Idiopathic generalized epilepsies (IGEs)

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Generalized epileptic disorders

- Characterized by seizures, symptoms of bilateral cerebral involvement, and EEG shows synchronous abnormal activity in both hemispheres at onset

- Generalized epilepsy syndromes are often classified as
  - Idiopathic
  - Symptomatic

CLINICAL NOSOLOGY

- Idiopathic epilepsies described as disorders "not preceded or occasioned by another" (i.e., with no underlying cause possible hereditary predisposition) include
  - Benign neonatal (familial) convulsion (video)
  - Benign myoclonic epilepsy in infancy
  - Childhood (myoclonic) and juvenile absence epilepsies
  - Juvenile myoclonic epilepsy
  - Epilepsy with grand mal seizures on awakening
  - Seizures precipitated by specific modes of activation (video)

- Cryptogenic or symptomatic
  - West syndrome (infantile spasms, Bötz-Wilson-Kaye syndrome)
    Lennox-Gastaut syndrome
    Epilepsy with myoclonic-astatic seizures
    Epilepsy with myoclonic absences

Table 1. International Classification of Epileptic Seizures

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Partial (focal) seizures</td>
<td>A. Simple partial seizures</td>
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<td>1. Simple partial seizures</td>
<td>1. With motor symptoms</td>
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<td>1. With sensory symptoms</td>
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<td>1. With autonomic symptoms</td>
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<td>1. With psychic symptoms</td>
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<td>1. With impairment of consciousness</td>
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<tr>
<td>2. Complex partial seizures</td>
<td>2. With impairment of consciousness</td>
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<td>3. Simple partial seizures evolving to complex partial seizures</td>
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<tr>
<td>4. Complex partial seizures evolving to secondarily generalized seizures</td>
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<tr>
<td>5. Generalized seizures (with or without origin in one hemisphere)</td>
<td>A. Absence seizures</td>
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<tr>
<td>6. Generalized seizures (with or without origin in one hemisphere)</td>
<td>1. Absent seizures</td>
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<td>7. Myoclonic seizures</td>
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<td>8. Tonic seizures</td>
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<td>9. Atypical absences</td>
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<td>10. Atypical absences</td>
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<tr>
<td>11. Myoclonic seizures</td>
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<tr>
<td>12. Myoclonic-astatic seizures</td>
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<tr>
<td>13. Atypical seizures (atonic seizures)</td>
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<td>14. Unclassified epileptic seizures</td>
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GENETICS OF GENERALIZED EPILEPSIES

- Examples of symptomatic generalized epilepsy syndromes with an established genetic defect include: myoclonic epilepsy and ragged red fiber disease (MERRF) syndrome patients (type IV) have a point mutation affecting the UBE3A gene
- Miller–Ocner Essencephalhy, in which cortical mal-development is associated with a defect in the LIS-1
- Progressive myoclonus epilepsy of the Unverricht–Lundborg type (EPM1), in which there is a mutation in the gene for cystatin B, a protein inhibitor of cysteine proteases (video)

GENETICS OF GENERALIZED EPILEPSIES

- Genetic defects in several other progressive myoclonus epilepsies including Lafora disease (EPM2) and certain forms of neuronal ceroid lipofuscinoses
  - In EPM2, defect in a gene encoding the protein laforin
  - At least eight genes underlie the neuronal ceroid lipofuscinoses (CLN1–8)
  - Angelman syndrome, results from a complex defect affecting imprinted genes on maternal chromosome 15q11-q13
  - Recent evidence suggests that defects in associated with GABAA

GENETICS OF GENERALIZED EPILEPSIES

- Major progress has recently been made in understanding the pathogenesis of certain idiopathic generalized epilepsies.
  - Benign familial neonatal convulsion (BFNC)
  - Generalized epilepsy with febrile seizures plus (GEFS+): defects have been identified in genes coding for subunits of voltage-gate channels
- It has long been recognized genetic factors play a role in the idiopathic generalized epilepsies
- Most common forms, including childhood absence epilepsy (incidence, one in 1,000), juvenile myoclonic epilepsy (incidence, one in 2,000), and juvenile absence epilepsy (incidence, one in 3,000)

GENETICS OF GENERALIZED EPILEPSIES

- BFNC occurs in two genetic forms:
  - (a) EBN1, whose gene has been localized to chromosome 20q13.3
  - (b) EBN2, a rarer form gene on chromosome 8q24
  - Genes affected in EBN1 and EBN2 have recently been identified and shown to encode the two novel homologous voltage-gated K⁺ channels KCNQ2 and KCNQ3

M-Current Potassium Channels

KCNQ2, KCNQ3

Singh et al. Brain, 2003
KCNQ2, KCNQ3
GENETICS OF GENERALIZED EPILEPSIES

- Recently voltage-activated Na+ channels implicated in seizure susceptibility in the complex syndrome “generalized epilepsy with febrile seizures plus” (GEFS+), a phenotypically diverse disorder; febrile seizures in childhood and afebrile seizures later in life
- Two genetically distinct forms of GEFS+ have been described, the first associated with mutations Na+ channel subunit SCN1B (GEFS+1) and Na+ channel subunit SCN1A (GEFS+2)
- Both of these disorders are inherited in an autosomal dominant fashion

GEFS+ Phenotypes

<table>
<thead>
<tr>
<th>Age</th>
<th>Febrile Seizures</th>
<th>Febrile Seizures Plus</th>
<th>FS/FS+ with other seizures</th>
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<tbody>
<tr>
<td>3 m</td>
<td>Adolescence</td>
<td>Febrile convulsions</td>
<td>Absence</td>
</tr>
<tr>
<td>6 y</td>
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<td>Myoclonic</td>
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</table>

Dravet syndrome

- Severe myoclonic epilepsy in infancy was described by Dravet in 1978, incidence 1 per 40,000
- Severe myoclonic epilepsy begins during 1st year of life. Development is normal prior to onset of seizures, develop either generalized or unilateral clonic seizures. Myoclonic jerks and partial seizures usually appear later. Psychomotor retardation and other neurologic deficits occur
- 1st seizure association with fever, often recur in 6 to 8 weeks and may be prolonged, leading to status epilepticus
- Later on non-febrile Sz, generalized clonic and tonic-clonic or unilateral hemiclonic

Dravet’s syndrome

- Psychomotor retardation is observed usually during the second year after the onset
- Some overlapping in GEFS+
- Mutations in the sodium-channel gene SCN1A
EEG: Dravet syndrome

generalized spike waves and polyspike waves in the EEG

EEG: Dravet’s syndrome, hemiclonic

Juvenile absence epilepsy

- Develops insidiously in physically and mentally healthy adolescents
- Age onset usually 10-17 yrs, with peak 10-12 yrs (Wolf 1992)
- Males and females affected equally
- Because frequency of the absences low, symptoms relatively trivial, the disorder may go unnoticed until generalized tonic-clonic seizures appear

Juvenile absence epilepsy

- Semiology not significantly different from those seen in childhood absence epilepsy. Differences in duration of absence, and much more sporadic
- Incidence GTCS seems to be higher than CAE
- Most GTCS occur upon awaking

EEG finding
Juvenile absence epilepsy

- M 17 yrs
- Presenting with GTCS, no aura, generalized tonic-clonic of both limbs, lasting 5-10 minutes with postictal sleepiness
- PH: healthy, Dad notice the patient frequent having blank staring
- PE general and neuro exam normal study
- EEG study- see next slide

Case

- F 18 yrs
- Hx of several episodes of blank staring for a year
- Presenting with generalized tonic-clonic seizures Jan 2003
- Hx of father had seizure, had one younger brother feeling fine.
- PE normal general and neuro exam
- EEG generalized spike and slow wave complexes 3-3.5 Hz

What is the appropriate medication?

- A. Phenytoin
- B. Valproate
- D. Lamotrigine
- E. Both B and D

What is the diagnosis?

- A. Childhood absence epilepsy
- B. Juvenile absence epilepsy
- C. Juvenile myoclonic epilepsy
- D. GEF+ (Generalized epilepsy with febrile convulsion)

Case

- M 15 yrs (younger brother of the previous case)
- Had two episodes of GTCS on March 2005
- No aura, sleep deprived, had generalized tonic-clonic of both limbs, lasting 5 minutes
- Also had frequent jerking of both limbs particularly in the morning
- EEG generalized polyspikes and slow wave complexes 3 Hz
What is the diagnosis?

- A. Childhood absence epilepsy
- B. Juvenile absence epilepsy
- C. Juvenile myoclonic epilepsy
- D. GEF+ (Generalized epilepsy with febrile seizure plus)

Family pedigree

Juvenile absence epilepsy

- Etiology
  - Approximately 11% of patients reveal a family history of epilepsy (Wolf 1992)
  - Genetic relationship among JAE, CAE, JME, and epilepsy with grandmal seizures on awaking

Juvenile absence epilepsy

- Biological basis
  - Mechanisms JAE unknown
  - However, animal models of absence seizures suggest that rhythmic thalamic projections to diffusely epileptogenic cortex produce characteristic hypersynchronous discharges

EEG-unit correlation for a cortical and a thalamocortical neuron during spike-and-wave discharges

Juvenile absence epilepsy

- Incidence and prevalence of JAE in general population not known
  - In survey of 7332 patients from 14 epilepsy centers in Lombardy, 1494 (17.4%) had some kind of idiopathic generalized epilepsy, and 160 of these diagnosed as having juvenile absence epilepsy
Juvenile absence epilepsy

- Differential diagnosis
  - Onset in adolescence and frequency of absences distinguish from CAE
  - Grandmal seizures on awaking generalized convulsions are presenting feature
  - JME, bilateral myoclonic seizures most prominent symptom; however, some overlap between CAE, JAE and JME
  - Complex partial seizures of temporal lobe origin can occasionally mimic absences

- Diagnostic workup
  - Ictal and interictal EEG characterized by symmetrical, generalized spike-wave discharges most prominent in the frontal region
  - Frequency 3.5 Hz to 4.5 Hz than in typical CAE (3 Hz to 3.5 Hz)
  - EEG paroxysms precipitated by sleep deprivation and by hyperventilation, less commonly by photic stimulation
  - Video EEG may be required to ascertain whether a patient has absences or only subclinical spikes and waves
  - Neurologic exam and neuroimaging results normal

- Neuroimaging PET demonstrates normal cerebral glucose metabolism and benzodiazepine receptor density in absence epilepsies with diffuse hypermetabolism during 3-Hz spike-and-wave discharges
- No evidence of any interictal overall abnormality of opioid receptors, though typical absences on 11C-diprenorphine from the association areas of the neocortex
- fMRI-EEG study of absences seizures in adult patients with JAE demonstrated bilateral activation of the thalamus and widespread deactivation of the cortex maximal in frontal regions

- Subtraction interictal-ictal single photon emission computed tomography (SPECT) coregistered to MRI (SISCOM) during the ictal and immediate postictal phase in four children with CAE
  - Showed widespread decrease of CBF during ictal phase and an increase during post ictal phase.
  - Those studies confirm crucial role of the thalamo-cortical loop and specific metabolic modifications during absences seizures.
Juvenile absence epilepsy

• Prognosis and complications
  – Response to therapy is good
  – Approximately 82% of cases will become seizure-free with valproate (Wolf and Inoue 1984)
  – With the advent of lamotrigine this figure should have improved
  – Factors associated with suboptimal control include
    • absences with mild clonic components,
    • > 10 GTCS
    • GTCS during sleep and at random
    • Hx of absence status
    • Developmental delay, mental retardation
    • Spike-wave bursts of more than 5 seconds
    • Asymmetry of spike-waves
    • Persistence of absences beyond age 25
    • Persistence of absences for more than 12 years (Wolf and Inoue 1984).

Epilepsy with grand mal seizures on awakening

• Clinical manifestations
  – Age onset varies relatively widely
  – Majority of patients, 1st seizures begin in the second decade, around puberty (Commission 1989; Janz and Wolf 1997)
  – Slightly male preponderance (Janz and Wolf 1997)
  – Generalized tonic-clonic seizures, predominant seizure type (video)
  – Seizures may be associated with absences or generalized myoclonic seizures

Epilepsy with grand mal seizures on awakening

• Management
  – Traditionally, absences successfully treated in most cases by ethosuximide, valproate, or a combination of both
  – Valproate is appropriate monotherapy
  – If GTCS or myoclonic jerks or both also part of clinical presentation, LTG is additional option and considered especially in female patients of childbearing age because of the increased teratogenic risk with valproate
Epilepsy with grand mal seizures on awakening

• Seizures typically occur shortly after awakening from night or nap sleep but may also occur in evening period of relaxation or drowsiness

• Seizures characteristically precipitated by factors such as sleep deprivation and excessive alcohol ingestion

Epilepsy with grand mal seizures on awakening

• Etiology
  — Idiopathic disorder
  — Approximately 12.5% of cases have a family history of seizure disorder (Janz and Wolf 1997)
  — Mode of inheritance is not known
  — Genetic relationship between this disorder and other idiopathic generalized epilepsies such as JME or CAE and JAE, since more than one phenotype may occur in the same family

Epilepsy with grand mal seizures on awakening

• Biological basis

• In eight cases of epilepsy with GTCS on awakening that came to autopsy, microdysgenesis as such as
  — Increased nerve cell density in stratum moleculare,
  — Indistinct boundary between lamina 2 and stratum moleculare,
  — Protrusion of nerve cells into the pia mater,
  — Increased number of nerve cells in white matter,
  — Disorganized columnar cortical neuronal architecture,
  — Purkinje cell dystopia (Mencke and Janz 1984).

Epilepsy with grand mal seizures on awakening

• Epidemiology

• Incidence and the prevalence are unknown

• In a large survey of 8570 patients of 14 epilepsy centers in Lombardy (Osservatore Regionale per l'Epilessia Lombard 1996),
  — 1,494 (17.4%) had an unequivocal diagnosis of idiopathic generalized epilepsy
  — In 176 of these (11.8%, or 2.1% of all patients) the diagnosis was epilepsy with grand mal seizures on awakening.

Epilepsy with grand mal seizures on awakening

• Prevention

• GTCS on awakening is a syndrome characterized by most severe, potentially dangerous type of epileptic seizures, i.e., GTCS

• Prevention both following an isolated seizure with typical precipitation, e.g., by irregular sleep habits, excess alcohol intake, or intermittent lights if photosensitivity is present (Wolf 1997)

• When onset is with a minor seizure type such as absence or generalized myoclonic, and these are correctly diagnosed and treated before first convulsive seizure

Epilepsy with grand mal seizures on awakening

• Differential diagnosis

• GTCS a common feature of many idiopathic and symptomatic, generalized and localization-related epilepsies.

• GTCS on awakening, are primarily generalized, i.e., they have no aura or other focal onset

• They may, however, develop out of a series of absences or myoclonic jerks that must not be mistaken as focal signs (Janz and Wolf 1997).
Epilepsy with grand mal seizures on awakening

- If seizures occur during sleep, they start in a so-called "silent area" of cortex, they can appear to be generalized from the start
- EEG is helpful when typical generalized spikes and waves are found; if it shows no epileptiform activity, a focal is more likely than a generalized epilepsy
- Overlap between GTCS on awaking, CAE, JAE, and JME
- In epilepsy with grand mal on awaking the generalized convulsions are the presenting feature of the disorder, whereas in JME, the bilateral myoclonic seizures most prominent symptom

Diagnosis workup
- Detailed history is pivotal for the correct diagnosis
- Relation of the seizures to sleep-waking cycle is missed when patients are asked about the preferred "hour" of seizure occurrence because seizures on waking may occur after an afternoon nap or at night, and may occur often when the patient has slept over time, and possible second seizure peak in the evening leisure
- General exam and neurologic examinations and neuroimaging studies are normal
- EEG shows one of the typical patterns of idiopathic generalized epilepsies (Janz and Wolf 1997). Photosensitivity may be found in about 13% of cases (Wolf and Goosses 1986).

Prognosis and complications
- With correct treatment, long-term prognosis is good
- However, risk of relapse after reduction or withdrawal of drugs is relatively high (about 8% if drugs are reduced or withdrawn after a minimum of 2 years without seizures) (Janz and Wolf 1997).

Management
- Since disorganized sleep is one of the precipitating factors for epilepsy with GTCS on awaking, patients need to adopt regular sleep-wake cycle, and avoidance night-shift work
- Avoidance of other precipitating factors, such as excessive alcohol intake
- Valproate drug of first choice, with phenobarbital possible alternative (Bourgeois et al 1987; Wolf 1996).

GTCS may respond to carbamazepine and phenytoin, but these drugs carry risk to increase concomitant absences and myoclonic seizures

Possible role of the new AEDs for this syndrome not yet established.

Juvenile myoclonic epilepsy (JME)
Juvenile myoclonic epilepsy (JME)

- Juvenile myoclonic epilepsy (JME) is a common type of idiopathic generalized epilepsy (IGE).
- Major landmark of JME is the occurrence of adolescent-onset myoclonic seizures.
- JME is both genetically and clinically heterogeneous, suggesting that different pathophysiologic mechanisms might be involved.

Onset is usually in adolescence but seizures may begin or be diagnosed only in the early 20s.

- Patients frequently come to medical attention only after a generalized convulsion, and the history of earlier myoclonic jerks is often obtained retrospectively.
- More recently, myoclonic epilepsy with adult onset (37 to 39 years) has been highlighted by different group.

Prevalence JME accounts for up to 26% of IGE and up to 10% of all cases of epilepsy.

- Misdiagnosis and delayed diagnosis remain common.
- Based on a 1% population risk for epilepsy by age 20, Risk of JME in the general population would be 1 per 1,000 to 2,000.
- Less frequently seen in children and more frequently in adolescents and adults, in adults with IGE, JME should be strongly considered, history of myoclonus beginning in the teens are essential.

Sex Ratio

- Sex ratio slight female predominance, with 515 males to 615 females, based on the summation of ten different studies.
- Only one of the studies showed male preponderance (33 males to 20 females), whereas another study showed marked female preponderance (77 males to 104 females).
- Recent Irish study also showed significant female predominance for JME.
- A large family study has also confirmed a very high female-to-male risk ratio.

Age of Onset; onset of JME is clearly age related.

- It varies between 8 and 26 years, with the majority between 12 and 18 years.
- The average age of onset of myoclonic jerks is usually earlier than that of generalized tonic-clonic seizures.
- Onset age of JME is generally earlier in photosensitive than in non-photosensitive patients.
Juvenile myoclonic epilepsy (JME)

- **Etiology and Basic Mechanisms**
- Pathophysiology of JME is unknown.
- Although suggest that this stereotyped clinical pattern may be the result of different genetic, pathologic, and pathophysiologic processes.
- EEG pattern and other neurophysiologic studies, suggest a variable focal or regional frontal hyperexcitability in many cases.
- Subtle frontal morphologic changes can be found, not universal in JME, association with photosensitivity is also variable.

- **Association with clinical and EEG findings of a clearly focal epilepsy, idiopathic photosensitive occipital epilepsy (IPOE), raises questions about the nosologic purity of JME as a generalized epilepsy syndrome**
- Classic electrophysiological studies conducted by Gloor led to the corco-resecular theory of generalized epilepsy:
  - This theory postulates an underlying cortical hyperexcitability and abnormal response to thalamocortical input
  - Genetic animal models of generalized epilepsy confirm the role played by thalamocortical circuits in cortical spike-wave generation, genetically determined dysfunction of reticular thalamic neurons is responsible for the abnormal excitation.

- Much genetic heterogeneity in JME.
- A positive family history of epilepsy is common
- Recent evidence that JME constitutes a single gene syndrome in some families, although most families show complex inheritance.
- Some JME cases apparently sporadic, others occur in families with other IGE syndromes, and occasional families have a pure autosomal dominant JME phenotype
- Various mutations suggested for JME are all believed to influence neuronal excitation but involve different mechanisms.
- Both direct ion channel mechanisms and nonionic mechanisms have been proposed.
- How these interact with other possible susceptibility genes and with environmental factors is not yet clear.
**Juvenile myoclonic epilepsy (JME)**

- Clinical Presentation
  - Age-dependent disorder with onset usually in 2nd decade, but occasionally earlier and not infrequently later.
  - Generally fully controlled on valproate in about 80%, but require lifelong treatment.
  - Myoclonic seizures, mainly involving the arms and occurring preferentially in the post awakening period, correlated with short bursts of generalized spike-wave or polyspike-wave complexes.

- Myoclonus usually responds to antmyoclonic agents such as valproate, clonazepam, piracetam, or levetiracetam, but it may be difficult to control during certain periods of the patient’s life.
  - The loss of seizure control may be correlated with emotional factors.
  - Generalized attacks often precipitated by the concurrence of sleep deprivation and being woken up from sleep, and this sequence should obviously be avoided.

- Diagnostic Evaluation
  - Although JME is considered a typical generalized epilepsy, earlier and more recent reports of clinical, EEG, and imaging studies have raised questions regarding the degree to which this classification can be strictly maintained.
  - Clinical and EEG studies of JME and of reflex seizures in generalized epilepsy suggested localized or regional hyperexcitability in generalized epilepsy syndromes, especially in JME.

**Juvenile myoclonic epilepsy (JME)**

- Myoclonus variable in intensity, often unreported by patients until a GTCS occurs.
  - Often not considered to represent a major inconvenience to patients, who frequently prefer not to take medication.
  - When minor manifestations such as myoclonus or absence coexist with major seizures, treatment with antiepileptic drugs (AEDs) such as valproate or clonazepam is mandatory.

- In an effort to better define syndromes for genetic study, Taylor et al., working with Berkovic and Scheffer, showed overlap between the clusters of clinical features used to diagnose JME and IPOE (video), suggesting a relationship with this focal epilepsy syndrome, especially with respect to visual auras and conscious head version (which are typical of IPOE) in patients with JME.
  - Coexistence of myoclonic seizures and occipital EEG spikes in the same individuals in both syndromes. The probands and their families were evaluated in detail, such overlap exists more commonly than is currently realized but that patients are not usually questioned as carefully.

- EEG Findings
  - Typical abnormality on EEG is bilateral multiple spike- or polyspike-wave complexes at a rate of four to six per second, with anterior predominance.
  - Photosensitivity occurs in about 30%, especially in women, but the two disorders appear to be inherited separately.
  - Scalp EEG showed focal interictal epileptiform discharges in 30.3% of JME patients.
Juvenile myoclonic epilepsy (JME)

- Frequent unilateral or bilateral temporal EEG abnormalities are seen as patients age.
- Panayiotopoulos et al. also commented on the precipitation of seizures by mental activation as part of the syndrome, which may represent seizures induced by thinking.
- Wolf emphasized typical fronto-central predominance of ictal EEG activity recorded with myoclonic jerks of JME.

Juvenile myoclonic epilepsy (JME)

- Neuroimaging
  - Although JME classified idiopathic epilepsies, evidence from structural and functional imaging highlights existence of underlying abnormalities.
  - Studies in patients with JME shown abnormalities in mesial frontal structures and some have more widespread abnormalities of cortical gray matter.

Juvenile myoclonic epilepsy (JME)

- Using MRS, Savic et al. showed reduction in frontal lobe N-acetyl aspartate (NAA) in JME, and later confirmed that frontal NAA was reduced in patients with JME but not in those with generalized epilepsy with tonic-clonic seizures.
- Also showed reduced thalamic choline and myoinositol concentrations
- Mory et al. studied thalamic MRS in JME and reported reduced NAA/phosphocreatine ratios in nine out of ten patients.

Juvenile myoclonic epilepsy (JME)

- Combined EEG and fMRI in patients with IGE, including JME, demonstrated bilateral thalamic activation, with increased blood oxygenation level-dependent (BOLD) signal during bilateral spike-wave activity in most individuals and deactivation in bilateral frontal, parietal, and posterior cingulate
- MRS and fMRI studies support role for thalamic abnormalities in IGE, they also implicate more localized cortical neuroanatomic mechanisms in JME in particular.
- MRI and MRS studies support frontal cortex is in some way preferentially involved in JME

Juvenile myoclonic epilepsy (JME)

- Biochemical studies have also sought evidence of systemic metabolic abnormalities that would, when expressed in the brain, alter cortical function in generalized epilepsy. Platelets have been used as a model of GABAergic neurotransmission.
- Rainesalo et al. reported reduced platelet GABA uptake in patients with JME and increased activity of the catabolic enzyme GABA-transaminase, which may indicate impaired cerebral GABAergic function.
- Reported increased interictal plasma glutamate in JME patients, with no significant change in the postictal period.

Juvenile myoclonic epilepsy (JME)

- Genetic Studies
  - Based on family and twin data, respectively, Andermann, Berkovic et al., concluded most IGEs, as well as most idiopathic focal epilepsies, are inherited as multifactorial or complex traits, with the additive effects of several or many susceptibility genes and interaction with environmental factors to produce the final phenotype.
  - Multiple IGE syndromes may exist in the same family, even in those with a single gene defect.
  - Marni et al. reported that, although childhood and juvenile-onset absence epilepsies share a close genetic relationship, JME appears to be genetically more distinct.
Juvenile myoclonic epilepsy (JME)

- The discovery that some well-defined epilepsy syndromes are channelopathies fueled efforts to describe the mechanisms underlying JME.
- Mulley et al. pointed out that “all but one of the idiopathic epilepsies with a known molecular basis are channelopathies. Where the ion channel defects have been identified, however, they generally account for a minority of families and sporadic cases.
- Suggest ion channel mutations of large effect are a common cause of rare monogenic idiopathic epilepsies, but are rare causes of common epilepsies.

Juvenile myoclonic epilepsy (JME)

- When a positive family history of epilepsy can be obtained, most JME occurs in families with a variety of IGE syndromes.
- Several loci have been mapped for IGE in such families, including 8q, 3p, and 1p.
- Sander et al., reported linkage to chromosome 3q includes the gene ClCN2 coding for the ClC-2 voltage-dependent Cl⁻ channel, largely expressed in cerebral neurones and inhibited by GABA.
- Haug et al. reported three different heterozygous mutations in this gene in three unrelated families with IGE. These mutations segregate with the epilepsy phenotype in each family and all cause changes in function associated with neuronal excitability. also detected a novel polymorphism in the ClCN2 gene.

Juvenile myoclonic epilepsy (JME)

- Another gene located in the 3q26 region, KCNMB3, codes for regulatory subunits associated with calcium-activated potassium channels (B channels).
- Four polymorphisms in this gene were detected in a variety of patients with epilepsy including JME.
- These variants were found to be associated with functional deficits of the BK channel.

Juvenile myoclonic epilepsy (JME)

- A recent genetic study of a large French-Canadian family with autosomal dominant JME (ADJME) showed that affected individuals are heterozygous for a missense mutation (A322D) in the gene coding for the α1 subunit of the GABAA receptor (GABRA1) on chromosome 5q34.
- This region overlaps the locus for GABRG2, one of the genes responsible for GEFS+ (generalized epilepsy with febrile seizures plus) syndrome but autosomal dominant JME accounts for only a small proportion of JME.
- This suggested that polymorphisms in a potassium channel gene, KCNQ3 (EBN2, 8p24), may be important in predisposing to JME.

Juvenile myoclonic epilepsy (JME)

- Other families exhibit linkage to the 6p21.3 region associated with HLA rather than to 6p12. Pal et al. suggested that JME at the 6p21 locus may be caused by a mutation in the BRD2 gene.
- Abnormal MRI in JME would be consistent with involvement of BRD2.
- Association studies suggest that the α1A subunit of the voltage-gated calcium channel gene (CACNA1A) may affect susceptibility to IGE.
Juvenile myoclonic epilepsy (JME)

- In summary, although several major genes have recently been identified for IGE, and for JME in particular, only mutations in the CICN2 and EFHC1 genes have been replicated by different groups.
- No consistent genetic pattern has been revealed by association studies for any common idiopathic epilepsy syndrome.
- A number of association studies of other ion channels in IGE, including JME, have yielded negative results.

Differential Diagnosis

- Two main differential diagnoses have to be considered here. In the cases where myoclonus is not well characterized, it may be confused with a partial seizure with motor manifestations and, in this situation, a detailed clinical history is important.
- The main implication of the misdiagnosis of JME as a partial epilepsy is, of course, the choice of the wrong AED, and further classification of the epilepsy as a refractory one.

Juvenile myoclonic epilepsy (JME)

- The second differential diagnosis is for those patients who do not clearly report myoclonus, which may delay the diagnosis of JME.
- These patients may be diagnosed as having one of the various forms of idiopathic generalized epilepsies with generalized tonic-clonic seizures.
- Detailed clinical history essential tool.
- Other rare differential diagnoses include the progressive myoclonus epilepsies, especially Lafora disease and Unverricht-Lundborg disease, which also present in adolescence and may resemble JME in the early stages.

Juvenile myoclonic epilepsy (JME)

- Treatment and Outcome Valproate is drug of choice.
- Newer AEDs, such as lamotrigine and topiramate, result in variable control of the myoclonus, but good efficacy for the GTCs in JME.
- Levetiracetam appears to have significant antmyoclonic effect.
- Clonazepam is a good add-on drug for myoclonis, and can be used in monotherapy only in patients who have never had GTCs.

Long-term Prognosis

- Prognosis of myoclonus in this form of epilepsy is not entirely clear.
- Although AEDs can be withdrawn in only a minority (10% to 20%) of patients,
- Generally accepted that there may be improvement over time, particularly with respect to myoclonus, and that the process may be less active, but without complete remission in adult life.
- The great majority of patients responds to treatment with appropriate antmyoclonic and antiepileptic medication, and has an otherwise benign outcome with no other neurologic disturbances.
Juvenile myoclonic epilepsy (JME)

• Summary and Conclusions
  – JME is a frequent type of IGE characterized by myoclonic seizures, most often implicating a lifetime use of valproate
  – Recent work suggests that JME may represent several different disorders with different genetic and pathophysiologic signatures found in patients who are clinically or practically indistinguishable

Progressive myoclonic epilepsy

• Unverricht-Lunborg disease
  – Onset 6-15 yrs
  – Seizures – stimulus sensitive myoclonic seizures including face in 50%; tonic-clonic and absence seizures, marked photosensitivity, worsen on PHT
  – Ataxia, dementia (mild and late)
  – Death 50-60 yrs
  – AR trait mapped to 21q22.3 (EP1 gene) encodes cystatin B that inhibit papain family of cystatin proteases that involved in initiation of apoptosis

• Lafora disease
  – Onset 10-18 yrs
  – Seizures – stimulus sensitive tonic-clonic, absences, drop attacks at onset in 75% seizures; myoclonus and rapid progressive cognitive decline (1-2 yrs after onset)
  – Death 20-25 yrs (10 yrs after onset)
  – AR mapped to 6q24 in 80% patients (EPM2A) that encodes for laforin, a dual specificity protein tyrosine phosphatase primary associated with ribosomes

• MERRF: Mitochondrial encephalopathy with ragged red fibers
  – Onset 3-65 yrs
  – Associated with photosensitive generalized or partial seizures with lactic acidosis and neuropathy, short stature, migraine, deafness
  – Slowly progressive dementia
  – Death 3-30 yrs after onset
  – Adenine to Guanine mutation on mtDNA, tRNA mutation

ANTIEPILEPTIC DRUGS AND GENERALIZED EPILEPSIES

• AEDs useful in the treatment of generalized epilepsy syndromes fall into two classes: broad-spectrum and specific anti-absence agents
• Broad spectrum AEDs (including valproic acid (VPA), lamotrigine (LTG), and topiramate (TPM)) act at least through state-dependent block of voltage-gated Na+ channel
ANTIEPILEPTIC DRUGS AND GENERALIZED EPILEPSIES

- Protective activity against GTCS occurs mainly through actions in the neocortex, which is where these seizures seem to originate.
- This neocortical action could also interfere with mechanisms mainly through actions in the neocortex, also interfering with the thalamocortical synchronization.

ANTIEPILEPTIC DRUGS AND GENERALIZED EPILEPSIES

- Absence drugs such as ESM, methsuximide (MSM), and dimethadione may act by reducing T-type Ca2+ currents in thalamocortical relay neurons preventing burst firing and abolishing the rhythmic thalamocortical synchronization.
- It is well recognized that barbiturates lack absence activity, whereas benzodiazepines (BZDs), such as clonazepam (CZP), highly effective.