Generalized Epilepsy Semiology

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Why classification? And How

- Better diagnosis and management of seizures and epilepsy
- the clinical features of epilepsy are categorized into three levels:
    - the seizures
    - the epilepsies
    - the epilepsy syndromes

definition

- **Seizures:** transient symptoms and signs due to abnormal excessive or simultaneous neuronal activity
- **Epilepsy:** recurrent unprovoked seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition.
    - The diagnosis of epilepsy requires at least two unprovoked seizures occurring greater than twenty-four hours apart

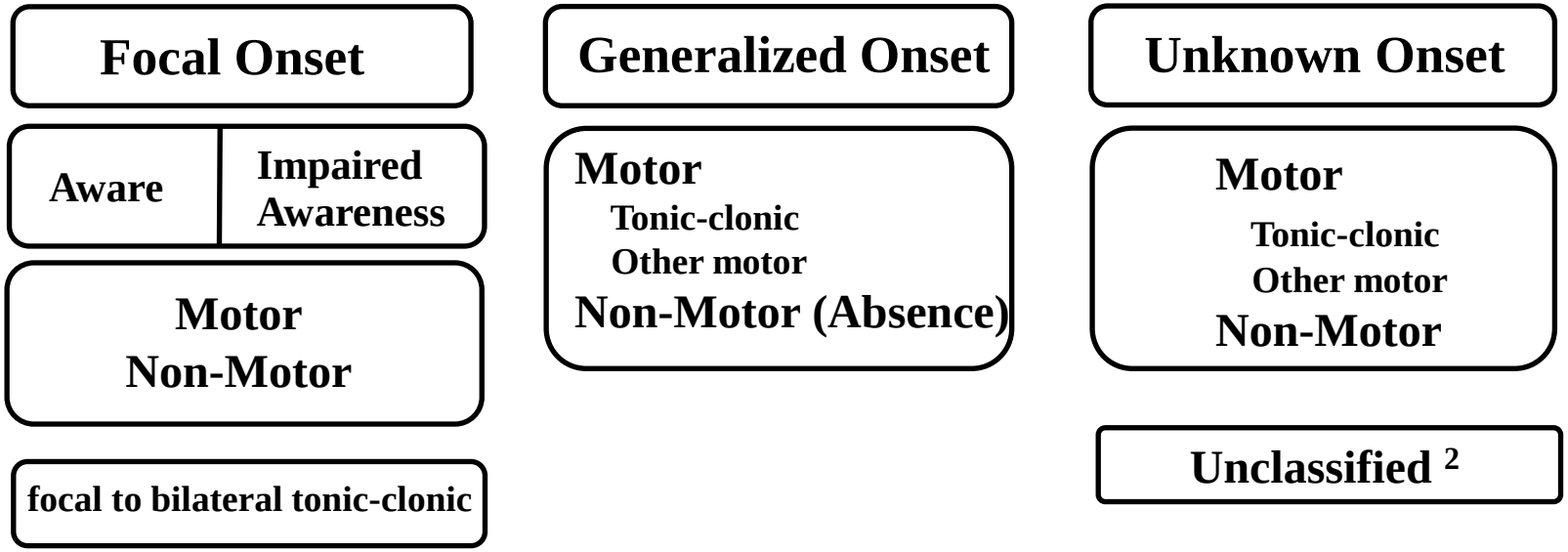
factors are considered during the classification of epilepsy

- mode and age of onset,
- seizure pattern,
- family history,
- EEG,
- MRI findings

Framework of the Classification

1. Seizures (focal onset, generalized onset, unknown onset)
2. Epilepsies (focal, generalized, combined generalized, and focal, unknown)
3. Epilepsy syndromes
4. Etiology (structural, genetic, metabolic, infectious, immune, unknown)

ILAE 2017 Classification of Seizure Types Basic Version [1]



[1] Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

[2] Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

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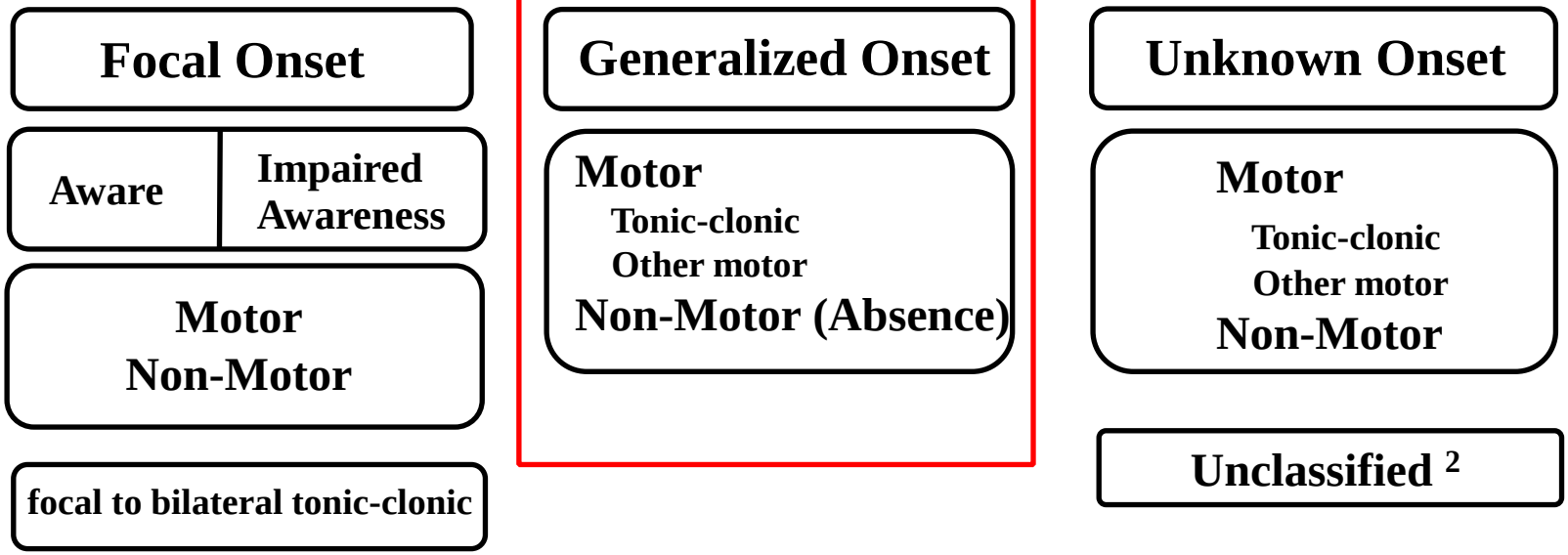

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ILAE 2017 Classification of Seizure Types Expanded Version[1]

Focal Onset

Aware	Impaired Awareness

Motor Onset

- automatisms
- atonic[2]
- clonic
- epileptic spasms[2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset

- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor

- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms[2]

Non-Motor (absence)

- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor

- tonic-clonic
- epileptic spasms

Non-Motor

- behavior arrest

Unclassified[3]

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.

2 These could be focal or generalized, with or without alteration of awareness

3 Due to inadequate information or inability to place in other categories

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Some Seizure Onsets can be Focal or Generalized

Focal Onset

atonic

clonic

epileptic spasms

myoclonic

tonic →

tonic-clonic

Generalized Onset

atonic

clonic

epileptic spasms

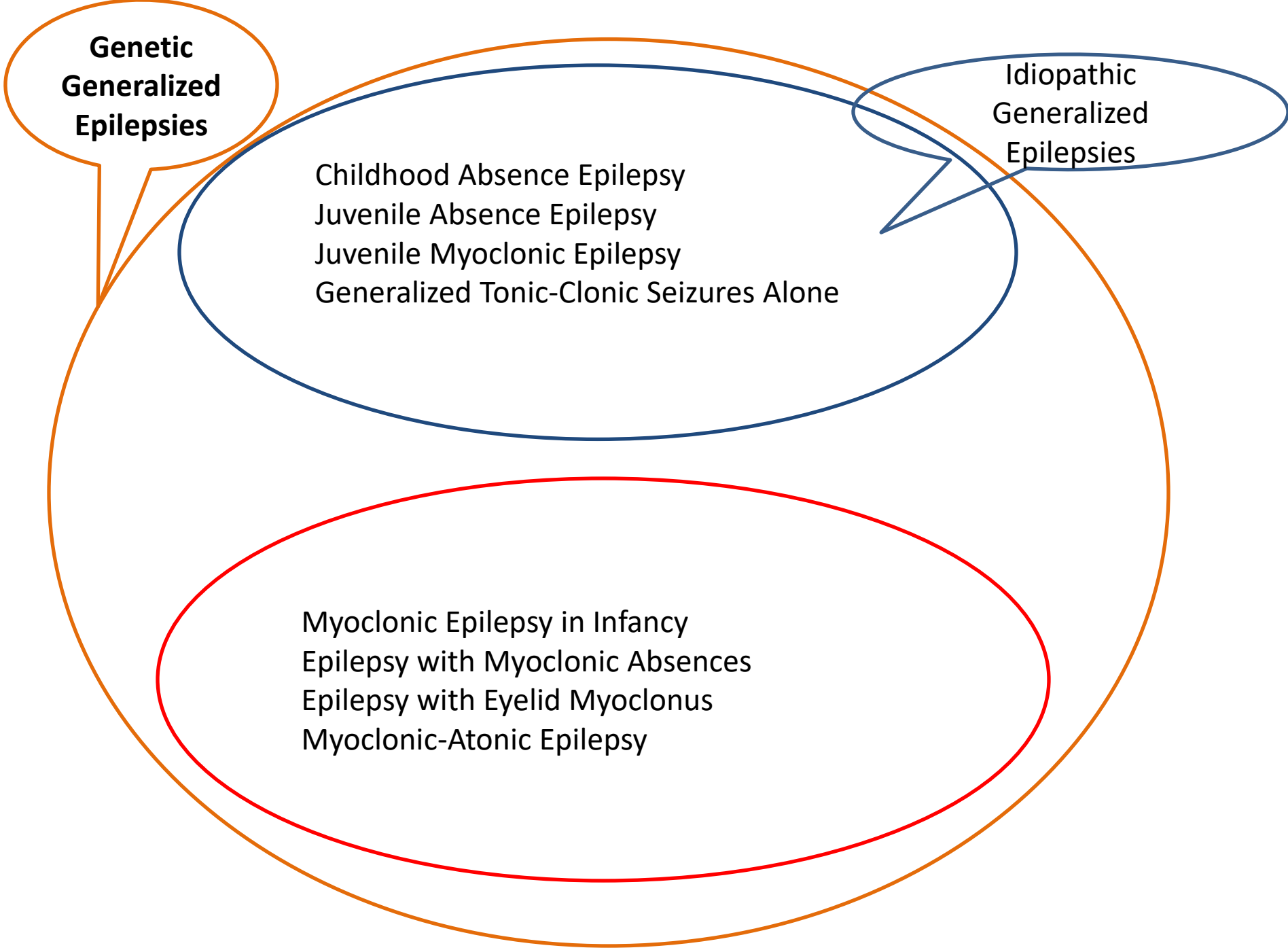
myoclonic

← tonic

tonic-clonic

Loss (or Impairment) of Consciousness

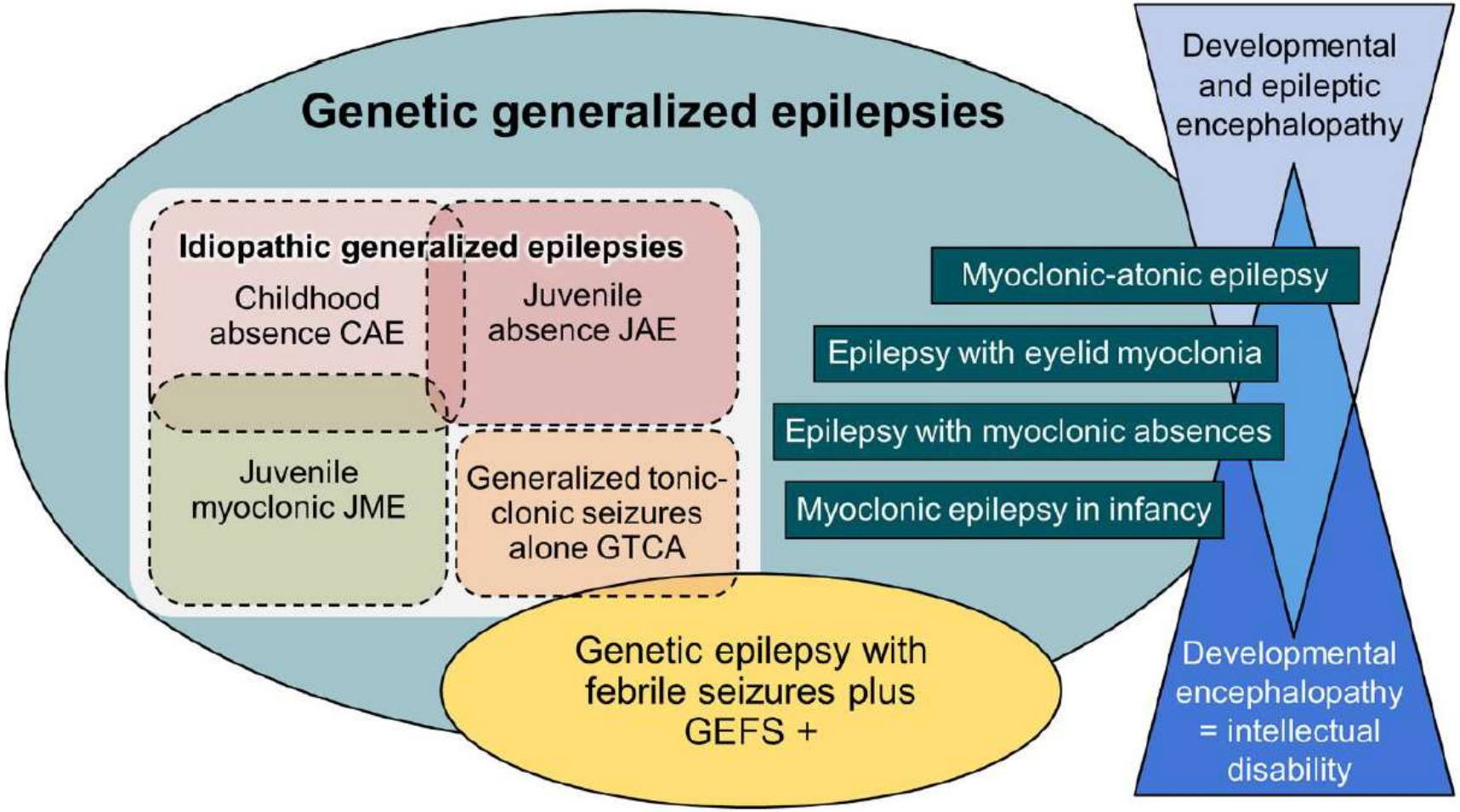
Two types of seizures with loss of consciousness

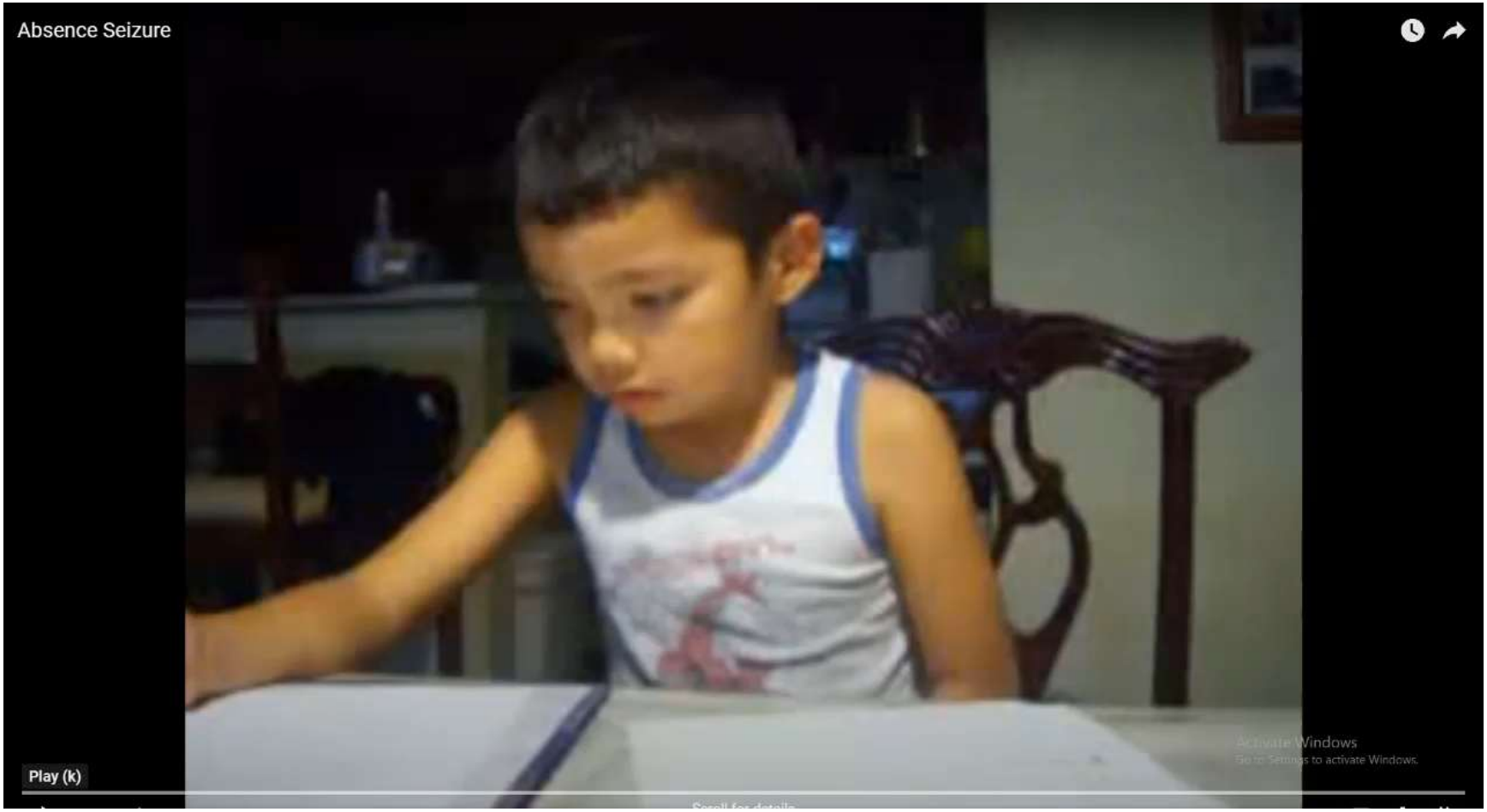

Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
Childhood Absence Epilepsy
Juvenile Absence Epilepsy
Juvenile Myoclonic Epilepsy
Generalized Tonic-Clonic Seizures Alone
Myoclonic Epilepsy in Infancy
Epilepsy with Myoclonic Absences
Epilepsy with Eyelid Myoclonus
Myoclonic-Atonic Epilepsy

Idiopathic Generalized Epilepsies

1. Childhood Absence Epilepsy
2. Juvenile Absence Epilepsy
3. Juvenile Myoclonic Epilepsy
4. Epilepsy with Generalized Tonic-Clonic Seizures Alone

- **GGE (Genetic Generalized Epilepsies)**
  - Patients that do not fulfill criteria for one of above syndromes, but that have one, or a combination, of the following generalized seizure types


Genetic generalized epilepsies
Idiopathic generalized epilepsies
Childhood absence CAE
Juvenile absence JAE
Juvenile myoclonic JME
Generalized tonic-clonic seizures alone GTCA
Genetic epilepsy with febrile seizures plus GEFS +
Developmental and epileptic encephalopathy
Myoclonic-atonic epilepsy
Epilepsy with eyelid myoclonia
Epilepsy with myoclonic absences
Myoclonic epilepsy in infancy
Developmental encephalopathy = intellectual disability


Absence Seizure
Play (k)
Activate Windows
Go to Settings to activate Windows.

Childhood Absence Epilepsy (CAE)

Epidemiology CAE

- 18% of epilepsy in school-aged children

Clinical Context CAE

- Age at onset: typically 4-10 years (range: 2-13 years)
  - *onset at age 10 and older, the distinction between CAE and JAE depends on the frequency of absence seizures.*
- CAE is more common in *girls* (60-75% cases)
- history of febrile seizures: in 10-15% of children
- Development is typically **normal**
  - *may have* specific learning difficulties and ADHD; both may be ***subtle and easily missed***
- In cases with onset of absence seizures under 4 years, a diagnosis of glucose transporter 1 deficiency disorder (associated with *SLC2A1* pathogenic variants) is found in 10% of patients

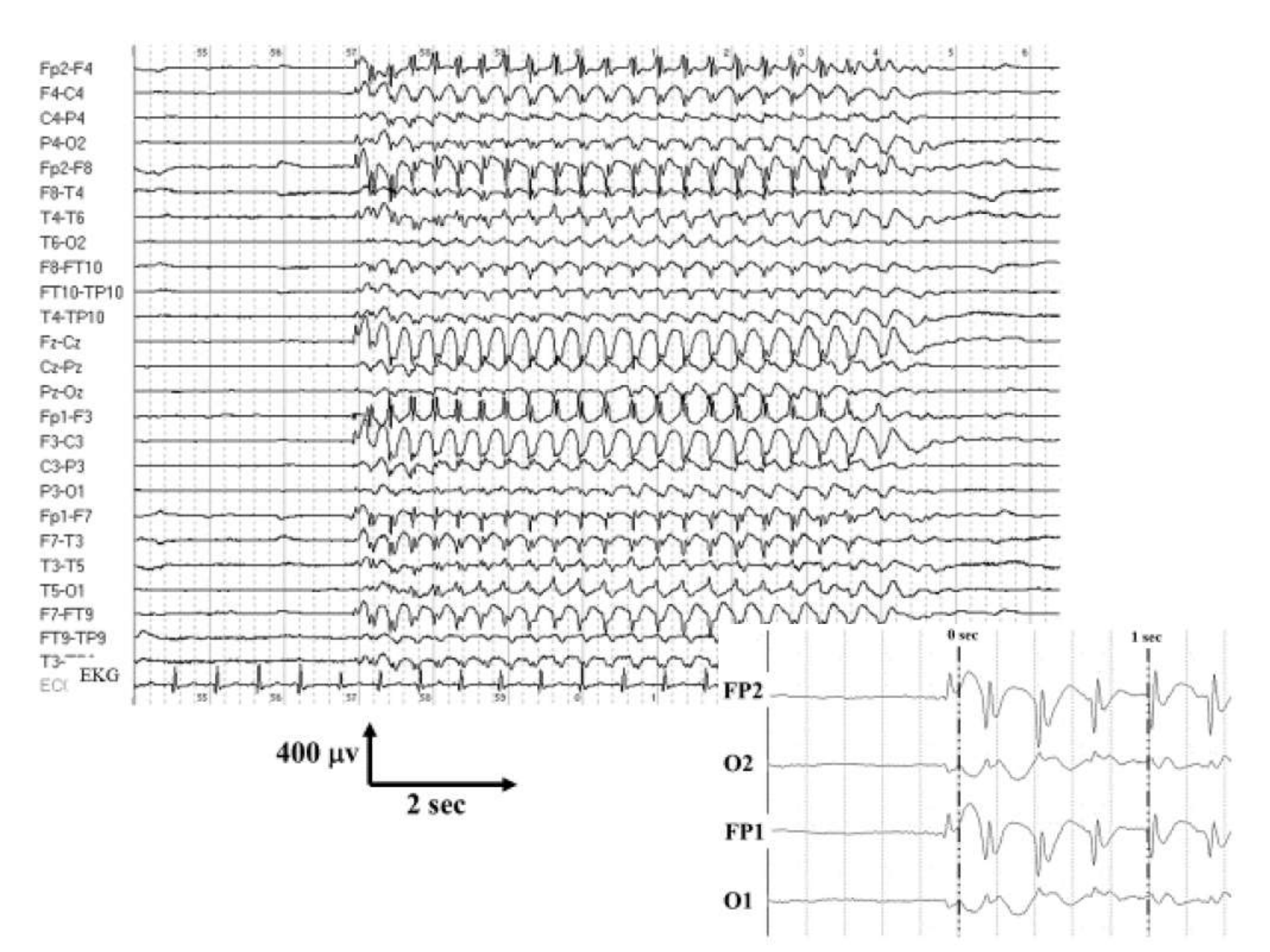
Seizure Types CAE

- *sudden onset* of impaired awareness, with staring, loss of facial expression, interruption of activity, with or without oral and manual automatisms, and immediate return to normal activity, although children may be *momentarily confused*
- Duration: typically 3-20 seconds
- *Incontinence* and *loss of postural control* can be seen
- Generalized tonic-clonic seizures rarely precede or occur during the period of frequent absence seizures in childhood.
  - *More commonly, they begin in adolescence, often after resolution of absence seizures, and may herald evolution to another IGE syndrome (eg. JME, JAE, GTCA)*

- Myoclonic seizures, other than subtle myoclonus occurring during an absence seizure are not seen in CAE.
- Prominent myoclonus during absence (ratcheting up of both upper limbs with tonic posturing) should suggest a rare seizure type, myoclonic absences, which are seen in the **syndrome Epilepsy with Myoclonic Absences**

EEG *of* CAE

- The background is normal
  - (OIRDA) occurs in 21-30% {at a frequency of 2.5-4 Hz }
- Paroxysms of 3 Hz (range 2.5-4 Hz) generalized spike-wave are seen which may become fragmented in sleep
  - Polyspike-wave may be seen in drowsiness and sleep only, but not during wakefulness
  - IPS triggers generalized spike-wave in 21%
  - Disorganized discharges, brief (<1 second) or transient interruptions in the ictal rhythm, or waveforms of different frequency or morphology are significantly less common than in JAE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FT10-TP10
T4-TP10
Fz-Cz
Cz-Pz
Pz-Oz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
F7-FT9
FT9-TP9
EKG
400 µv
2 sec
0 sec
1 sec
FP2
O2
FP1
O1

- If an untreated child performs hyperventilation well for three minutes and no generalized spike-wave is seen, childhood absence epilepsy can be excluded.

Imaging OF CAE

- **Normal**
- When considered imaging?
  - atypical features of CAE,
  - if seizures are drug-resistant
  - if there is persistent focal slowing on EEG

Genetics Of CAE

not part of current routine diagnostic evaluation

- genes conferring risk for CAE are know
  - GABRG2, GABRA1, SLC2A1
- some recurrent copy number variants
  - 15p13.3 microdeletion
- **When considering Genetic?**
  - if absence seizures begin under 4 years (eg. *SLC2A1* testing)
  - if there are atypical features such as intellectual disability, movement disorders, or drug resistance
  - if there is a strong family history of seizures

Differential diagnoses Of CAE

- Epilepsies:
  - Epilepsy with Eyelid Myoclonia
  - Epilepsy with Myoclonic Absences
  - Other Generalized Epilepsies with Atypical absence
  - Juvenile Absence Epilepsy
  - Focal impaired awareness seizures

- *Non-epileptic disorders:*
  - Daydreaming
  - Inattention
  - Ocular tics

Juvenile Absence Epilepsy

- occur less than daily in the untreated state
- associated with >3 Hz (range 3-5.5.5 Hz) generalized spike-wave in an otherwise normal adolescent.
- Generalized tonic-clonic seizures are seen in more than 90% of cases,
    - most commonly **beginning shortly after onset of absence** seizures.
- Neurological examination is normal.
    - Development and cognition are typically normal although ADHD and learning difficulties may occur.
- seizures may be controlled with anti-seizure medications, lifelong treatment is typically required.

Epidemiology of JAE

- JAE is less common than CAE, accounting for 2.4-3.1% of new-onset epilepsy

Clinical context:

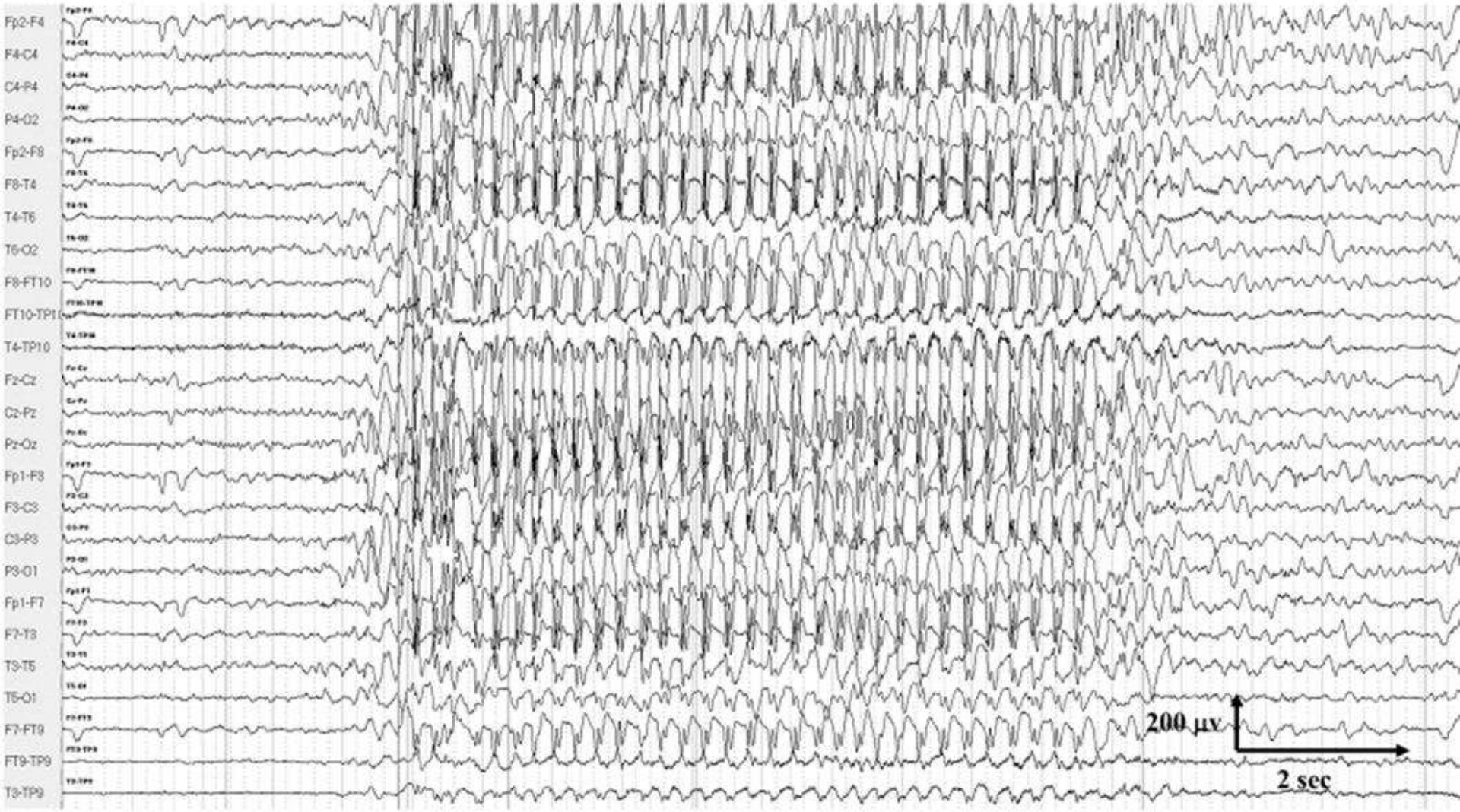
- Typical age at onset is between 9-13 years, with a range of 8-20 years
- < 9 Year difficult to Different
    - EEG features are similar however in CAE; OIRDA is not seen and generalized discharges may be of slightly higher frequency and more irregular in JAE.
- Development and cognition prior to presentation are typically normal.
    - Significant cognitive impairment should suggest an alternate diagnosis.
- PMH of febrile seizures: 6-33% of cases

Seizure Types

- Absence seizures are mandatory
  - abrupt onset of impaired awareness, staring with loss of facial expression, interruption of activity, with/without oral automatisms, and immediate return to normal activity
    - Loss of awareness is **often less complete** than in CAE (may be *able to respond to commands but has difficulty doing complex tasks*)
- Typical duration: 5-30 seconds, with occasional longer
- Frequency is typically **less** than daily
- Subtle myoclonus may be seen during an absence seizure
- Absence status epilepticus: ~ 20%
- Generalized tonic-clonic seizures **> 90%**
    - GTCS usually after onset of absences, (in 14-27% precede)

EEG

- Interictal:
  - The *background is normal*
  - Paroxysms of GSW 3-4 Hz (range 3-5.5 Hz) are seen which may become fragmented in sleep
  - Generalized discharges: enhanced by sleep deprivation both in awake and sleep recordings
  - In untreated patients, hyperventilation provokes absence seizures in approximately 87%
  - Intermittent photic stimulation triggers generalized spike-wave in 25% of individuals
  - Slow spike- wave (<2.5Hz) is not seen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Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
F7-FT9
FT9-TP9
T3-TP9
200 µv
2 sec

EEG

- Ictal:
  - Generalized spike-wave at > 3-5.5 Hz occurs at onset of absence seizures
  - *Disorganized discharges* are eight times more common in JAE than CAE
  - If a staring spell occurs without EEG correlate, an absence seizure can be ruled out for that event
  - The EEG during generalized tonic-clonic seizures is similar to that seen with GTC alone

Neuroimaging:

- Neuroimaging is **normal**
- When Imaging considered?
  - if atypical features of JAE
  - drug-resistant seizures are present,
  - presence of persistent focal slowing on EEG

Genetic studies:

- not part of the current routine diagnostic evaluation
- Polygenic
  - Genes conferring risk for this syndrome include *GABRG2*, *GABRA1*, *CACNA1A* and *SLC2A1*)

Differential diagnoses Of JAE

- Epilepsies:
  - CAE
  - JME
  - Epilepsy with Eyelid Myoclonia
  - Epilepsy with Myoclonic Absences
  - Other Generalized Epilepsies with Atypical absence
  - Epilepsy with GTCS Alone
  - Focal impaired awareness seizures
- *Non-epileptic disorders:*
  - Daydreaming
  - Inattention
  - Ocular tics

Features in Childhood and Juvenile Absence Epilepsy

		CAE	JAE
Age at onset	Usual	4-10	9-13 years
	Range	2-13 (caution if <4 years)	8-20 years
Development		*Typically normal, but may have learning difficulties or ADHD*	
Absences	Frequency	At least **daily to multiple per day**	**Less than** daily
	Duration	3-20 seconds	5-30 seconds
	Impaired awareness	**Severe** loss	**Less** complete
Other seizure types	-Febrile	Occasional	Occasional
	Generalized tonic clonic seizure	Rarely precede	May precede and commonly occur during
	Myoclonic	***Prominent myoclonus exclusionary***	

Features in Childhood and Juvenile Absence Epilepsy

		CAE	JAE
EEG	Backgroun	OIRDA in 21%	Normal
Epileptiform discharge	Awake	2.5-4 Hz generalized spike-wave	3-5.5 Hz generalized spike-wave
	-Asleep	Polyspike and wave may be seen in drowsiness and sleep only	Polyspike and wave may be seen in drowsiness and sleep only
	Irregular GSW	Uncommon	More common than CAE
Photoparoxysmal response		Rare	Rare
	IPS triggers GSW but does not induce seizures	15	25
Hyperventilation induction		87%	87%


INTERNATIONAL
LEAGUE
AGAINST
EPILEPSY
ILAE
Established 1909

Juvenile Myoclonic Epilepsy (JME)

- the most common ***adolescent and adult*** onset IGE

Epidemiology: JME

- approximately 9.3% of all epilepsies
  - the most common adolescent and adult onset IGE

Clinical context : JME

- Typical age at onset is 10-24 years, (8-40)
- slight female preponderance.
- *5-15%* evolve from CAE to JME.
- If myoclonic seizures start before the age of 8 years, *another diagnosis* should be considered.
- A history of febrile seizures ~ 4-5%
- PMH & cognition are typically normal
  - Progressive decline in cognition after seizure onset should suggest a progressive myoclonic epilepsy

Natural History : JME

- drug responsive : 67-92% of patients with JME
  - Myoclonic seizures may be more difficult to control than generalized tonic-clonic seizures
- **trigger of seizure** is sleep deprivation, tiredness
- Sodium channel blockers such as CBZ, OXC, PHT aggravates myoclonic and absence seizures
- Lamotrigine may aggravate myoclonic seizures
- a lifelong disorder

Seizure Types of JME

- Myoclonic seizures: mandatory for diagnosis
  - may be unilateral or bilateral.
    - frequently involving the upper extremities, involve the lower limbs and cause falls
    - can be reflex, triggered by photic stimulation or praxis
  - Myoclonic status epilepticus can occur rarely
- GTCS: >90%
    - often preceded by a series of myoclonic seizures that increase in frequency and severity resulting in a myoclonic-tonic-clonic seizure.
    - often occur on awakening or with sleep deprivation
    - Generalized tonic-clonic status epilepticus is uncommon
- Absence seizures occur in one third of cases


INTERNATIONAL
LEAGUE
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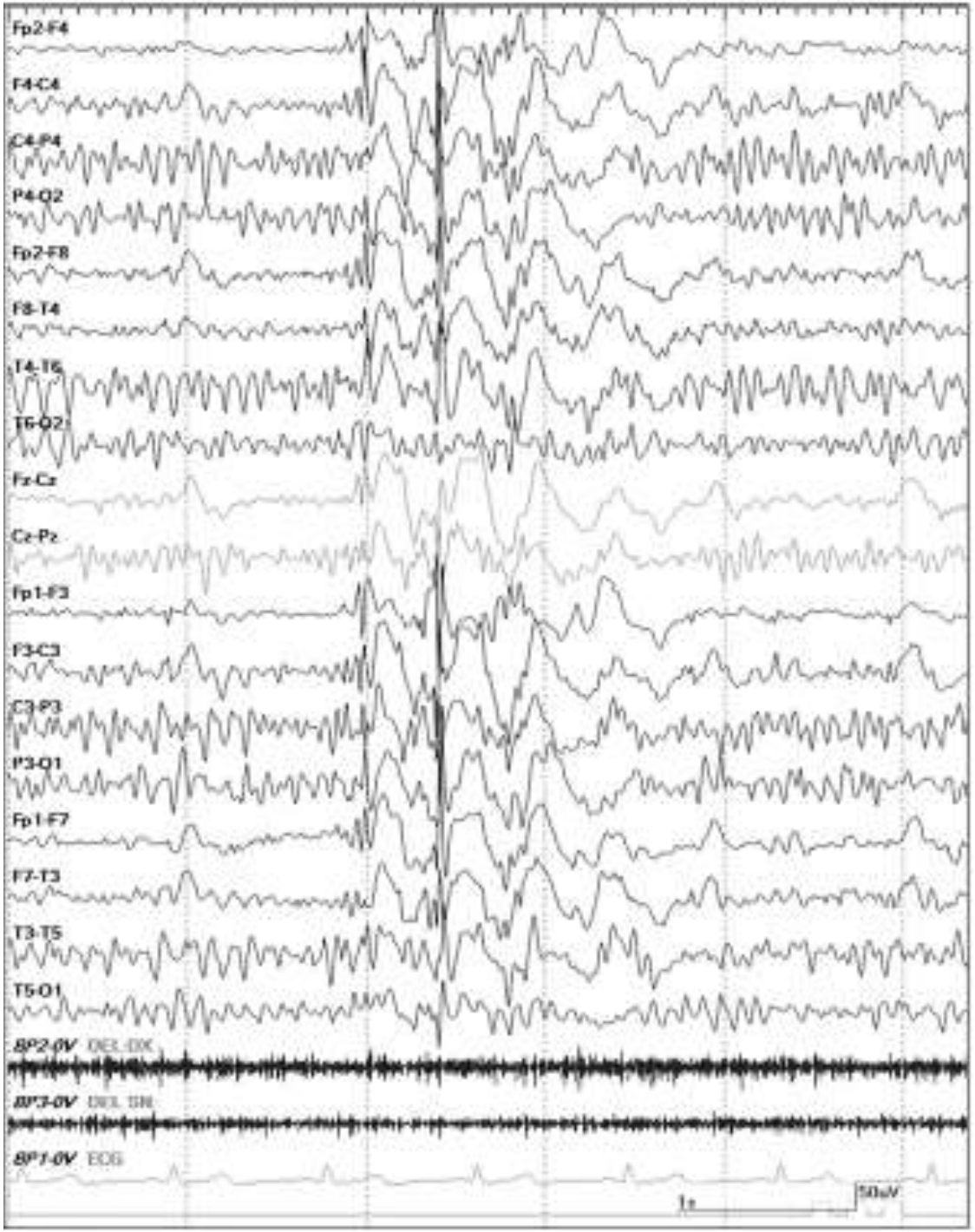
EPILEPSY
ILAE
Established 1909

EEG

- Interictal:
  - GSW activity, typically with generalized polyspike-wave (GPSW), is mandatory for a definitive diagnosis
    - Irregular, GPSW and SW(>3-5.5 Hz), both wakefulness and sleep
    - is brought out by sleep deprivation.
    - In sleep, the discharges often fragment
  - A photo-paroxysmal response to IPS > one third
    - with specialized testing in up to 90% of untreated patients
      - IPS may induce myoclonic seizures, eyelid myoclonia and rarely, GTCS
  - Hyperventilation may provoked: GSW-GPSW-and clinical absence seizures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P3-O1
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BP1-0V
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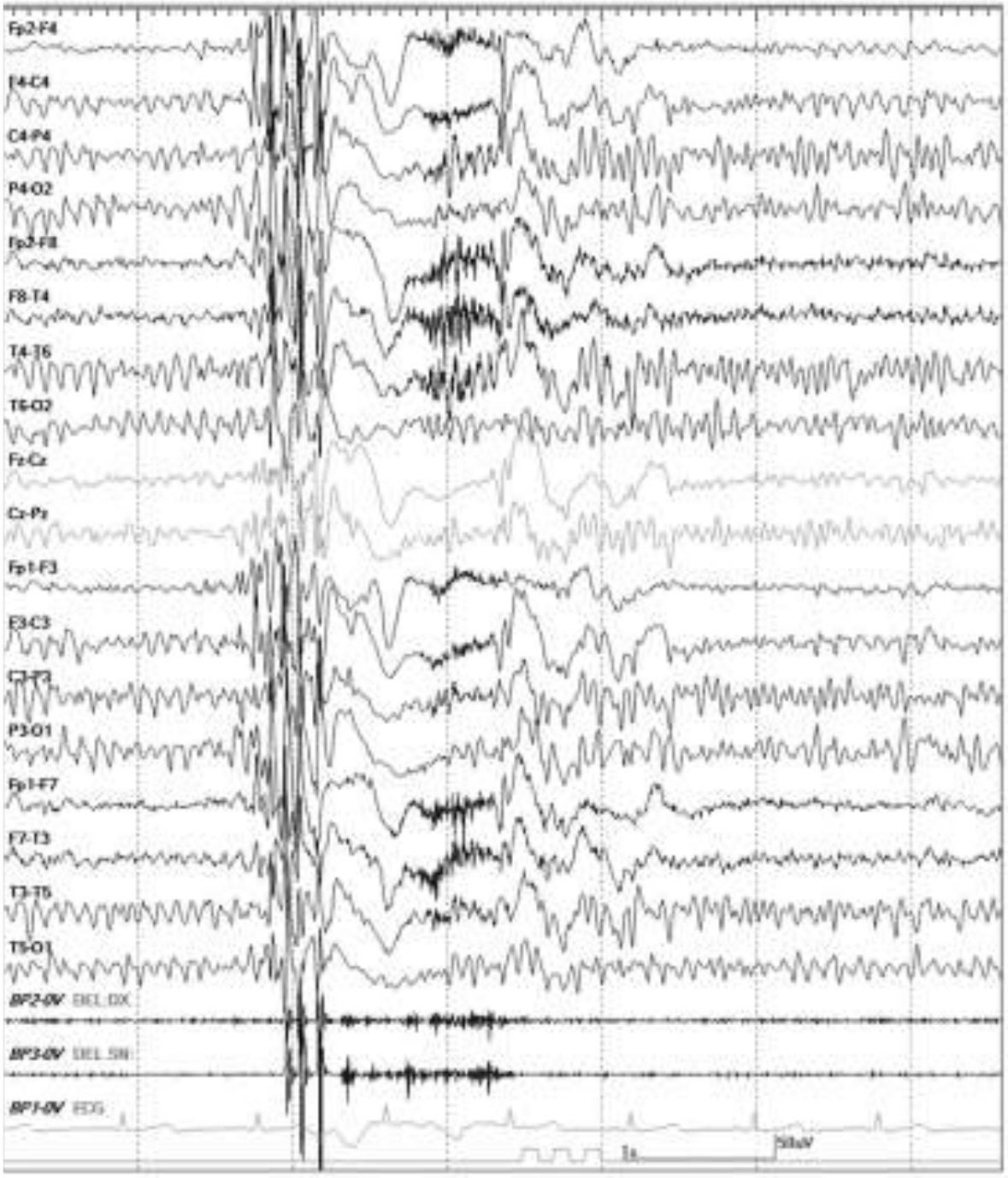
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C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
BP2-0V DEL DX
BP3-0V DEL SN
BP1-0V ECG
1s
50uV

Neuroimaging

- Neuroimaging is **normal**
- When imaging is mandatory?
  - if atypical features of JME
  - drug-resistant seizures are present
  - persistent focal slowing on EEG

Genetic findings

- is not part of the current routine diagnostic evaluation
  - susceptibility alleles for JME
    - Rare pathogenic variants
      - *CACNB4*, *GABRA1*, *GABRD* and *EFHC1*
    - recurrent microdeletions,
      - 15q13.3, 15q11.2 and 16p13.11

Differential diagnoses

- *Other Epilepsies*
  - Myoclonic Epilepsy in Infancy
  - JAE
  - GTCS alone
  - Epilepsy with Eyelid Myoclonia
  - Epilepsy with Myoclonic Absences
  - Progressive Myoclonic Epilepsies
  - Epilepsy with reading-induced seizures
  - Late-onset Lennox-Gastaut syndrome
  - Focal epilepsy
  - Familial Adult Myoclonic Epilepsy (FAME)
- *Non-epileptic disorders*
  - Hypnic jerks
  - PLMs
  - Propriospinal myoclonus
  - Non epileptic jerks
  - Encephalopathies
    - Metabolic
    - Toxic
    - Neurodegenerative (AD)
    - Genetic (Trisomy 21)

Generalized Tonic-Clonic Seizures Alone (GTCA)

Epidemiology: GTCA

- accounted for one third of all adolescent-onset IGEs

Clinical Context: GTCA

- Age at onset: 10-25 years (80% have their first tonic-clonic seizure in the second decade)
  - a range of 5-40 years.
  - Seizure onset is on average *about 2 years later* than in JAE or JME
- There is **no** clear sex difference
- Birth and antecedent history are typically **normal**
- A history of febrile seizures may be present
- Cognition is typically normal

Course of Illness: GTCA

- Seizures are typically infrequent,
  - sometimes yearly or less.
- Treatment is often required for life.
- **Trigger:** Sleep deprivation, fatigue and alcohol
- Seizures are usually drug-responsive

Seizure Types: GTCA

- GTCS are mandatory for this epilepsy syndrome.
  - often occur *within 2 hours of awakening* but can also be seen at other times in both awake and sleep states.

- Other seizure types such as absence or myoclonic seizures *are exclusionary*

EEG: GTCA

- The EEG background is normal
- Interictal
  - GSW or PSW at >3-5.5 Hz is seen,
    - 50% only showing these abnormalities in sleep.
    - In sleep, often fragment and can appear focal or multi-focal
  - A photo-paroxysmal response may be seen
  - enhanced by sleep deprivation

Neuroimaging: GTCA

- Neuroimaging is normal
- should be considered with
  - atypical features,
  - drug-resistant seizures
  - with persistent focal slowing on EEG

Genetic studies GTCA

- is not part of the current routine diagnostic evaluation
- A first degree family history of epilepsy is present in approximately 12% of cases in one study
- If seizures are drug-resistant, a chromosomal microarray should be performed to look for recurrent copy number variants

Differential diagnoses GTCA

- *Other Epilpsies:*
  - Juvenile Myoclonic Epilepsy
  - Juvenile Absence Epilepsy
  - Febrile Seizures Plus
- *Non-epileptic disorders*
  - *PNES (*Psychogenic non-epileptic seizures)
  - Syncope with motor phenomena

Features in (JME) and Juvenile Absence Epilepsy

		(JME)	GTCA
Age at onset	Usual	10-24 years	10-25 years
	Range	8-40 years	5-40 years
Development		Typically normal, but may have learning difficulties or ADHD	
Main seizure type		Myoclonic seizures predominantly on awakening	GTCS typically within 2 hours of awakening
Other seizure types	Febrile seizures	May occur in approximately 15%	
	GTCS	>90%	100%
	Absence seizures	33%	Absence or myoclonic seizures are not present
Triggers		Sleep deprivation Photic stimulation	Sleep deprivation

Features in Childhood and Juvenile Absence Epilepsy

		JME	GTCA
EEG	Backgroun	Normal	Normal
Epileptiform discharge generalized 3-5.5 Hz spike-wave and polyspike-wave	regularity	Irregular	regular
	Time seen	in all states	**only** in sleep
	sleep	May fragment in sleep	May fragment in sleep
Photoparoxysmal response		33% may trigger myoclonic jerks or generalized myoclonic-tonic-clonic seizures	May be seen
Hyperventilation induction		33% have hyperventilation-induced generalized spike-wave discharge but rarely induces absence seizures	May be seen

Idiopathic Generalized Epilepsies

- **new-onset epilepsy** in children and adolescents: 23-43% have generalized epilepsy
  - these, 53-58% have one of the IGE syndromes
- **age of onset:** typically ranges from 3-25 years
  - Rarely, onset can occur as late as 40 years
- the IGE syndromes are usually drug-responsive (about 80%)
- Importantly sodium channel blockers and GABAergic agents, including carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, tiagabine and vigabatrin typically exacerbate seizures in IGE, and may even provoke absence or myoclonic status epilepticus
- Patients may sometimes evolve from one IGE syndrome to another

Seizure types of IGE

- one, or a combination, of
  - absence, myoclonic, tonic-clonic and myoclonic-tonic-clonic
    - Generalized tonic-clonic seizures may have focal or asymmetric features such as head and eye deviation or version (only if it occurs after loss of awareness)
    - myoclonic seizures may be focal or asymmetric

- **Exclude:**
  - Generalized tonic, atonic, myoclonic-atonic, focal seizures and epileptic spasms

EEG

- generalized spike-wave discharges
  - 2.5-5.5 Hz
  - *often brought out during* drowsiness, sleep, and on awakening
    - Discharges often appear fragmented during sleep and can have focal features (consistent focal spikes or focal slowing should not occur)
  - A photoparoxysmal response: minority of patients
  - *Hyperventilation: often triggers* generalized spike-wave discharge
  - Appropriate ASMs may abolish generalized spike-wave discharges at appropriate doses

Comorbidities

- Mood disorders, anxiety, ADHD and learning disorders

- IGEs are not associated with intellectual disability or DEEs (developmental and epileptic encephalopathies)

Genetics

- Monozygotic twins are highly concordant with 100% concordance for the EEG trait of generalized spike-wave activity and 70% concordance for seizures
- monogenic causes: small proportion of cases
  - GABA receptor subunit genes (eg. *GABRG2*, *GABRA1*)
  - gene encoding glucose transporter 1 (*SLC2A1)*
- a polygenic basis, ±a contribution from environmental factors

Genetics

- Although a family history of epilepsy associated with generalized seizures is supportive, it is most common for patients with IGE not to have a family history of epilepsy