Seizures**

**During a Convulsion**

A person falls, their body becomes rigid, muscles jerk, and breathing may become shallow.

What should you do?

- Stay calm. Most seizures last less than five minutes.
- Do not restrain the person during the seizure.
- Protect the person from injury. If possible, ease the person to the floor. Move hazardous objects out of their way.
- As soon as possible, gently roll the person onto their side.
- Loosen anything around their neck and remove their eyeglasses.
- Check for medical identification: a medical bracelet or necklace.
- Do not put anything in their mouth. A person cannot swallow their tongue.
- Afterwards, talk gently to comfort and reassure the person. Stay with them until they are re-oriented.
## Table 1 Drug options by seizure type

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>First-line drugs</th>
<th>Second-line drugs</th>
<th>Other drugs that may be considered</th>
<th>Drugs to be avoided (may worsen seizures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised tonic–clonic</td>
<td>Carbamazepine*</td>
<td>Clozapine</td>
<td>Acetazolamide*</td>
<td>Tiagabine*</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine*</td>
<td>Levetiracetam</td>
<td>Clonazepam*</td>
<td>Vigabatrin*</td>
</tr>
<tr>
<td></td>
<td>Sodium valproate</td>
<td>Oxcarbazepine*</td>
<td>Phenobarbital*</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>Ethosuximide</td>
<td>Clonazepam</td>
<td>Phenytoin*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamotrigine*</td>
<td>Topiramate*</td>
<td>Primidone*</td>
<td></td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Sodium valproate</td>
<td>Clozapine</td>
<td></td>
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<tr>
<td></td>
<td>(Topiramate*)</td>
<td>Levetiracetam</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Oxcarbazepine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic</td>
<td>Lamotrigine*</td>
<td>Clonazepam</td>
<td>Acetazolamide*</td>
<td>Carbamazepine*</td>
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<tr>
<td></td>
<td>Sodium valproate</td>
<td>Levetiracetam</td>
<td>Phenobarbital*</td>
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<td></td>
<td></td>
<td>Topiramate*</td>
<td>Phenytoin*</td>
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<td>Atonic</td>
<td>Lamotrigine*</td>
<td>Clozapine</td>
<td>Acetazolamide*</td>
<td>Carbamazepine*</td>
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<td></td>
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<td>Phenobarbital*</td>
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<td></td>
<td></td>
<td>Topiramate*</td>
<td>Primidone*</td>
<td></td>
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<tr>
<td>Focal with/without secondary</td>
<td>Carbamazepine*</td>
<td>Clozapine</td>
<td>Acetazolamide*</td>
<td>Carbamazepine*</td>
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<td>generalisation</td>
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<td>Gabapentin</td>
<td>Phenobarbital*</td>
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<tr>
<td></td>
<td>Sodium valproate</td>
<td>Phenytin*</td>
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<td></td>
<td></td>
<td>Tiagabine</td>
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</tbody>
</table>
Treatment of epilepsy in ASD patients

- There are several clinical reports of the use of valproic acid in children with autism with or without clinical seizures but with epileptiform abnormalities on the EEG


In a double-blind placebo controlled study with lamotrigine in children with autism without seizures, no favorable effects were observed on the outcome measures for autistic symptoms

ASD patient who has no clinical seizure but EEG abnormalities

- Controversial issue ??

- A limited number of clinical reports on the effectiveness of valproate in reducing overactivity instability and impulsivity in children with autism and abnormal electroencephalograms

- There are reports that the language of limited numbers of children with LKS and of those with autism has improved in response to anticonvulsants, especially valproic acid, ethosuximide, and benzodiazepines

Marescaux C et al  Epilepsia 1990; 31: 768–77
ASD patient who has no clinical seizure but EEG abnormalities

No definite recommendations can be made
Is there any other modality of treatments?

- Epilepsy surgery
- Vagal Nerve stimulation
- Ketogenic diet
Treatment of epilepsy in ASD patients

- **Surgical treatment:**
  - Surgery may improve the seizures but not the autism
  - Multiple subpial transections used in patient with LKS however it is not well validated
Medically refractory epilepsy in autism

*Gemma Sansa, *Chad Carlson, †Werner Doyle, †Howard L. Weiner, *Judith Bluvstein,
*William Barr, and *†Orrin Devinsky

Departments of *Neurology and †Neurosurgery, NYU Langone School of Medicine, New York, New York, U.S.A.

SUMMARY

Purpose: Epilepsy and electroencephalographic abnormalities are frequent in idiopathic autism, but there is little information regarding treatment-resistant epilepsy (TRE) in this group. We sought to define the clinical and electrophysiologic characteristics and treatment outcomes in these patients.

Methods: We retrospectively reviewed clinical and laboratory data of patients with idiopathic autism evaluated at NYU Epilepsy Center during a 20-year period.

Key Findings: One hundred twenty-seven patients had idiopathic autism and at least one epileptic seizure; 33.9% had TRE and 27.5% were seizure free. The remaining 38.6% of patients had infrequent seizures or insufficient data to categorize. Patients with TRE had a significantly earlier onset of seizures than seizure-free patients, and a trend for more developmental regression and motor and language delays. Three patients had surgical resection (two had limited improvement and one had no improvement) and one had an anterior callosotomy (no improvement). Vagus nerve stimulator (VNS) implantation provided limited improvement (2 patients) and no improvement (7).

Significance: This study found that TRE is common in idiopathic autism and more common with early age of seizure onset. Relatively few patients underwent surgical resection due to multifocal partial epilepsy, comorbid generalized epilepsy, or limited impact of ongoing partial seizures given other problems related to autism. Our small sample suggests that surgical and VNS outcomes in this group are less favorable than in other TRE populations.

KEY WORDS: Autism, Seizures, Epilepsy surgery.
127 patients identified

33.9% had Treatment Resistant Epilepsy (TRE)

27.5% were seizure free

38.6% had infrequent seizures

Earlier onset seizures were in TRE patients

3 patients had surgery, 1 with no improvement

9 had VNS, 2 patients with limited improvement
Surgery and VNS outcomes are less favorable than in other TRE populations
Outcome:

Epilepsy in Young Adults with Autism: A Prospective Population-based Follow-up Study of 120 Individuals Diagnosed in Childhood

*Susanna Danielsson, †I. Carina Gillberg, †Eva Billstedt, ††Christopher Gillberg, and *Ingrid Olsson

Departments of *Pediatrics and ††Child and Adolescent Psychiatry, Queen Silvia Children’s Hospital, Göteborg, Sweden; and †St. George’s Hospital Medical School, London, England
Outcome:

- 108 patients included
- 43 pat. ASD with Epilepsy
- 65 pat. ASD without Epilepsy
- Both the cognitive level and the adaptive behavior level were lower in the epilepsy group than in the nonepilepsy group
- Remission of epilepsy was seen in 16%
Conclusion:

- Epilepsy is common and should be routinely investigated in patients with ASD.
- Epilepsy and ASD share a common pathway and genetic susceptibility and environmental factors play a role in pathophysiology of both conditions.
- Epileptic encephalopathy and epileptic syndromes like LKS, CSWS should be rolled out in patients with ASD.
- The treatment of epilepsy in ASD children is not different from the treatment of other children with epilepsy however the choices of antiepileptic drugs may be different.
Thank You

fbashiri@ksu.edu.sa