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.
Epilepsia. 2003;44 Suppl 2:2-6. Review.

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 perioralmyoclonia 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, $GAB_{A(B1)}$, $GAB_{A(B2)}$)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 remission9.5 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,[87] 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

MatricardiS, Verrotti A, Chiarelli F, et.al. Current advances in childhood absence epilepsy. Pediatr Neurol. 2014 Mar;50(3):205-12

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.
- InterictalEEG 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 ≥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

IGE

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

Beydoun A1, D'Souza J.
Treatment of idiopathic generalized epilepsy - a review of the evidence.
Expert OpinPharmacother. 2012 Jun;13(9):1283-98.

IGE with GTCS on awakening

- Tends to present at a somewhat later age than JAE and JME.
- Age of onset6 - 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.
Epilepsia. 2006;47 Suppl 2:107-10.

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
Syndromes of idiopathic generalized epilepsies not recognized by the International League Against Epilepsy. Epilepsia. 2005;46 Suppl 9:57-66.

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.

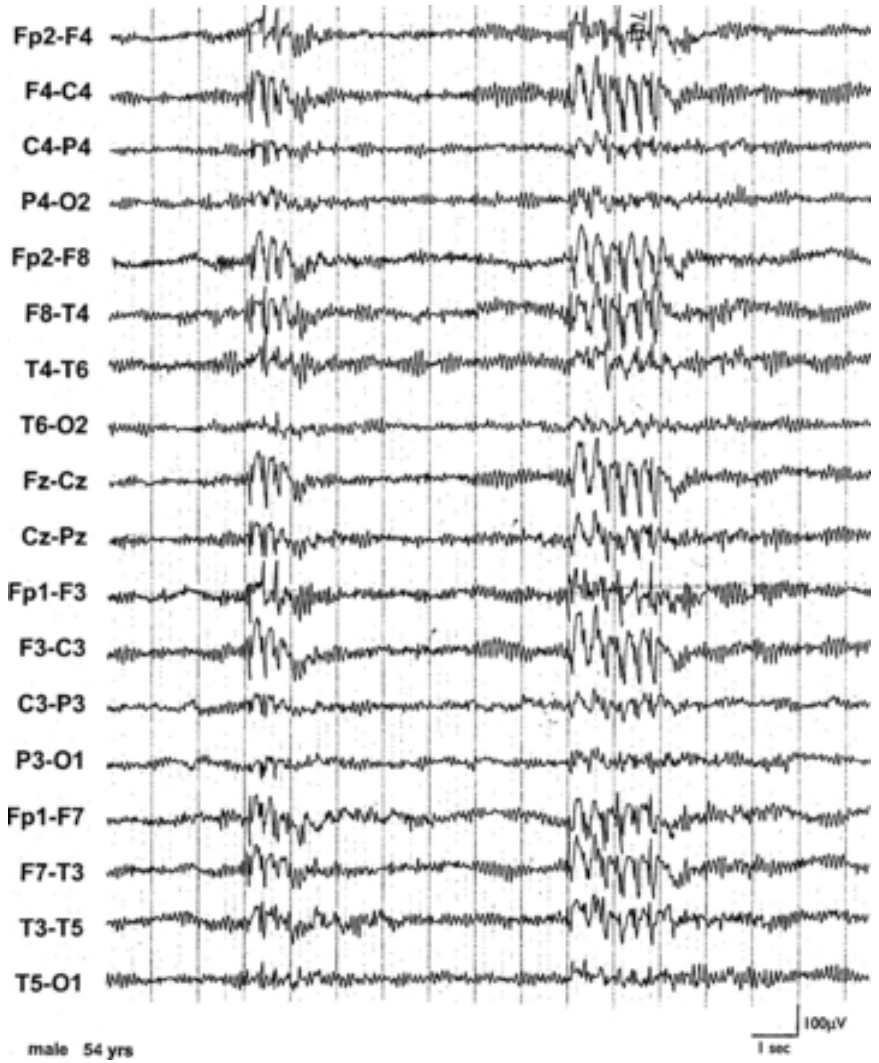
IGE with phantom absences

- “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

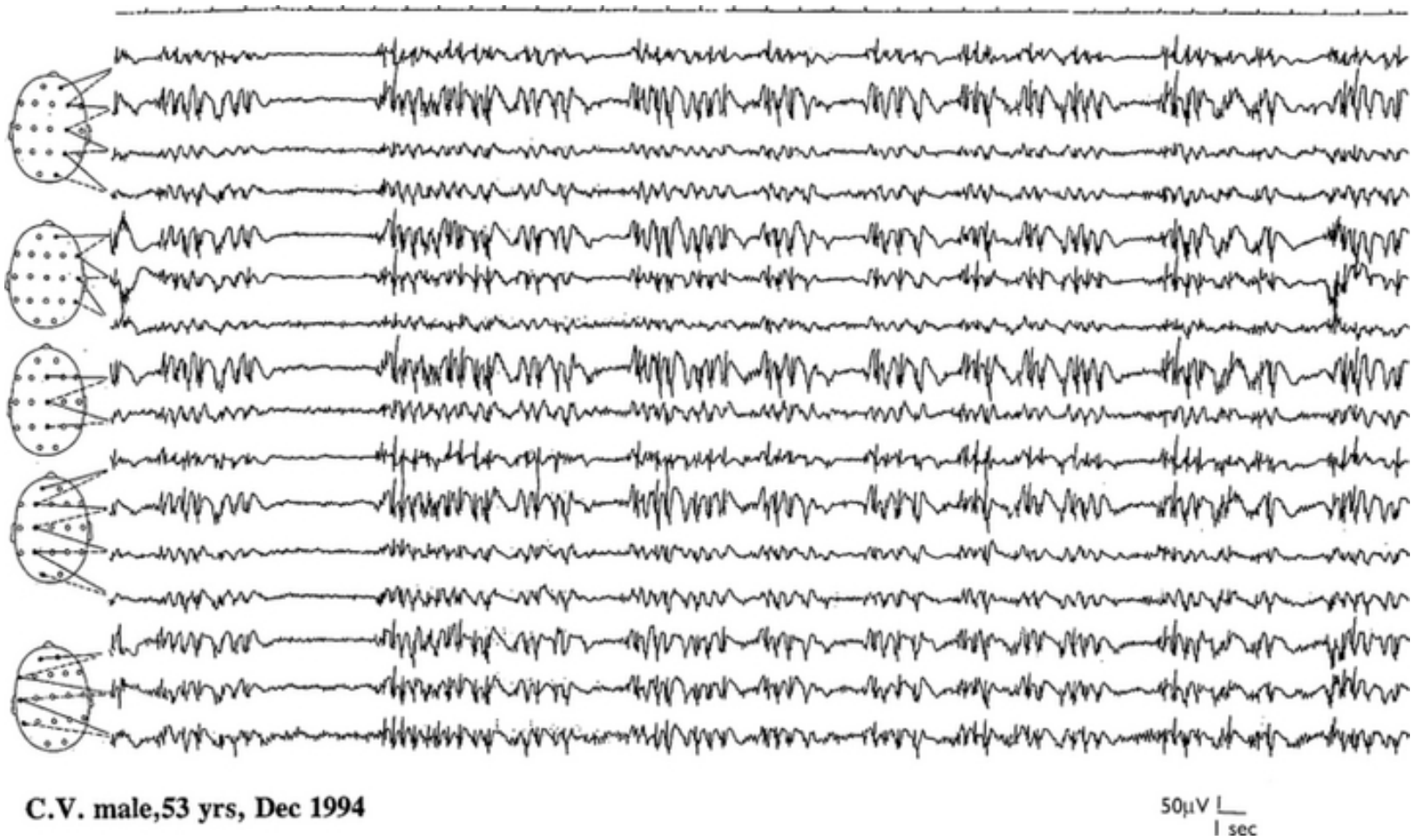
- Recognition of this condition may be difficult, as phantom absences may be undetected even by the patient himself
- Whereas the confusional state associated with absence status may be interpreted as a focal seizure (particularly when the interictal EEG shows focal abnormalities), which eventually ends 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



Epilepsia
pages 24-28, 4 MAY 2009 DOI: 10.1111/j.1528-1167.2009.02116.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2009.02116.x/full#f1

Idiopathic generalized epilepsy (IGE) syndromes in development: IGE with absences of early childhood, IGE with phantom absences, and perioralmyoclonia with absences



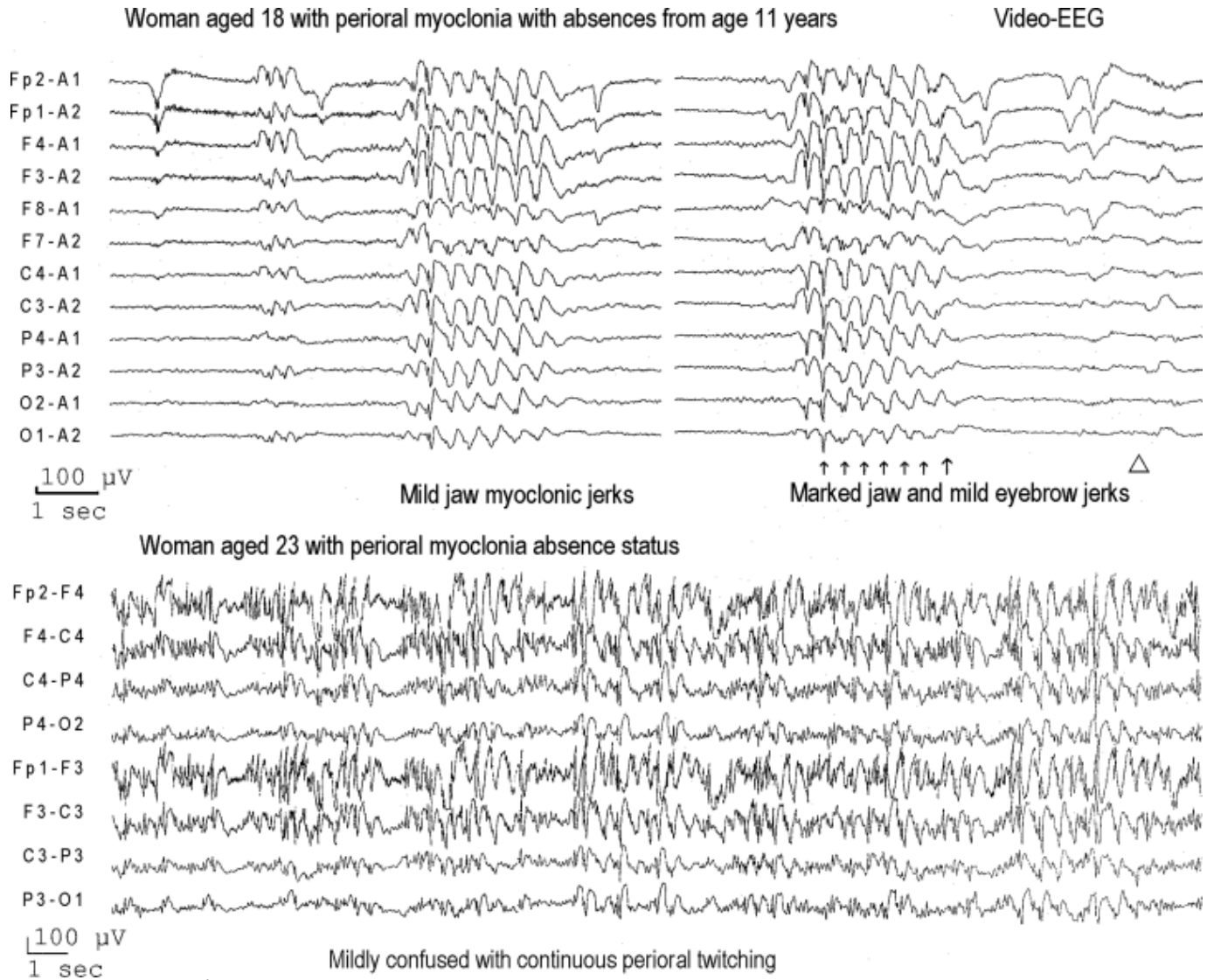
Epilepsia
pages 24-28, 4 MAY 2009 DOI: 10.1111/j.1528-1167.2009.02116.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2009.02116.x/full#f2

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

Sharma S1, Jain P, Aneja S. **Teaching video neuroimages: perioralmyoclonia with absences in a 12-year-old boy.** Neurology. 2013 Oct 8;81(15)

Syndromes of Idiopathic Generalized Epilepsies Not Recognized by the International League Against Epilepsy



Epilepsia
pages 57-66, 18 NOV 2005 DOI: 10.1111/j.1528-1167.2005.00314.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2005.00314.x/full#f1

Eyelid myoclonia with absences (Jeavons syndrome)

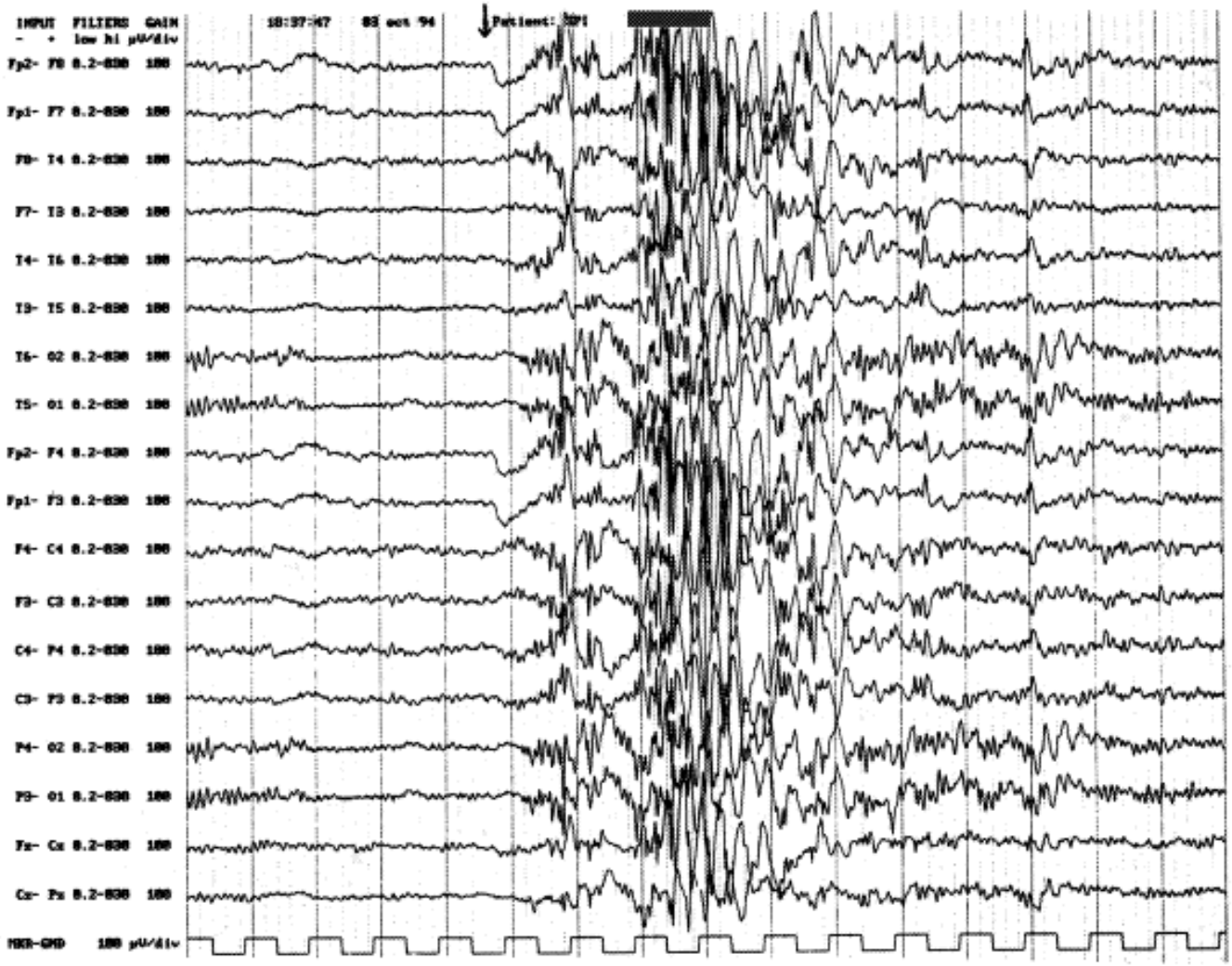
- Jeavons clearly delineated this condition: “Eyelid myoclonia and absences show a marked jerking of the eyelids immediately after eye closure and there is an associated brief bilateral spike and wave activity …. Brief absences may occur spontaneously … accompanied by 3/sec spike-waves. The spike-waves ... 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.

Charateristics

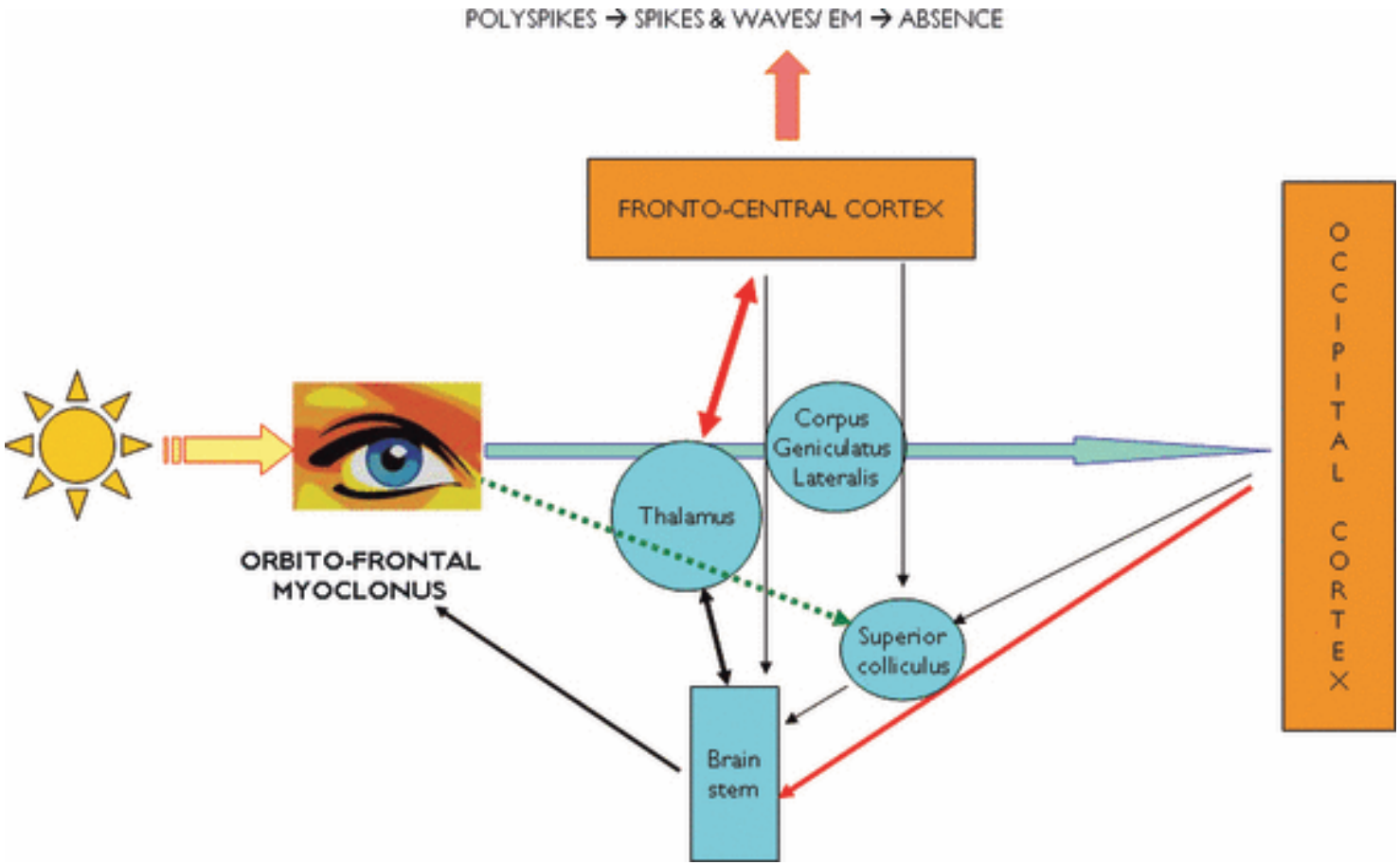
- EMA onset is typically in childhood, with a peak at 6–8 years.
- Eyelid jerks are frequently misinterpreted as tics or mannerisms, and absences may be overlooked.
- Treatment : Levetiracetam, Zonisamide
- Some patient: poor response to treatment



A

Eyelid myoclonia with absences: an overlooked epileptic syndrome?Neurophysiologie Clinique/Clinical Neurophysiology, Volume 32, Issue 5, 2002, 287 - 296

Eyelid myoclonia with absences (Jeavons syndrome): A well-defined idiopathic generalized epilepsy syndrome or a spectrum of photosensitive conditions?



Epilepsia
pages 15-19, 4 MAY 2009 DOI: 10.1111/j.1528-1167.2009.02114.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2009.02114.x/full#f1