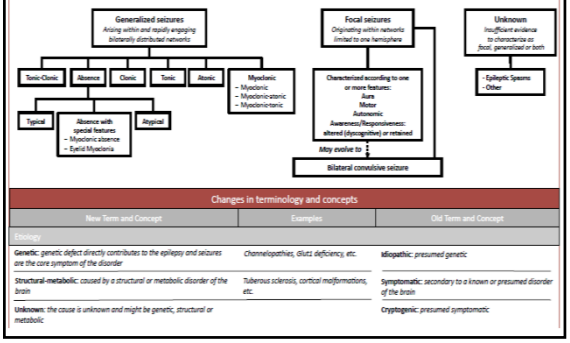
MAHIDOL UNIVERSITY
Wisdom of the Land

# Idiopathic Epilepsy Syndromes

Lunliya Thampratankul, MD
Division of Neurology, Department of Pediatrics
Ramathibodi Hospital, Mahidol University

## Classification of Seizure

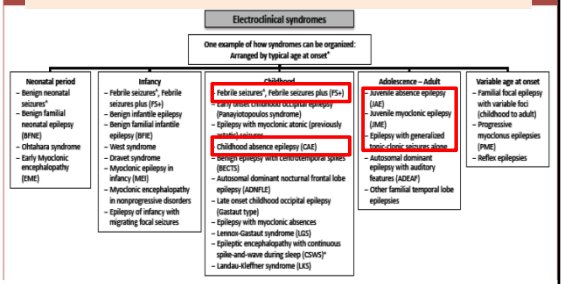



## Seizure Type VS Epileptic Syndrome

- A seizure type is determined by the patient's behavior and EEG pattern during ictal event
- An epileptic syndrome is defined by
  - Age
  - Seizure type(s)
  - Etiology
  - Neurological status
  - Natural history
  - EEG (ictal & interictal)
  - Response to AEDs



## Classification of Electroclinical Syndromes




*Epilepsia*, 51(4):676–685, 2010
doi: 10.1111/j.1528-1167.2010.02522.x

**SPECIAL REPORT**

### Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

*†Anne T. Berg, ‡Samuel F. Berkovic, §Martin J. Brodie, ¶Jeffrey Buchhalter, #**J. Helen Cross, ††Walter van Emde Boas, ‡‡Jerome Engel, §§Jacqueline French, ¶¶Tracy A. Glauser, ##Gary W. Mathern, ***Solomon L. Moshé, †Douglas Nordli, †††Perrine Plouin, and ‡Ingrid E. Scheffer

*Epilepsia*, 52(6):1058–1062, 2011
doi: 10.1111/j.1528-1167.2011.03101.x

**CRITICAL REVIEW AND INVITED COMMENTARY**

### New concepts in classification of the epilepsies: Entering the 21st century

*Anne T. Berg and †Ingrid E. Scheffer

*Epilepsy Center, Nothwestern Children's Memorial Hospital, Chicago IL, U.S.A.; and †Epilepsy Research Centre, Department of Medicine, University of Melbourne, Austin Health, and Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Vic., Australia

## Advantage of Determination of Electro-clinical Syndrome

- Drives the etiologic evaluation
- Determines the best choice AEDs
- Suggests duration of AED therapy
- Broad forecasts the prognosis & comorbid
- Useful tool for genetic linkage analysis

## Idiopathic Epilepsy Syndromes (IES)

- Idiopathic Generalized Epilepsies (IGE)
  - Childhood absence epilepsy (CAE)
  - Generalized epilepsy with febrile seizures plus (GEFS+)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with myoclonic absences
  - Juvenile absence epilepsy (JAE)
  - Epilepsy with grand mal (generalized tonic-clonic) seizures on awakening
  - Benign myoclonic epilepsy in infancy
- Idiopathic Focal Epilepsies (IFE)
  - Benign childhood epilepsy with centrotemporal spikes (BCECTS)
  - Benign childhood occipital epilepsy (BCOE)
  - Benign familial neonatal/infantile seizures (BFNS, BFNIS, BFIS)
  - Autosomal nocturnal frontal lobe epilepsy (ADNFLE)

Engel, Epilepsia 42:796-803, 2001

## A girl with frequent staring spells

## Idiopathic Generalized Epilepsy
**ILAE 1989**

Benign myoclonic epilepsy in infancy
Generalized epilepsy with febrile seizures plus*
Epilepsy with myoclonic absences
Epilepsy with myoclonic-astatic seizures
Childhood absence epilepsy
Idiopathic generalized epilepsies with variable phenotypes
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with generalised tonic-clonic seizures only

## Typical Absence Seizures

A sudden onset, interruption of ongoing activities, a blank stare, possibly a brief upward rotation of the eyes.

If the patient is speaking, speech is slowed or interrupted, if walking, he stands transfixed; if eating, the food will stop on his way to the mouth. Usually the patient will be unresponsive when spoken to.

The attack lasts from a few seconds to half a minute and evaporates as rapidly as it commenced.

## New ILAE Diagnostic Scheme vs ILAE Classification 1989

(1). The syndromes of JAE, JME and IGE with GTCS only are considered as phenotypical variants of IGE of adolescence

(2). A new syndrome of 'IGE with GTCS only' has been proposed to replace 'epilepsy with GTCS on awakening'

(3). 'Epilepsy with myoclonic-astatic seizures' and 'epilepsy with myoclonic absences' are included among idiopathicgeneralised epilepsies; these were previously categorised as symptomatic or cryptogenic generalised epilepsies.

(4). 'Generalised epilepsy with febrile seizures plus' is proposed as a new syndrome in development

## Typical Absence Seizures

- Absence with impairment of consciousness only.
- Absence with mild clonic components.
- Absence with atonic components.
- Absence with tonic components.
- Absence with automatisms.
- Absence with autonomic components.
- Mixed forms of absence

| | Absence | CPS |
|---|---|---|
| Duration for less than 30 sec | as a rule | exceptional |
| Duration for more than 60 sec | exceptional | as a rule |
| Daily frequency | as a rule | rare |
| Simple automatisms | frequent | Frequent |
| Complex automatisms | exceptional | Frequent |
| Bilateral facial myoclonic jerk | frequent | exceptional |
| Sudden onset and termination | as a rule | Frequent |
| Postictal symptoms | never | frequent |

## Absence Epilepsy

- Childhood absence epilepsy
- Juvenile absence epilepsy

| | Absence | CPS |
|---|---|---|
| Evolving to other focal seizures | never | frequent |
| Elicited by photic stimulation | frequent | exceptional |
| Reproduced by hyperventilation | As a rule | exceptional |
| EEG | | |
| Ictal: generalized 3-4 Hz spike-wave | exclusive | never |
| Interictal generalized discharges | frequent | exceptional |
| Interictal focal abnormalities of slow wave | exceptional | frequent |
| Normal EEG in untreated state | exceptional | frequent |

## Childhood Absence Epilepsy

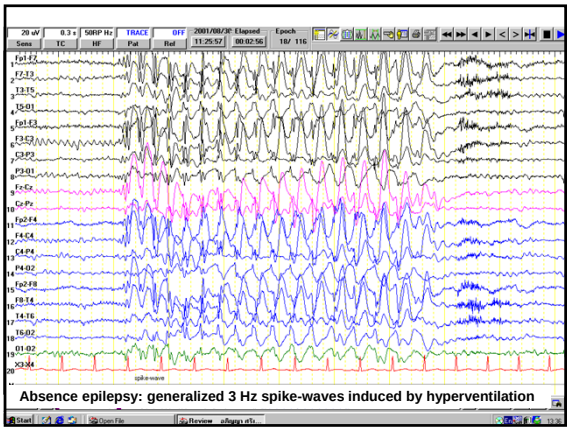
- Incidence: 7/100,000 of children < 15 years
- Onset: mostly 4 - 10 years
- Normal neurological state and development
- Genetics: Polygenic transmission/ some AD
- Induction: Hyperventilation-induced
- Brief (4–20 seconds, exceptionally longer) and frequent (tens per day) absence seizures with abrupt and severe impairment (loss) of consciousness.
- Automatisms are frequent but have no significance in the diagnosis.

# Absence Epilepsy

## Childhood Absence Epilepsy

EEG

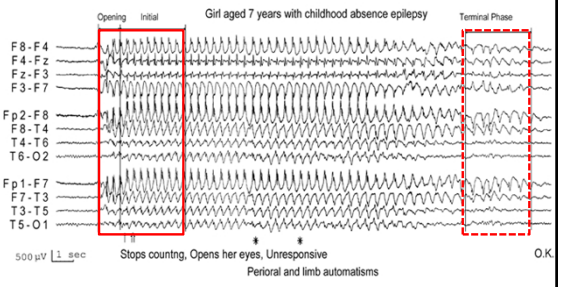
- ictal discharges: generalized high-amplitude 3- Hz-spike and slow wave complexes.
- Spike-wave is rhythmic at around 3 Hz with a gradual and regular slowdown from the initial to the terminal phase of the discharge.
- The duration of the discharges varies from 4 to 20 seconds.




## Treatment & Outcome

- Drugs of choice
  - ethosuximide, valproate, lamotrigine
  - clonazepam, nitrazepam, acetazolamide
- Usually respond to treatment
- Transform to other type of seizure
- Recurrent: not common
- Prognosis: favorable

Absence seizure during hyperventilation in a 7 y/o girl




## A 15 y/o girl with GTC upon awakening

(after late party and alcohol consumption)
(clumsiness)

## Juvenile Absence Epilepsy

- Onset: late childhood, 9 - 13 years
- Seizure:
  - absence seizures
  - Nearly all patients may have GTCS.
  - More than half have myoclonic jerks but these are mild and do not show the circadian distribution of JME.
  - Consistent visual, photosensitive and other sensory precipitation of clinical absences is probably against the diagnosis of JAE.
  - However, on EEG, intermittent photic stimulation often facilitates generalized discharges and absences.

| | 1º GTC | 2º GTC |
|---|---|---|
| GTCs with other clinically evident sz | 90% | 90% |
| Typical absence | 60% | None |
| Myoclonic | 40% | none |
| Focal seizure | none | 90% |
| GTCs without other clinically evident sz | 10% | 10% |
| Precipitating factors | > 60% | < 10% |
| Consistently on awakening | common | uncommon |
| Family history of similar epilepsy | common | uncommon |
| EEG in untreated patients | | |
| Generalized discharges | 80 | Exceptional |
| Focal abnormalities alone | 10 | 60 |
| Generalized + focal abnormalities | 10 | 30 |

## Juvenile Myoclonic Epilepsy (Janz Syndrome)

## Comparison Between Absence & JME

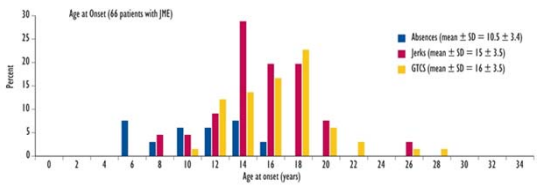
| | Childhood | Juvenile | JME |
|---|---|---|---|
| Age of onset | 2 -12 yrs | puberty | puberty |
| Frequency | multiple/D | rarely/D | variable |
| EEG | 3 Hz.S+W | 3.5-4 Hz S+W | 3.5-6 Hz.S+W |
| GTC | 40-60% | 80% | 80 - 85 % |
| AED | ETH, VPA | VPA | VPA |
| Prognosis | favorable | favorable | favorable |

## Juvenile Myoclonic Epilepsy

- Sudden , mild to moderate myoclonic jerks(shoulder & arm) during awake, GTC
- Precipitating: sleep deprivation, alcohol intake, fatigue
- Chromosome 6 , AD
- Onset 12 - 18 years (mean 14.6 years)
- Normal examination

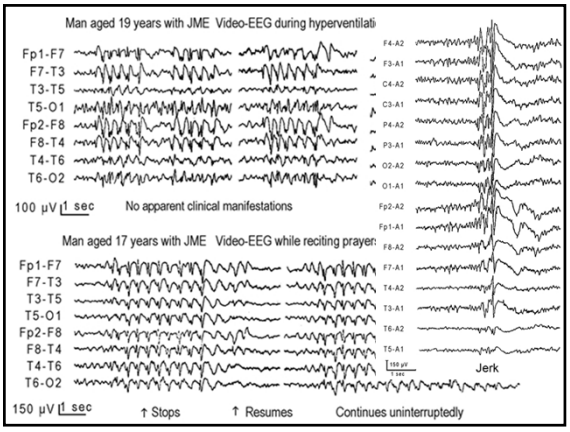
| | JME | JAE |
|---|---|---|
| Main type of seizures | Myoclonic jerks | Typical absences |
| Circadian distribution | Mainly on awakening | Any time during the day |
| Typical absences | Mild and often imperceptible; 1/3 of patients | Defining seizure type; very severe, all patients |
| Myoclonic jerks | Defining seizure type; all patients, mainly on awakening | Mild; 1/3 of patients, random |
| GTCS | mainly occur after a series of myoclonic jerks on awakening | mainly occur independently or less commonly after a series of absence seizures |
| EEG | Brief (1–3 s) 3–6 Hz GSWD, usually asymptomatic | Lengthy (8–30 s) 3–4 Hz GSWD, usually associated with impairment of consciousness. |

## Age onset of different seizure type in JME




Age at onset of absences, myoclonic jerks and GTCS in 66 consecutive patients with JME.

[Modified from Panayiotopoulos et al, Epilepsia, 1991]



## Clinical Course & Treatment

- Life-long treatment & respond to AED
  - Valproate (usually low dose)
  - Lamotrigine
  - Benzodiazepines
- Awareness of teratogenic effect of VPA in pregnancy
- Excellent prognosis

## Idiopathic Generalized Epilepsy with GTC Seizures Only

- Age at onset: 6 to 47 yrs (peak at 16–17 yrs)
- Men (55%) predominate slightly
- GTCS occur exclusively shortly after awakening regardless of the time of day or in a second seizure peak in the evening period of relaxation.
- With age, GTCS tend to increase in frequency and become more unpredictable
- Precipitating: sleep deprivation, alcohol, fatigue, shift work

## Diagnostic Tips for JME

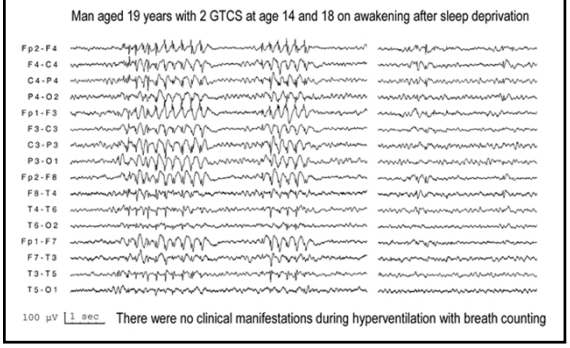
- GTCS, usually preceded by myoclonic jerks, are nearly pathognomonic of JME if they occur in the morning after:
  - a party to celebrate a birthday, end of school term or New Year's eve
  - waking up early in the morning to travel on a vacation, particularly after a late night
  - replacement of valproate with carbamazepine in women wishing to start a family
  - withdrawal of appropriate medication after many seizure-free years.

## Idiopathic Generalized Epilepsy with GTC Seizures Only

- Genetic predisposition is relatively frequent.
- EEG: generalized epileptiform discharge, photosensitive
- Normal MRI brain
- Lifelong disease
- Treatment: VPA, LTG, LEV

## Idiopathic Generalized Epilepsy with GTC Seizures Only

- a newly proposed IGE syndrome of undetermined definition and boundaries.
- patients suffer from primarily GTCS occurring at any time in wakefulness, sleep or awakening.
- Thus, this syndrome is to include 'epilepsy with GTCS on awakening' which has been extensively studied by Janz



**A boy with recurrent febrile seizures from aged of one year to 8 year**

## GEFS+

- marked genetic and phenotypic heterogeneity,
- extreme intra-familial and inter-familial clinical variations regarding seizure type, seizure frequency, severity and prognosis.
- SCN1A, SCN1B and SCN2A genes ; GABRG2 gene
- Same spectrum with more severe syndromic phenotypes: Dravet syndrome, epilepsy with myoclonic-astatic seizures of Doose

## GEFS+

- Generalized Epilepsy with Febrile Seizures plus
- Autosomal Dominant Epilepsy with Febrile Seizures plus

- GEFS+ has been described by Berkovic and his associates and has been recognized as a syndrome in development by the ILAE Task Force.

## GEFS+

- Brain MRI: normal
- EEG: depend on the clinical phenotype,
  - usually normal
  - generalized discharges, focal sharp waves
- Prognosis: usually benign and self-limited
  - non-febrile seizures occur in only 25%, infrequent, often remit by mid-childhood (median 11 years).
- Treatment: valproate, levetiracetam, topiramate

## GEFS+

- Age at onset: first months of life to childhood
- Male = Female
- Heterogeneous clinical phenotypes
  - febrile seizures plus (FS+)
  - non-febrile generalized convulsions, absences, myoclonic, atonic, myoclonic-atonic seizures.
  - focal frontal and temporal lobe seizures may occur

## Idiopathic Localization-related Epilepsy

- Benign childhood epilepsy with centrotemporal spikes (BCECTS)
- Benign childhood occipital epilepsy (BCOE)

**Benign Epilepsy with Centrotemporal Spikes**
**(BECTS)**
**or**
**Benign Rolandic Epilepsy**
**or**
**Benign Childhood Epilepsy with Centrotemporal Spikes**
**(BCECTs)**

## Characteristics

1. Onset between 2 and 14 years (3 – 10 years)
2. Simple focal motor seizure
3. Characteristic EEG foci over rolandic (centrotemporal region) with normal posterior dominant rhythm

## Benign Epilepsy with Centrotemporal Spikes

- Most common partial epilepsy
  - 10 – 20% of childhood epilepsy
  - 15.7 % of epilepsy before 15 years old
  - 24 % of epilepsy with onset 5 - 14 years
- Male predominance
- Frequent seizures: those with age of onset prior to 3 years

## Clinical Presentations

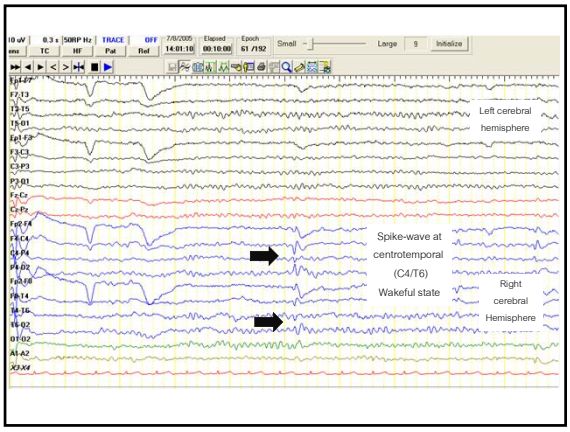
- Unilateral facial sensorimotor symptoms (>30%)
  - Tingling face or hand
  - Tonic-clonic movements of face or hand
- Oropharyngeal manifestation (>50%)
- Speech arrest (40%)
- Excessive salivation (30%)
- Nocturnal
- Status epilepticus
- Presentation as 1st unprovoked seizure

## Benign Epilepsy with Centrotemporal Spikes

- Unclear genetic basis
  - Genetic predisposition (40%)
  - Complex inheritance
  - AD trait, Chromosome 15q14, 16p
  - Mutation of potassium channel gene KCNQ2

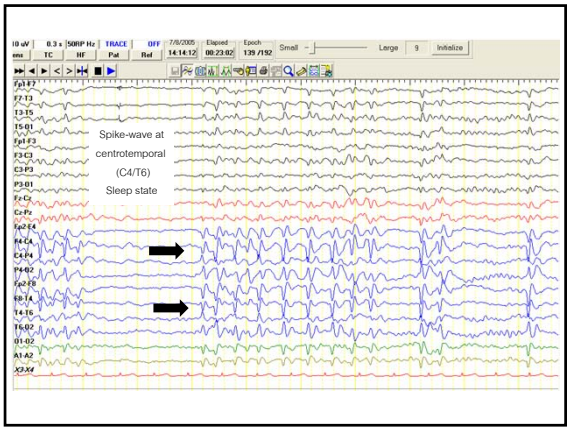
## Prognosis

- Excellent prognosis
- Spontaneous remission
- Some with neuropsychological disorders
- Evolution to or relationship with
  - Landau-Kleffner syndrome
  - Epilepsy with continuous spike-wave during slow-wave sleep




## Treatment

- To treat or not to treat: not to be treated with long-term prophylactic AED
- Weigh between risk of seizure and risk of treatment
- Rx may be considered in
  - Repeated frequent seizures
  - Status epilepticus
  - Parents' request
- Single AED therapy with excellent response




## Risk from Treatment

- Adverse effects from antiepileptic drugs
  - Hematopoietic system: aplastic anemia
  - Liver, pancreas, cardiac functions
  - Idiosyncratic drug reactions: SJS, TEN
  - Cognitive dysfunction
  - Mood and behavior problems
  - Others: weight gain or loss, tremor, etc….

## Investigation

- EEG: Wakeful, drowsy & sleep recording
- Brain imaging
  - Not necessary in typical presentation & EEG findings
  - Non-specific finding may be found in 15% without any affect to decision-making for long-term treatment
- Other blood tests
  - Not necessary

## Prognosis

- Spontaneous remission by age of 16 years
- Seizure recurrence
  - 2 – 4 yrs after onset
  - 10 -20% few seizures
- Some children with minor neuropsychiatric or neurodevelopment disability
  - Cognitive dysfunction
  - Learning disability
- Some overlap with Landau-Kleffner syndrome & ESES

## Cognitive Dysfunctions & Other Co-morbid

| Author | Year | Country | Subjects | Results | Ref: |
|---|---|---|---|---|---|
| Deonna T. | 2000 | Switzerland | 22 | Delayed speech 18%, transient weak scores (verbal, behavioral problem 31% | DMCN 2000;42:595-603 |
| Yung AWY. | 2000 | USA | 78 | LD 17% | Pediatric Neurology 2000;23:391-5 |
| Vinayan KP. | 2005 | India | 50 | Educational problems: 54% LD: 38% | Seizure 2005;14:207-212 |
| Northcott E. | 2005 | Australia | 42 | Difficulties in memory & phonological awareness | Epilepsy Res 2007;75:57-62 |
| Connolly AM. | 2006 | Australia | 30 | Lower psychological scores (than control) | Pediatr Neurology 2006;35:240-245. |
| Riva D. | 2007 | Italy | 24 (16 control) | Mild language deficits | Epilepsy& Behavior 2007;10:278-285 |
| Picinelli P. | 2008 | Italy | 20 (21 control) | Specific LD higher than control | DMCN 2008;50:353-356 |
| Boatman DF | 2008 | USA | 7 (7 control) | Impaired speech recognition | Epilepsia 2008;49:1018-26 |
| Danielsson J. | 2009 | Germany | 25 (4-7 yrs) (25 control) | 5/7 memory, language comphrehension) | Epilepsy Behavior 2009;16:646-651. |
| Volkl-Kernstock S. | 2009 | Austria | 20 (20 control) | Exhibition of attention problems & aggressive behavior | Seizure 2009;18:320-326 |
| Ay Y. | 2009 | Turkey | 25 | reading ability | Pediatr Neurology 2009;41:359-363. |
| Goldberg-Stern H. | 2010 | Israel | 36 (15 control) | Impaired attention to verbal stimuli Verbal functioning: lower than control | Seizure 2010;19:12-16. |

## Practical points

- EEG during awake and asleep in each epilepstic syndrome may have different characteristics
  - BECT: maybe only abnormal during sleep
- Both awake and asleep EEG, as well as certain activation methods should be done in individual patients with different syndrome
  - Absence: hyperventilation
  - JME: sleep deprivation, awaken during EEG

## Seizure & Cognitive Outcomes in Thai Children with Benign Rolandic Epilepsy

Cross-section study from 2002 – 2009

46 Children with BRE as the first diagnosis at Ramathibodi Hospital

- 23 boys & 23 girls
- Age range 5 – 14.5 yrs.
- Mean FU duration 19.5 mo.
- 31 pts (67.4%): taking AED
- 15 pts (32.6%): no AED without seizure recurrence

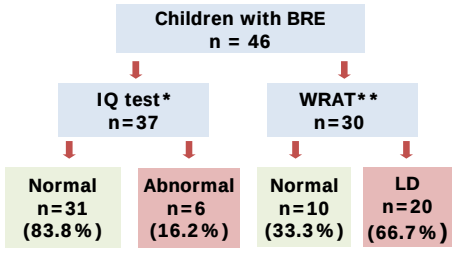
Visudtibhan A, Sakpichaisakul K, Khongkhatithum C, Thampratankul L, Chiemchanya S, Visudhiphan P.
Poster Presentation, The 8th AOEC, Melbourne, Australia 2010

## Practical point

- Physicians who order the EEG should give adequate information regarding the clinical information and other information to increase yield of diagnosis
  - Absence: adequate hyperventilation
  - BRE: include sleep portion
  - BEOP: include eye open, eye closing
  - JME: include EEG after awakening

## 46 Thai children with BRE: IQ & WRAT

**Ramathibodi Hospital 2002 - 2009**




*WISC-III (n=36) or Stanford-Binet IV (n=1)
**WRAT: Wide Range Achievement Test-Thai version

Visudtibhan A, Sakpichaisakul K, Khongkhatithum C, Thampratankul L, Chiemchanya S, Visudhiphan P.
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**THANK YOU FOR YOUR ATTENTION**