IDIOPATHIC GENERALIZED EPILEPSY

MONTIDA VEERAVIGROM, MD
IGE

• Genetically determined epilepsy syndrome
• Prevalence 15-30% of all patients with epilepsy
Characteristics

• Characterized by different combinations of primary generalized seizure types
  – Absence seizures (AS)
  – Generalized tonic clonic seizures (GTCS)
  – Bilateral myoclonic seizures (BMS)
• Age dependent seizure onset
• Typical pathological EEG pattern
• Lack of apparent MRI abnormalities
Characteristics

• Interictal EEG showed generalized epileptiform discharge
• Neurological exam and intelligence were normal
• Highly response to appropriate AED treatment
IGE

• Underemphasize topic for adult neurologist
• Lack of attention because of
  – Easily controlled than symptomatic partial and
generalized epilepsy
  – Thought to be pediatric problem. However, large
  number of patient continue to have seizure during
  adult life.

Overview: idiopathic generalized epilepsies.
Mattson RH.
IGE Syndrome

- Childhood Absence Epilepsy (CAE)
- Juvenile Absence Epilepsy (JAE)
- Juvenile Myoclonic Epilepsy (JME)
- IGE with GTCS on awakening
Childhood Absence Epilepsy (CAE)

- 10% to 17% of all cases of epilepsy diagnosed in school-aged children
- CAE, with some exceptions, is clearly more frequent in girls than in boys (11.4% vs. 2.5%).
- CAE usually begins between 4 and 10 years with a peak at 5-7 years.
Clinical Presentation

• The striking impairment of consciousness is the essential feature of absence seizures in CAE.

• Other associated ictal clinical features in CAE consisted of
  – staring
  – 3-Hz regular eyelid movement
  – eye opening that usually occur in an inconsistent manner during seizure.
  – Automatisms occur frequently in CAE during longer seizures or during hyperventilation
Clinical presentation

- Mild clonic or tonic movements often occur during the first seconds of the absence seizure.
- Atonic falls never occur.
Seizure Duration

• Seizure duration is influenced by factors
  – provocation (hyperventilation and intermittent photic stimulation)
  – state of arousal
  – sleep deprivation
  – medication
  – individual factors.

• Seizure duration of less than 4 seconds or more than 30 seconds is not typical of CAE.
Exclusion Criteria

• The presence of seizures other than typical absence seizure such as generalized tonic-clonic seizure (GTCS) or myoclonic jerks before or during the active stage of absences.

• Eyelid and perioral myoclonia and single violent jerks.
Ictal EEG

- The typical pattern is a bilaterally synchronous and symmetrical discharge of rhythmic 3-Hz spike-wave complexes that start and end abruptly.
- Hyperventilation and intermittent photic stimulation induce absence seizures in 83% and 21% of patients, respectively.
Interictal EEG

• The interictal EEG in CAE is characterized by a normal background activity.
• Interictal paroxysmal activity consisting of fragments of generalized spike-wave discharges can be documented in up to 92% of patients.
• Focal epileptiform interictal discharges may be present.
• Occipital intermittent rhythmic delta activity
Neuropsychological/cognitive aspects

• cognitive and linguistic impairment as well as behavioral disorders

• Cognitive difficulty
  – The attentional domain
  – The executive functions
  – Verbal memory
  – Visuospatial memory

• Language and reading disabilities

• ADHD, Depression, Anxiety disorder.
Pathophysiology

• An intact thalamocortical circuitry is required for the generation of typical spike-wave discharges.

• In two series, epilepsy was found in 17% of first-degree relatives of patients affected by CAE.

• In studies on twins
  – 84% of monozygotic twins showed typical spike-wave discharges on EEG recordings
  – 75% developed absence seizures.
Genetics

• Although CAE is genetically determined, the precise mode of inheritance and the genes involved remain largely unidentified.

• GABA A and B receptors (GABRG2, GABRA1, GABRB3, GABA_{A(B1)}, GABA_{A(B2)}) which are involved in the generation of spike wave discharge.

• Ca channels (CACNA1 A, CACNA1 H, CACNA1 G, CACNA1I, and CACNG3) contribute to “thalamocortical dysrhythmia,”
Evolution and Prognosis

- Excellent prognosis
- Remission rate range from 56-84%
- Callenbach et al., noted in their prospective study
  - total duration of epilepsy 3.9 years
  - and mean age at final remission 9.5 years
- 7% still have seizures after 12-17 years of follow-up
Prognostic factor

• Poor
  – absence status
  – late onset of absence seizures (more than 8 years)
  – an abnormal background activity on EEG
  – multiple spikes
  – focal abnormalities

• Good
  – prompt seizure control after introduction of an appropriate AED treatment.
Treatment

- Ethosuximide
- Valproate
- Ethosuximide and valproate
- Lamotrigine
  - Two double-blind, randomized controlled clinical trials comparing the efficacy, tolerability, and neuropsychological effects of ESM, VPA, and LTG in children with newly diagnosed CAE
    - VPA and ESM were more effective than LTG
    - ESM was associated with fewer cognitive side effects.
    - These studies indicate that ESM is the optimal initial empiric monotherapy for CAE
Treatment

• Levetiracetam
  – One RCT showed moderate efficacy for absence seizure control
  – Auvin et al., however, reported six children with CAE who showed an aggravation of absence seizures after starting LEV.

• Topiramate
  – Only class III and IV evidence to support the use of TPM in absence seizures
  – in a recent pilot study of TPM in CAE, Piña-Garza et al. showed that, although well-tolerated, TPM monotherapy was ineffective for absence seizures.
Treatment

- **Zonisamide**
  - Although some authors have suggested that ZSM is effective for absence seizures, there are no well-controlled studies evaluating its efficacy and tolerability in these types of seizures.

- **Contraindicated AEDs**
  - Phenytoin, Phenobarbital
  - CBZ, Oxcarbamazepine
  - Gabapentin, Vigabatrin, Tiagabine

GLUT1 Deficiency

- Glucose Transporter Type I Deficiency syndrome
- Early onset absence seizures
- Refractory absence seizures
- Low CSF glucose
- Treatment: Ketogenic diet
Juvenile Absence Epilepsy

- Appears between age 10 and 16 years (average 13)
- This clinical condition has a strong genetic component (linkage to chromosomes 5, 8, 18, and 21).
- The absences of JAE are not phenomenologically different from the absences of CAE.
  - Clinically less frequent (sporadic)
  - Less severe impairment of consciousness.
  - They tend to be of longer duration than those in CAE.
Juvenile Absence Epilepsy

- No significant differences in sex distribution.
- Clinically isolated absences are rare.
- 46% also have generalized TCS and sporadic myoclonic jerks.
- In most cases absence seizures precede the onset of TCS
- 25% TCS precede the occurrence of absences.
Juvenile Absence Epilepsy

• TCS are often precipitated by sleep deprivation or awakening.
• Interictal EEG abnormalities are mostly slow waves >3 Hz.
• The prognosis of this syndrome is good; although seizures tend to persist for many years.
• Patients have a good response to antiepileptic drugs.
Juvenile Myoclonic Epilepsy

- Relatively common epilepsy syndrome, comprising 5–10% of all epilepsies.
- Age of onset is similar to JAE, namely 12–18 years with an average of 15 years.
- The hallmarks of JME are single or arrhythmical bilateral myoclonic jerks with retained consciousness.
Juvenile Myoclonic Epilepsy

- Patients often also have generalized TCS.
- Absence seizures are present in 1/3 of the cases.
- Seizures may be precipitated by disturbances of the sleep-wake cycle, such as sleep deprivation or by alcohol abuse.
- Reflex seizures in this syndrome include
  - photosensitivity (up to 50%)
  - praxis (≥30%)
  - perioral reflex myoclonias (∼ 25%)
  - eye-closure sensitivity (3–4%).
Ictal EEG

• Characterized by polyspike and waves $\geq 3$ Hz.
Interictal EEG

• It is not specific: all types of generalized epileptiform discharges may be present.
Treatment and Prognosis

• Excellent response to adequate AED treatment but this treatment may need to be continued.

• Even if the patient has been free of seizures for many years, there is a high risk of relapse if the antiepileptic medication is stopped.

• Valproate: first line treatment

• Alternative: Lamotrigine, Levetiracetam
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age at onset (years)</th>
<th>Predominant seizure types</th>
<th>EEG</th>
<th>Response to AED, Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAE</td>
<td>4 – 10</td>
<td>Typical absence seizures, Rare GTC seizures</td>
<td>3-Hz spike and wave</td>
<td>Good; most remit by adolescence</td>
</tr>
<tr>
<td>JAE</td>
<td>10-17</td>
<td>Typical absence seizures, Infrequent myoclonus, Infrequent GTC seizures</td>
<td>3 – 4-Hz spike and wave</td>
<td>Good; easy to control but tend to persist through life</td>
</tr>
<tr>
<td>JME</td>
<td>10-16</td>
<td>Myoclonus, GTC, absence seizures in ~ 1/3 of patients</td>
<td>3.5 – 4-Hz spike and polyspikes</td>
<td>Good; easy to control but usually persist through life</td>
</tr>
</tbody>
</table>

**Beydoun A1, D'Souza J.**  
*Treatment of idiopathic generalized epilepsy - a review of the evidence.*  
IGE with GTCS on awakening

• Tends to present at a somewhat later age than JAE and JME.
• Age of onset - 28 years, with a peak at 17 years.
• Generalized TCS occur predominantly within 1–2 h after awakening; the second seizure peak is during the evening.
• Most patients (81%) have, in addition, absences or myoclonic jerks (or both).
IGE with GTCS on awakening

- A genetic predisposition is frequent.
- There are nonspecific bilateral epileptiform patterns in the EEG.
- In this syndrome, a response to adequate antiepileptic medication is good.

Beghi M1, Beghi E, Cornaggia CM, Gobbi G.  
Idiopathic generalized epilepsies of adolescence.  
Syndromes of Idiopathic Generalized Epilepsies Not Recognized by the International League Against Epilepsy

- IGE with absences of early childhood
- IGE with phantom absences
- Perioralmyoclonia with absences
- Eyelid myoclonia with absences

Panayiotopoulos CP
IGE with absences of early childhood

• An epileptic condition characterized by absences with onset in early childhood, before the age of 4.
• Absence of neurologic and cognitive deficits.
• Possible occurrence of GTCS, myoclonic jerks, and myoclonic–astatic seizures (in about 40% of children)
IGE with absences of early childhood

• IctalEEG showing irregular 3–4 Hz spike-and-wave complexes that end progressively in a sequence of slow waves

• A family history of IGE and generalized spike-wave abnormalities in the EEG of unaffected members.

• This condition bears a worse prognosis than CAE.
IGE with phantom absences

• “phantom absences” has been introduced to define absence seizures so mild and short-lasting to be barely perceived by the patient or the observer.
• Approximately 2–4 s without other clinical features.
• Might be the cardinal manifestation of a specific epileptic syndrome characterized also by infrequent generalized tonic–clonic seizures, usually appearing in adulthood, and absence status epilepticus
IGE with phantom absences

• Recognition of this condition may be difficult, as phantom absences may be undetected even by the patient himself.

• Whereas the confusional state associated with absence status may be interpreted as a focal seizure (particularly when the interictal EEG shows focal abnormalities), which eventually ends with a secondary generalization.
Idiopathic generalized epilepsy (IGE) syndromes in development: IGE with absences of early childhood, IGE with phantom absences, and perioralmyoclonia with absences
Idiopathic generalized epilepsy (IGE) syndromes in development: IGE with absences of early childhood, IGE with phantom absences, and perioralmyoclonia with absences
Perioralmyoclonia with absences

- The symptom of perioralmyoclonia may rarely occur in absence seizures of other IGEs.
- GTCS that often start early prior to or together with the absences
- Frequent occurrence of absence status epilepticus (ASE)
- Resistance to treatment
- Persistence in adult life.
- No photosensitivity
Syndromes of Idiopathic Generalized Epilepsies Not Recognized by the International League Against Epilepsy

Woman aged 18 with perioral myoclonia with absences from age 11 years

Video-EEG

Mild jaw myoclonic jerks

Marked jaw and mild eyebrow jerks

Woman aged 23 with perioral myoclonia absence status

Mildly confused with continuous perioral twitching

Epilepsia

Eyelid myoclonia with absences (Jeavons syndrome)

• Jeavons clearly delineated this condition: “Eyelid myoclonia and absences show a marked jerking of the eyelids immediately after eye closure and there is an associated brief bilateral spike and wave activity .... Brief absences may occur spontaneously ... accompanied by 3/sec spike-waves. The spike-waves ... after eye closure do not occur in the dark. Their presence in the EEG is a reliable warning that abnormalities will be evoked by photic stimulation” (Jeavons, 1977).
Charateristics

- Eyelid myoclonia (EM) with or without absences
- Eye closure-induced electroencephalography (EEG) paroxysms
- Photosensitivity
- In addition, rare tonic–clonic seizures may also occur.
Characteristics

- EMA onset is typically in childhood, with a peak at 6–8 years.
- Eyelid jerks are frequently misinterpreted as tics or mannerisms, and absences may be overlooked.
- Treatment: Levetiracetam, Zonisamide
- Some patient: poor response to treatment
Eyelid myoclonia with absences (Jeavons syndrome): A well-defined idiopathic generalized epilepsy syndrome or a spectrum of photosensitive conditions?