Pediatrics Symptomatic Epileptic Syndromes
29 July 2009
TES meeting

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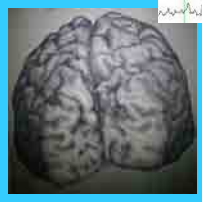
คณะแพทยศาสตร์
จุฬาลงกรณ์มหาวิทยาลัย

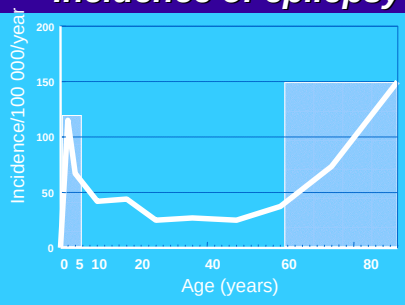
AN EPILEPTIC SEIZURE

excessive neuronal discharges



Clinical seizures

Incidence of epilepsy



PROPOSED DIAGNOSTIC SCHEME FOR PEOPLE WITH EPILEPTIC SEIZURES AND WITH EPILEPSY

Engel et al. *Epilepsia* 2001;42(6):796-803

Axis 1 **Ictal phenomenology**
- detailed description of symtoms during the seizure

Axis 2 **Seizure type or types**
- according to ictal phenomenology and EEG

Axis 3 **Syndrome**
- list of syndromes, syndromic diagnosing is not always possible

Axis 4 **Etiology**
- genetic defects, or specific pathological substrates for symptomatic focal epilepsies

Axis 5 **Impairment**
- disability caused by epilepsy

Epilepsy Classification: ILAE1981

1.Partial(Focal,Local) Seizures

A. Simple partial seizures
B. Complex partial seizures
w/ cons. impairment at onset
SPS=>CPS
C. Partial seizures (A,B) evolving into GTC.

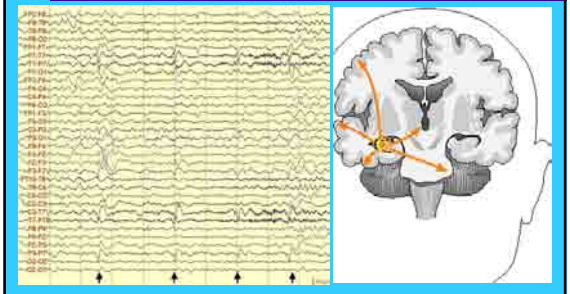
2.Generalized Seizures

Convulsive vs Non-convulsive

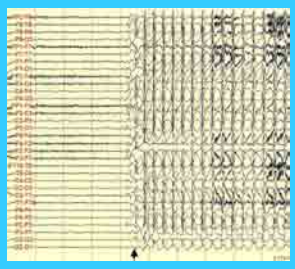
3.Unclassified Epileptic Seizures

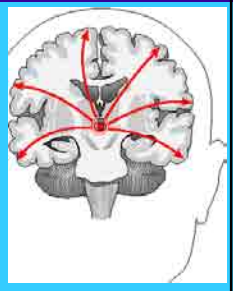
◆Based 1st on EEG then semiology

Focal seizure



Generalized seizure





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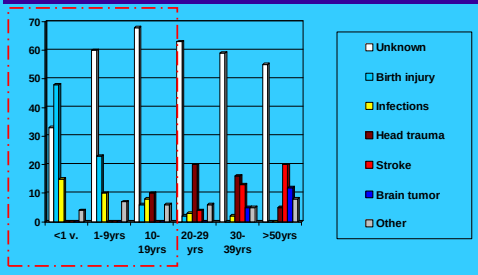
Etiology of epilepsy



Age at onset

Epileptic Syndromes #A collection of :

- most important clinical features
  - seizure type, frequency and sequence
  - age at onset, evolution and prognosis
  - mode of inheritance, family history
  - physical and mental signs and symptoms
  - response to treatment
- most important laboratory tests
  - EEG, videoEEG
  - imaging: structural and functional
  - hematological and biochemical investigations
  - molecular genetics

Syndrome Type Def:

- Idiopathic epilepsy syndrome: A syndrome that is only epilepsy, with no underlying structural brain lesion or other neurological signs or symptoms. Etiology presumed to be genetic. Usually age-dependent
- Symptomatic epilepsy syndrome: Epileptic seizures are result of an identifiable structural lesion
- Probably symptomatic epilepsy syndrome: Epileptic seizures are believed to be symptomatic, but no aetiology has been identified
- Benign epilepsy syndrome: Epileptic seizures are easily treated or need no treatment and remit without sequelae

ILAE Classification of Epilepsy

	Localization-Related (named by location)	*Generalized (named by disease)*
Idiopathic	Benign Rolandic epilepsy (Benign childhood epilepsy with centro-temporal spikes) Benign occipital epilepsy of childhood Autosomal dominant nocturnal frontal lobe epilepsy Primary Reading Epilepsy	Benign Neonatal Convulsions (+/- familial) Benign myoclonic epilepsy in infancy Childhood absence epilepsy Juvenile absence epilepsy Juvenile myoclonic epilepsy Epilepsy with GTCs on awakening Some reflex epilepsies
Symptomatic	Temporal lobe Frontal lobe Parietal lobe Occipital lobe (Rasmussen's encephalitis) (Most Reflex epilepsies)	Early myoclonic encephalopathy Early infantile epileptic encephalopathy with suppression- burst (Ohtahara's syndrome) Cortical abnormalities -malformations -dysplasias Metabolic abnormalities - amino acidurias - organic acidurias - mitochondrial diseases - progressive encephalopathies of childhood West's Syndrome Lennox-Gastaut Syndrome
Cryptogenic	(Any occurrence of partial seizures without obvious pathology.)	Epilepsy with myoclonic-astatic seizures Epilepsy with myoclonic absence

Idiopathic vs Symptomatic Generalized Epilepsies

	Idiopathic	Symptomatic
1. Etiology	Genetic	Acquired/Genetic
2. Seizure types	Absence Myoclonic Tonic-clonic	Atypical absences Myoclonic Tonic, atonic Tonic-clonic
3. Exam	Normal	Intellectual disability
4. EEG	Normal background, Spike-wave 3 Hz	Background Slowing, Spike-wave 2,5Hz
5. Imaging	Normal (cortical abnormality)	Often focal or diffuse lesions
6. Prognosis	Good	Poor

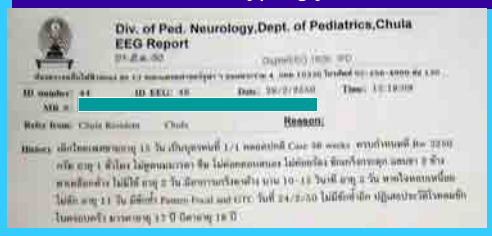
Early infantile epileptic encephalopathy with suppression-bursts (EIEE, Ohtahara´s syndrome)

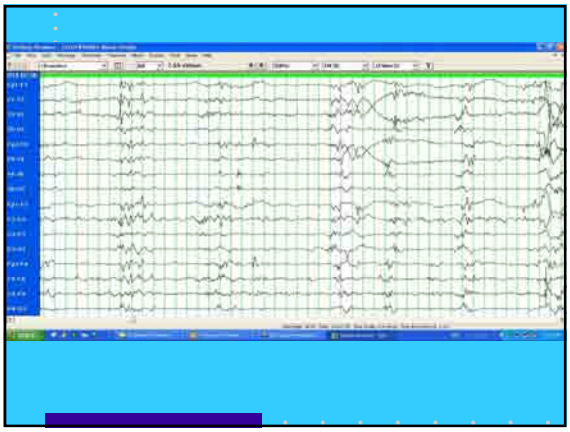
Insidence:	no data
Age of onset:	within first 3 months
Etiology:	cerebral dysgenesis, anoxia, cryptogenic
Seizures:	tonic spasm, focal motor, hemiconvulsions, generalized seizures
Background EEG:	suppression-burst
Ictal EEG:	diffuse synchronization, cluster of fast activity
Therapy:	ACTH, B6-vit., VPA, other AEDs, surgery
Prognosis:	static impairment to severe mental retardation, quadraplegia and bed-ridden, evolution to West and Lennox Gastaut syndrome, high incidence of death

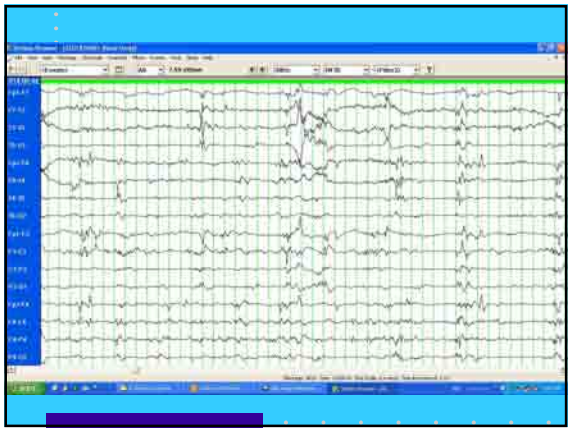
Early (neonatal) myoclonic encephalopathy (EME)

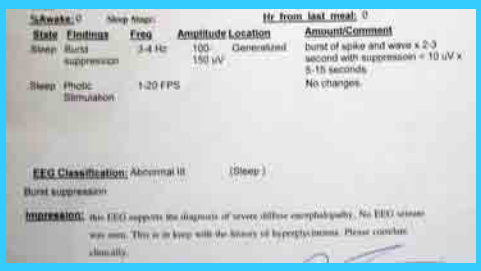
Insidence:	no data
Age of onset:	neonatal
Etiology: cryptogenic	inborn errors of metabolism, familial,
Seizures:	erratic or fragmentary myoclonus, massive myoclonus, simple partial seizures, infantile spasms, tonic
EEG:	suppression-burst
Therapy:	ACTH ineffectíve, pyridoxine may be tried
Prognosis:	progressive impairment to vegetative state, infantile spasms, high mortality in infancy

Non Ketotic Hyperglyinemia


Div. of Ped. Neurology,Dept. of Pediatrics,Chula
EEG Report



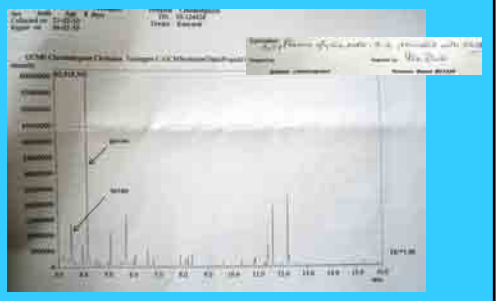




EEG Classification: Abnormal III (Sleep)
Burst suppression

Impression:

Dx : CSF / Srum Glycine Ratio



Imaging

Nonketotic Hyperglycinemia

Nonketotic Hyperglycinemia (NKH)

- **aka glycine encephalopathy**
  - Autosomal recessive hereditary metabolic disorder
    - affects the breakdown of the amino acid glycine in infants
  - Characterized by abnormally high levels of the amino acid glycine in the blood, urine, and the cerebrospinal fluid.
    - cause extensive neuronal damage in neonatal brain
    - via N-methyl-D-aspartate glutamate receptor-mediated

What is affected?

- **Glycine Cleavage System**
  - mutation in the GCS
    - inadequate supply of the enzymes necessary to the break down of glycine causing a build up of glycine in the body.
      - The *AMT* and *GLDC* genes

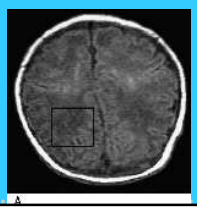


Fig. infant brain with NKH

Symptoms and Effects

Four forms of this disorder:

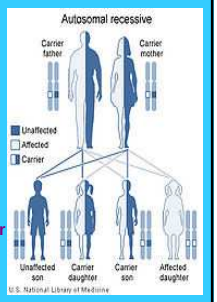
- **Neonatal form**
  - **seen in the first few days after birth**
    - low muscle tone (hypotonia), and drowsiness
    - seizures and mental retardation
- **Infantile form**
  - **six months of seemingly normal development**
    - with the exception of occasional feeding difficulties & seizures
    - varying degrees of mental retardation become evident.

Symptoms and Effects CONT.

- **Mild-episodic form**
  - **appears during childhood episodes of delirium; involuntary, jerky movements (chorea); inability to look upward (vertical gaze palsy)**
    - **fever and mild mental retardation**
- **Late-onset form**
  - **during childhood with progressive stiffness in both legs and degeneration of the optic nerve, leading to loss of sight.**
    - **Neither seizures nor mental retardation are associated**

How common is NKH?

- **Rare metabolic disorder that usually affects infants soon after birth.**
  - **Estimated 1 in 60,000**
- **Males & females appear to be affected in equal proportions.**
- **Both parents are carriers**
  - **25% chance child will be born with the disease**
  - **50% chance child will be a carrier for the gene defect.**



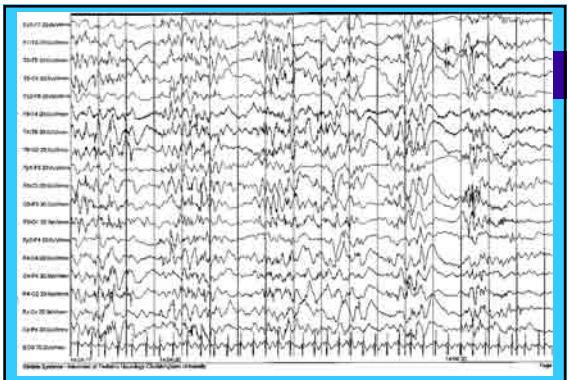
Can it be treated? How?

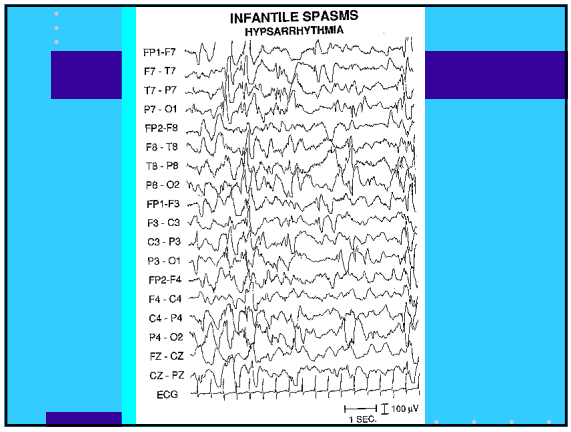
- **At this time there are no existing treatments.**
  - **Rarely children grow out of NKH and go on to live normal lives.**
- **For some individuals glycine levels have decreased but mental retardation and seizures may still persist.**

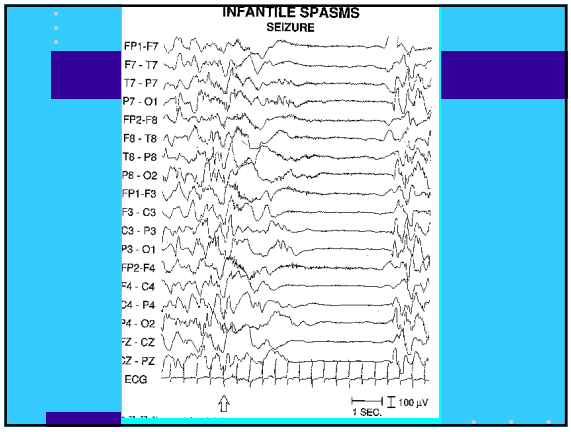
West syndrome

(infantile spasms, psychomotor deterioration, hypsarrhytmia)

Insidence:	3-5/10 000 live births
Age of onset:	50-77% between 3-7 mnths, 93% up to 2 yrs
Etiology:	Malformations, TS, 10-20% cryptogenic
Seizures:	Tonic spasms in clusters, partial seizures preceding or associated with spasms
EEG:	Ictal generalized fast activity, interictal hypsarrhytmia
Therapy:	VGB, ACTH
Prognosis:	mortality 5-31%, mental retardation 80%, epilepsy 60-80%, Lennox-Gastaut 40-60%







Lennox Gastaut syndrome

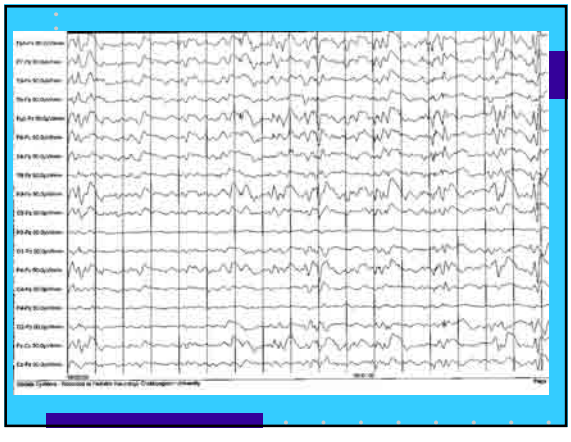
Prevalence:	2-3 % of childhood epilepsies
Age of onset:	1-8 years (peak 3-5 yrs)
Etiology:	malformations, neurocutaneous disorders, infections, 20-30% cryptogenic
Seizures:	tonic-axial, atonic and atypical absence seizures
EEG:	abnormal background activity, generalized slow spike-waves <3 Hz and, often multifocal abnormalities. During sleep, bursts of fast rhythms (~ 10 Hz) appear
Therapy:	VPA, LTG,TPM,LEV,benzodiazepines
Prognosis:	mental retardation 78-96%, resistant epilepsy

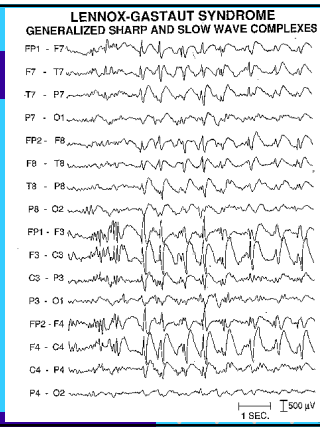
Lennox Gastaut syndrome

- Onset : Early childhood 3-5 Y(1-8 Y range)
- Clinical : MR, Multiple seizure types, Tonic seizures
- EEG : Slow SWC on abnormal background
- DOC : ?
- Precautions: benzodiazepine can induce tonic seizures

Lennox Gastaut syndrome

- ผู้ป่วยเด็กชายไทยอายุ 10 ปี มีประวัติมีไข้สูงเมื่ออายุ 4 เดือน แล้วมีพัฒนาการช้ามาตลอด แต่ไม่มีอาการชัก เริ่มมีอากรเกร็งเมื่ออายุ 5 ปี โดยจะเกร็งทั้งตัวตาเหลือก ปากเขียว นาน 2-3 นาที หลังได้รับยา carbamazepine สามวันเริ่มมีอาการหมุ่อ เรียกไม่รู้ตัวแต่ไม่เกร็งกระตุก อาการนี้หายไปเมื่อได้รับ diazepam เข้าหลอดเลือดดำ ผู้ป่วยได้รับการรักษาด้วย valproic acid และยังมีอาการชักเมื่อมีไข้หรือขาดยา Interictal EEG แสดง generalized 1-2 Hz waves maximum bifrontal





Acquired epileptic aphasia (Landau-Kleffner)

Insidence:	rare, exact numbers not available
Age of onset:	2-8 years (peak 5-7 years)
Etiology:	epileptogenic functional lesion in the speech cortex
Seizures:	sz's present in 70-80%: atypical absences, myoclonic sz, focal sz's w/ 2° generalization, variable prognosis
Clinical :	verbal auditory agnosia → aquired aphasia → behavioural and psychiatric problems
EEG:	bilateral symmetrical/asymmetrical multifocal spikes and SW in temporal and parieto-occipital regions, sleep enhances spiking up to CSWS (85% of slow wave sleep)
Therapy:	VPA, BZDs, ESM, TPM,(steroids, surgery, immunoglobulin)
Prognosis:	aphasia usually improves wtih EEG normalization before adulthood, 10-20 % may achieve complete normalization, others are left with permanent sequalae

Epilepsy & malformations of the cerebral cortex

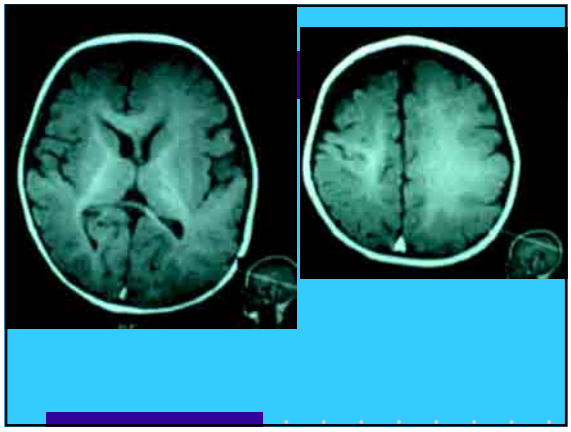
- abnormal proliferation of neurons and glia
  - hemimegalencephaly
  - focal cortical dysplasia
  - schizencephaly
- abnormal neuronal migration
  - gray matter heterotopia
  - bilateral periventricular nodular heterotopia
  - classical lissencephaly and subcortical band heterotopia
- abnormal cortical organization
- syndromes resulting from regional polymicrogyria

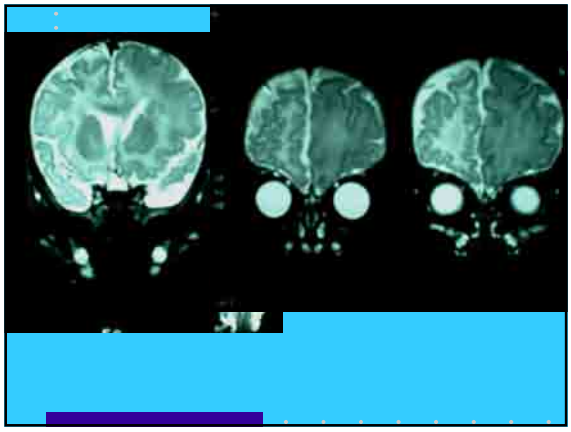
Hemimegalencephaly

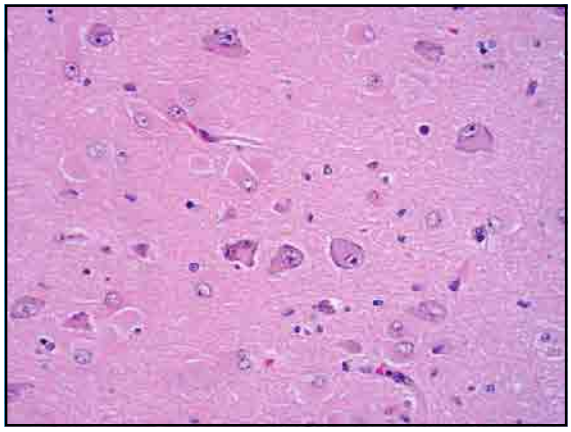
- A five month old girl who started having clonic jerking of the right arm at age four month
- NSVD, Uneventful prenatal history
- G+D Regrad face 2 m, Follow 3 m, Sit with support 5 m

- Med :
- Phenobarbital 20 mg/kg/day, Bl level > 130 uG/ml
- PHT, CBZ, Vigabatrin, Topiramate
- B6 100 mg trial

- Video-EEG monitoring :
- Interictal : > 90% Lateralized left hemisphere 10 % Rt C4 P4
- Ictal EEG : > 90 % Lateralized Lt Hemisphere







Diagnosis

Severe cortical dysplasia and hemimegalencephaly.

STURGE-WEBER SYNDROME:

STURGE-WEBER SYNDROME:

- Encephalotrigeminal angiomatosis
  - 1) leptomeningeal angiomatosis
  - 2) skin of face
  - typically the V1 and V2 portions of the Facial Nerve
- LA may be unilateral or bilateral
- Functional Neuroimaging:
  - may demonstrate a greater area of functional than anatomic abnormality

Neurologic Manifestations

- 1) Seizures
- 2) Focal deficits, such as hemiparesis and hemianopia
- 3) Stroke-like episodes
- 4) Headaches
- 5) Developmental delay
  - more common with bilateral hemangiomas

Classification

- Complete SWS: both brain and eye
- Incomplete: when only one area is affected
- Roach Scale:
  - I: Both facial and leptomeningeal angiomas
    - may have glaucoma
  - II: Facial angioma alone
    - may have glaucoma
  - III: Isolated LA;
    - usually not with glaucoma

Age of Presentation

- Typically presents at birth with facial angiomas
- However, not all children with PWS have SWS
- "Incomplete forms" occur without cutaneous features (Type III)
  - May have no suspicion until seizure or other neurolgic problem occurs
- Klippel-Trenauney-Weber: hemangiomas, hemihypertrophy

Seizures in SWS

- Incidence: 75 - 90%
- May have dual pathology: microgyria
- Survey SWF: seizures in 136/171
- Median age onset 6 months, range birth to 23 years
- Age of Sz onset:
  - 75% onset during first year
  - 86% before two years
  - 95% before 5 years
- Sz in 71% with unilateral and 87% with bilateral lesions

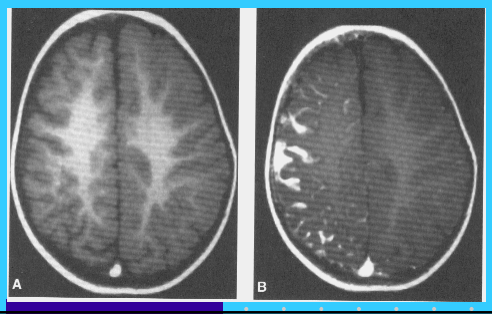
Seizures in SWS

- Majority focal
- SWF survey: 50% complete control, 39% had only partial control
- Later seizure onset: lower incidence dev delay, fewer special needs
- Roach: onset < 2 years: greater chance refractory epilepsy and MR
- Earlier onset with bilateral disease

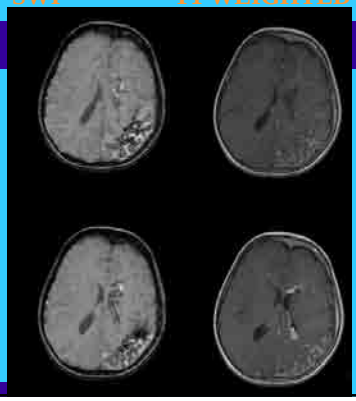
Predictors Poor Outcome

- Early Sz onset
- Extensive LA
- Refractory Sz
- Relapsing/permanent motor deficits
- HA, trauma with transient deficits
- Progressive neurologic disorder
- Focal Sz with II Genl
- Increasing Sz frequency, duration or post-ictal deficits
- Focal or diffuse atrophy
- Progressive atrophy and calcification
- Hemiparesis
- Intellectual regression

Sturge-Weber Syndrome: MRI

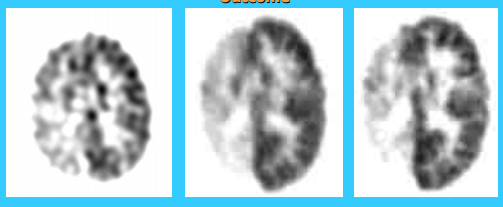


SWI T1 WEIGHTED



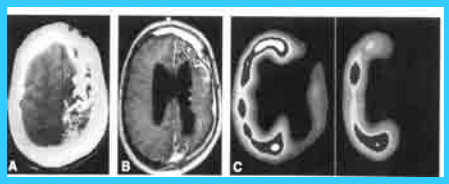
STURGE-WEBER SYNDROME:

Rapid Progression of Severe Hypometabolism is Associated with Good Cognitive Outcome



5 months 38 months 5 years

Sturge-Weber Syndrome: Neuroimaging



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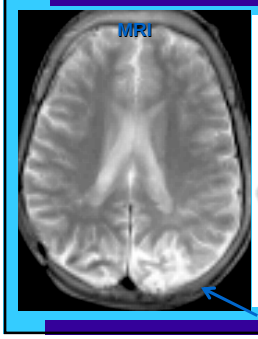
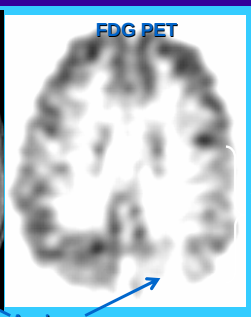


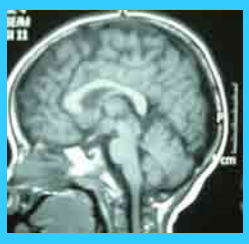


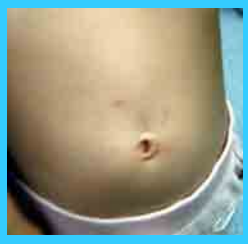
Large Area of Mild Glucose Hypometabolism is Associated with Poor Cognitive Outcome

Angioma

Tuberous Sclerosis

A 3 year old girl, presented with giggling!





Tuberous Sclerosis

- CNS pathology : Multiple cortical tubers / SEGA-> Hydrocephalus
- CCF :
  - Not all the tubers are epileptogenic,
  - Interictal EEG/Video EEG monitoring and Ictal SPECT can elucidate the tuber which is “epileptogenic”
  - Good Surgical outcome-> significantly improved seizure control

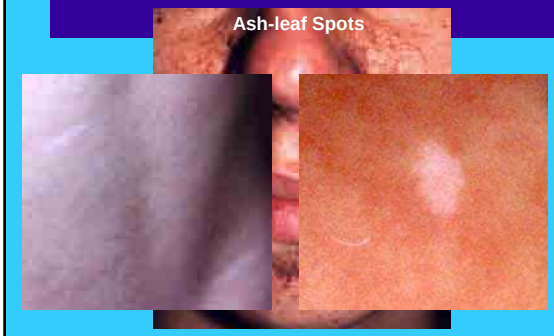
Tuberous Sclerosis

- Epiloia or Bourneville’s disease.
- 1:5000-1:10000
- Damage of one of two genes which regulate growth.
- Hamartomas in variety of organ.
- Most common - brain, kidneys, skin.
- Can present at any age.
- Variation in severity

Tuberous Sclerosis : Genetics

- AD transmission, variability in symptoms.
- Mutation on either TSC1 (Tuberous sclerosis) gene (chromosome 9) or TSC2 gene (chromosome 16).
  - Gross deletion/insertions and micromutations.
- 60-70% are sporadic (new mutations).

Adenoma Sebaceum



- Cutaneous Manifestations
  - **Others**
    - Cafe-au-lait spots (7-16%)
    - Fibromas: flattened and can appear on the trunk, gingivae, periungual region, and along the hairline or eyebrows.
    - Koenen's Tumors (20%): Subungual or periungual fibromas, usually first appear in adolescence, toes>fingers.

- Neurologic Manifestations
  - **Cortical tubers**
    - Focal, gray-white matter interface
    - Microscopically - loss of normal cytoarchitecture, abnormal neurons and glial cells.
    - MRI > CT
    - Number and size correlate with seizures and mental retardation.

- Neurologic Manifestations
  - **Subependymal nodules**
    - Usually line the third ventricle. Large, irregular cells that are more densely aggregated and more uniform in appearance compared with the cortical tubers.
    - Some will grow > than 3 cm in diameter => called subependymal giant cell astrocytomas (5%).
    - Histologic features similar to cortical nodules.
    - Subependymal giant cell astrocytomas can cause severe clinical manifestations: elevated intracranial pressure, diminished vision, hemiparesis.
    - Later in life, subependymal nodules often calcify.

- Neurologic Manifestations
  - **Seizures (60-90%)**
    - Most common symptom of TS.
    - Risk of sudden epileptic death.
    - Initially may present as infantile spasms:
      - 25-50% of patients with infantile spasms later develop signs of TS.
      - Can appear as early as 1 week of age.
      - Later develop other types of generalized seizures.

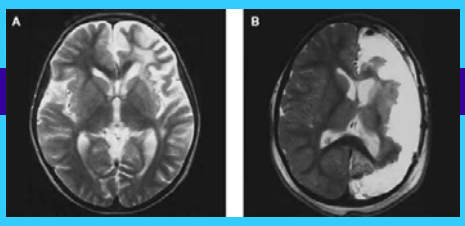
- **Mental health -**
  - Very common, very difficult.
  - More in children with epilepsy.
  - May be associated with tubers in temporal area.
  - Autism (25%) and autism spectrum disorders (50%).
  - Sleep disturbances.
  - ADDH +/- hyperactivity.
  - Anxiety and depression.

- **Development and learning disorders**
  - Developmental delay (40-60%).
  - Learning difficulties (40-60%).
  - More in children who present with infantile spasm and epilepsy.
  - The earlier the onset of seizures the greater the likelihood of mental retardation (if seizures begin <1 year of age a 92% chance of MR).

Rasmussen's Encephalitis

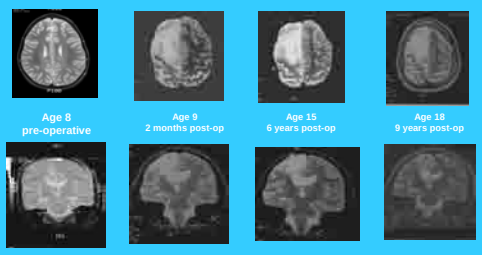
- A 9 year old girl with a 2-3 years Hx of Rt arm jerking.
- Initially controlled with CBZ for 1-2 months
- Progressively worsen to the face / leg with right hemiparesis

Figure 3 Epilepsy surgery in Rasmussen's encephalitis



Kuzniecky R and Devinsky O (2007) Surgery Insight: surgical management of epilepsy
Nat Clin Pract Neurol **3**: 673–681 10.1038/ncpneuro0663

Progression of a Rasmussen's Case



Age 8
pre-operative

Age 9
2 months post-op

Age 15
6 years post-op

Age 18
9 years post-op