Epilepsy
Minisymposium

- Clinical presentation – semiology
- Causes of epilepsy in childhood
  - Benign syndromes
  - Structural abnormalities
- Applied embryology and genetics
- Neuroradiology
- Goals in workup:
  - Anatomical imaging
  - Physiological imaging
  - New therapies
Epilepsy
Marriage law

• 1757
  • marriage is prohibited for people with epilepsy

• 1915
  • marriage is prohibited for people with epilepsy of internal cause

• 1969
  • by law acceptable to get married

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Epilepsy

Clinical definitions

Etiology → Epilepsy → Seizures → Semiology

- Tuberous Sclerosis → Temporal lobe epilepsy → Partial seizure
- West's syndrome → Spasms
- Lennox-Gastaut → Atypical absences → Tonic drop → GTCS

Epilepsy

Classification of epileptic seizures (ILAE, 1981)

- Partial seizures
  - Simple partial seizures
  - Complex partial seizures
  - Partial seizures ⇒ sec generalization
- Generalized seizures
- Unclassified epileptic seizures
### Epilepsy

#### The typical epileptic seizure

- Sudden change in conscious
- Tonic ⇒ clonic muscle contractions
- Cyanosis
- Tongue-bite
- Urination

<table>
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<tr>
<th>Ictal phase; 1-3 minutes</th>
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<th>Postictal phase; 5-60 minutes</th>
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<tr>
<td>Loss of conscious and noisy breathing</td>
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<td>Slowly waking up with transient confusion</td>
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#### The epileptic seizure

- **Aura**
  - abdominal
  - déjà vu
  - fear
  - taste
  - smell
  - visual
  - other sensory

Can’t see when looking at the pat.
Is a true seizure
Semiological seizure classification
Lüders et al., Epilepsia 1998;39:1006

<table>
<thead>
<tr>
<th>Aura</th>
<th>Somatosensory</th>
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<tr>
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<td>Auditory</td>
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<th>Autonomic sz</th>
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<td>Dialeptic sz</td>
<td>Simple motor sz</td>
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<td>Myoclonic sz</td>
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<td>Epileptic spasm</td>
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<td>Tonic-clonic sz</td>
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<td>Tonic sz</td>
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<td>Clonic sz</td>
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<td>Hypermotor sz</td>
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<td>Gelastic sz</td>
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<th>Motor sz</th>
<th>Complex motor sz</th>
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<td>Special sz</td>
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<td>Atonic</td>
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<td>Hypomotor</td>
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<td>Negative myoclonic</td>
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<td>Astatic, Akinetic, Aphasic</td>
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Partial seizures arising in the temporal lobe

Typical features:
- Postictal confusion
- Headache
- Secondary generalization much less common
- Duration longer (> 2min)

Distinction between:
- Mesial temporal lobe (limbic)
- Lateral temporal lobe

Subcategorization into e.g. opercular, temporal polar is seldom valid or useful.
Mesial temporal lobe (limbic seizures)

**Aura**
- Rising epigastric sensation
- Gustatory symptoms
- Affective symptoms
- Speech ceases - dominant side
- Simpl auditory phenomena - sup temp gyrus
- Unpleasant olfactory sense
- Autonomic symptoms
  - change in skin colour,
  - blood pressure, heart rate,
  - pupil size, piloerection

**Absence**
- Motionless stare
- Dystonic posturing or spasm of the contra lateral arm

**Automatisms**
- Gestural
- Fumbling
- Repetitive motor actions
- Undressing
- Walking
- Running
- Oro-alimentary
  - Lip-smacking
  - Chewing
  - Swallowing

Lateral temporal lobe (temporal neocortical seizures)

Consciousness preserved longer

Aura include hallucinations which are often structured
- Visual, auditory, gustatory, olfactory
- Illusions of size (micropsia, macropsia), shape,
  - Weight, distance or sound
Frontal lobe seizures

Clinicl features

- Frequent attacks with clustering
- Brief stereotyped seizures
- Nocturnal attacks
- Sudden onset and cessation
- No complex aura
- Version of head and eye common
- Prominent ictal posturing (SMA “en garde”)
- Prominent bilateral motor automatisms (typically lower limb)
- No postictal confusion
- Frequent secondary generalization
- History of status epilepticus

Partial seizures of central (peri-rolandic) origin

Clinicl features

- Often no loss of consciousness
- Contra-lateral jerking
- Contra-lateral tonic spasms or dystonia
- Posturing, often bilateral
- Speech arrest and paralysis of bulbar musculature
- Contra-lateral sensory symptoms
- Short frequent recurring attacks
Classification of epileptic seizures
(ILAE, 1981)

• Partial seizures
• Generalized seizures
  – Absence seizure
    • Typical absences
    • Atypical absences
  – Myoclonic seizures
  – Clonic seizures
  – Tonic seizures
  – Atonic seizures
• Unclassified epileptic seizures

Classification of the epilepsies
and epilepsy syndromes
(ILAE 1985)

• Generalized
• Localization-related
• Undetermined as to whether focal or
generalized
• Special syndromes
Classification of the epilepsies and epilepsy syndromes (ILAE 1985)

- Generalized
  - Idiopathic
    - Childhood absence epilepsy
    - Juvenile myoclonic epilepsy
  - Cryptogenic or symptomatic
    - West syndrome
    - Lennox-Gastaut syndrome
    - Myoclonic astatic epilepsy
  - Symptomatic
    - Localization-related
    - Undetermined as to whether focal or generalized
    - Special syndromes

Childhood absence epilepsy ("Petit mal")

- Boys:girls 1:2
- 4-10 years
- Sometimes
  - clonic phenomena
  - tonic phenomena
  - automatisms
- Provoked
- Often easy to treat
- Prognosis often good
Generalized epilepsy “with febrile seizures plus”

- Autosomal dominant; high penetrance
  - SCN1A Na-channel, α1-subunit 2q24
  - SCN1B Na-channel, subunit 19q13
  - SCN2A Na-channel, subunit 2q23-24
  - GABRG2 GABA-receptor, γ2-subunit 5q14-15
- Defect voltage-sensitive Na\(^+\)-channel
- Febrile seizures continuing after 6 years of age
- \(\Rightarrow\) puberty or 30-40 years
- 30% of relatives with the genetic abnormalities have other epilepsies: - severe infantile myoclonic epilepsy
- More unknown than unusual!

Classification of the epilepsies and epilepsy syndromes

- Generalized
- **Localization-related**
  - Idiopathic – with age-related onset
    - BECTS
  - Symptomatic
    - Temporal lobe epilepsies
    - Frontal, parietal, occipital lobe epilepsies
  - Cryptogenic
- Undetermined as to whether focal or generalized
- Special syndromes
Benign partial epilepsy with centro-temporal spikes  
(Rolandic epilepsy; BECTS)

- 15-25%
- 2-13 years, 3/4 between 5-10 years
- Boys:girls, 60:40
- Autosomal dominant gene
- Very easy to treat - 100% responders.
- Prognosis very good

Rolandic spikes in EEG 2-20 years

Hippocampal Region Asymmetry Assessed by 1H-MRS in Rolandic Epilepsy

Lundberg et al., Epilepsia 2003;44:205-210

A. Hippocampal abnormalities on MRI in 6/18 children with RE
B. Asymmetry of the tNAA/tCr ratios in hippocampal regions on MRS 
   -indicates an abnormal neuronal function in children with RE
Classification of the epilepsies and epilepsy syndromes

• Generalized
• Localization-related
• Undetermined as to whether focal or generalized
  – Severe myoclonic epilepsy in infancy
  – Electrical status epilepticus in slow wave sleep
  – Acquired epileptic aphasia (Landau.Kleffner)
• Special syndromes

Classification of the epilepsies and epilepsy syndromes

• Generalized
• Localization-related
• Undetermined as to whether focal or generalized
• Special syndromes
  – Febrile convulsions
  – Isolated seizures or isolated status epilepticus
Why important to classify among > 60 epilepsies?

Localization-related
- Idiopathic – with age-related onset
  - BECTS

Generalized
- Idiopathic – with age-related onset
  - Childhood absence epilepsy
  - Juvenile myoclonic epilepsy

When diagnosed (>35%) neuroradiological investigation is not necessary!

Epilepsy

Johan Lundgren, Lund, Sweden

Clinical presentation – semiology

Causes of epilepsy in childhood

- Benign syndromes
- Structural abnormalities
  - Refractory epilepsy
  - Catastrophic epilepsy
Epilepsy in Childhood

Structural abnormalities?
Regular MRI helps to:

• Diagnose etiology
• Chose the most adequate choice of treatment.
  Treatment is guided in relation to
  • etiology
  • epilepsy
  • seizure
• Estimate the prognosis

Nr AED ↑ - do all have to be tested??

• Camefield and Camefield (1996): 486 children, 417 followed 4 years,
• 83% responded on 1st AED, seiz free 1st year. 4% of these later refractory epilepsy
• 42% responded next 3 years on any AED or combination. “failure of three major AED’s at maximal tolerated dosages means that success with additional AEDs is extremely unlikely” (Camfield and Camfield)
Early identification of refractory epilepsy
(Kwan and Brodie; N Engl J Med 2000;342:314)

3% seizurefree 3:rd AED or 6% multiple AED

Epilepsy in Childhood
Refractory epilepsy:

- **Intractable Epilepsy**
  - period of > 2 years
  - NIH consensus
    - “have not been brought under acceptable control with the resources available to the primary care physician or neurologist”
    - “at least several seizures during each 6-month period”
    - “at least one seizure per month”
    - “at least one seizure per year”

- **Catastrophic Epilepsy**
Catastrophic Epilepsy in Infancy and Childhood
Ishii et al., 2002 Ped Neurol 2002:369

- Daily focal or generalized seizures
- Resistant to AED
- At least 3 months, onset before 5-6 years of age
- Catastrophic clinical course
  - Developmental arrest
  - Cognitive impairment
  - Negative social outcome

Epilepsy in Childhood
Questions?

- Could therapy alter outcome?
  - Seizures
  - Neurodevelopmental consequences
- What is the goal of therapy?
Epilepsy in Childhood

Treatment

• Initial goal for adequate treatment
  – recognition of that your patient do have a refractory epilepsy
  – etiology
  – act accordingly

Etiology

The most important clue to treatment
Classification of the epilepsies and epilepsy syndromes (ILAE 1985)

- Generalized
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    - Juvenile myoclonic epilepsy
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    - West syndrome
    - Lennox-Gastaut syndrome
    - Myoclonic astatic epilepsy
  - Symptomatic
    - Localization-related
    - Undetermined as to whether focal or generalized
    - Special syndromes

Catastrophic Epilepsies

- Ohtahara syndrome +
- Severe myoclonic epilepsy of infancy -
- Infantile Spasms ++
- Lennox-Gastaut syndrome +
- Epilepsy with myoclonic-astatic seizures (Doose) -
- Sturge-Weber syndrome ++
- Rasmussen encephalitis +++
- Partial epilepsies with CD ++
- Gelastic Epilepsy +
Epilepsy in Childhood

**Ohtahara syndrome**
Early infantile epileptic encephalopathy (EIEE)

- **Etiol:** Severe encephalopathy, major malformation,
- **Seiz:** Tonic
- **EEG:** Multifocal, burst suppression.
- **Progn:** Poor, IS, LGS.

- **Vit B6-dependency**
- **Folinic acid responder**
- **Glut-1 deficiency**

**AED**
VGB, LTG, ACTH

**Ep Surg**

**Ketogenic Diet**
VNS
New AED

Catastrophic Epilepsy in Childhood

**Severe myoclonic epilepsy of infancy**
Dravet syndrome

- **Etiol:** Genetic. SCN1A (2q24) and GABRG2.
- **Seiz:** Myoclonic. GTCS. Later atypical absences. Myoclonic SE.
- **EEG:** Normal → gen polyspike-slow waves
- **Progn:** CP. Ataxia. Mental Retardation.

- **Prolonged, unilateral,**
- **Clonic, longlasting**
- **febrile convulsions!**

**AED**
VPA, TPM, Benz.

**Ep Surg**

**Ketogenic Diet**
VNS
New AED
Infantil spasms
(Blitz-Nick-Salaam Krämpfe)
- 3-7 (-9) months of age
- 0.24 - 0.42 /1000
- Flexion-extension spasm. Series
- Patient and doctors delay, 2-5 m
- EEG: Hypsarrytmia
- Symtomatic
  - Tuberous Sclerosis 25%
  - Prenatal malformations
    - Aicardi. Lissencephaly. Down
  - Asfyxia
  - Mental retardation
- Idiopathic 20%
- Prognosis: Mentally normal - 12-25%
  (among idiopathic 40%)

Epilepsy in Childhood
Lennox-Gastaut syndrome

Etiol: Pre-, peri- and postnatal etiology. All kinds
Seiz: axial tonic ⇒ tonic/ataonic, atyp absences, myoclonia
EEG: Abnormal background. Multifocal slow wave. 10/sec
Progn: Poor. 80-90% cont seizures. Slow cogn devel - MR

AED
VPA, CLON, CLOB, LTG

Ep Surg

Ketogenic Diet
VNS

New AED
TPM, LEV, FEL
Epilepsy in Childhood

Epilepsy with myoclonic-astatic seizures (Doose)

- Polygenetic inheritance
  - Close relative 32% epilepsy onset <5 years (½-8 years)
  - SCN 2ANa-channel, subunit, 2q23-24
- 1-2%, M:F 2:1
- Normal development before onset seizures

- Seizures:
  - Myoclonic
  - Atonic, myoclonic-tonic
  - Short absences
  - GTCS
- Febril GTCS; the presentation seizures

Epilepsy with myoclonic-astatic seizures (Doose)

EEG: Generalised picture

A. initial EEG often normal
B. "preudofoci"

4 year old boy sudden onset with a jerk followed by a fall. Later absences.
Epilepsy with myoclonic-astatic seizures (Doose)

EEG: Generalised picture

Close to non-convulsive status epilepticus
Epilepsy in Childhood

Vascular malformation

- AVM
- Cavernous Angioma
  - Bleed
  - Presenting signs
    - Epilepsy
    - Headache
    - Psychiatric symptoms

Epilepsy in Childhood

Sturge Weber’s Syndrom

Epilepsy: 90%. Age onset median 31 mon
Seizures: Partial. Often SE.
EEG: Focal. 30% bilat synkr spike wave or polyspike-wave
Epilepsy in Childhood

Rasmussen’s encephalitis

Etiol: Viral. Autoimmune.
Seiz: Partial. All types. SE.
EEG: Focal. “jumping of ictal activity”
Progn: Fare after surgery

AED           Hemispherectomy

Ketogenic Diet  VNS  New AED

Rasmussen’s encephalitis


- Pediatric syndrome, mean age at onset 6.8 years (Montreal).
- Starts as partial seizures, initially benign appearance but evolving to refractory
- Hemiparesis and mental retardation
- Histology: cortical inflammation in one hemisphere, perivascular lymfocytic infiltration, microglia proliferation, neuronal loss and gliosis
Rasmussen’s Encephalitis

Definition:
(From Hart, Andermann et.al. Neurology 1994;44:1030).

• Epilepsia partialis continua +
  one of the following criteria
  • Progressive neurological deficit after ep onset
  • Progressive hemispheric atrophy without signal abnormalities (on MRI)
  • CSF showing mono- or oligoclonal banding.
  • Biopsy evidence of chronic encephalitis

Epilepsy in Childhood

Rasmussen’s encephalitis

• Presentation: Seizures + EEG
  – Often start as SE
  – All different types of seizures.
  – EEG often showing “jumping of ictal activity”.
• 38% associated infection.
• Autoimmun sjukdom
  – GluR3 autoantibodies
  – Respond to plasmafereses, IVG and corticosteroides
  – Ep-surgery - hemispherectomi
MB, Girl 8 years of age

- Vomiting, short periods of shaking L arm
- Absences, gaze upward to L,
- Part Status Epilepticus, R-side, face, arm, leg, language problems

Rasmussen's Encephalitis
MB, Girl 8 years of age

- No AED effective
- Anti-viral therapy, IVG, plasmapheresis, steroids ineffective
- Ketogenic Diet ineffective
- After surgery seizure-free without AED
Clinical outcome of hemispherectomy for epilepsy in childhood and adolescence

Devlin et al., Brain 2003;126:556

33 children, mean age at surg: 3.4y (0.33-17)

Pre-op development

Seizure outcome

4/30 ↑ developmental performance
5/6 with exp language difficulties improved
11/12 with behavioural problems improved
Epilepsy in Childhood

Girl 2 months old

• Norm pregn. GA 40. BWt 3760 g. R side of the face prominent. Naeveus.
• GTCS at age 17 days. Fenobarbital – seizure-free 3 weeks. Head drops + drop-attacks. +VGB. Some myoclonic jerks.
• Seizure-free 4 weeks.

Investigation - Imaging

• Thick cortex R. Volume ↑. Frontal heterotopic bands
Classification Scheme for Malformations of Cortical Development
Barkovich et al., Neuroped 1996;27:59-63

• I. Unnormal neuronal and glial cell proliferation
  – Non-malignant
    • Tuberous sclerosis
    • Focal cortical dysplasia balloon cells
    • Hemimegalencephaly
      – Isolated
        – With neurocutaneous syndromes
  – Malignant
    • DNET, Ganglioglioma

• II. Unnormal neuronal migration
  – A. Generalized
    • 1. Classical type 1 Lissencephaly
    • 2. Cobblestone type 2 lissencephalies
    • 3. Heterotopia
      – a) Subependymal (=periventricular nodular) -X-linked
      – b) Subcortical
  – B. Focal or multifocal malformation of neuronal migration
Catastrophic Epilepsy in Childhood

Hemi-megalencephaly: Genetic, clinical and imaging aspects
Flores-Sarnat J Child Neuro 2002;17:373

• Cranial asymmetry, facial asymmetry, language, mental retardation, hemiparesis hemianopia.
• Epilepsy, often intractable

Catastrophic Epilepsy in Childhood

Hemimegalencephali: Classification

• Isolated
• Syndromic
  – Epidermal nevus syndrome
  – Klippel-Trénaunay-Weber syndrome
  – Proteus syndrome
  – Hypomelanosis Ito
  – Neurofibromatosis
  – Tuberous sclerosis
  – Aicardi syndrome, Hirschsprung disease
• Total hemimegalencephali
Hemimegalencephali: Epilepsy
Flores-Sarnat J Child Neuro 2002;17:373

- 93%, onset neonatal period
- Refractory ⇒ catastrophic epilepsy
- Different epilepsy syndromes
  - Ohtahara syndrome
  - West syndrome 50%
- Different seizures
  - partial, complex partial, motor
  - sometimes sec generalization
  - spasms
  - myoclonic seizures
  - status epilepticus ⇒ death
  - Ep partialis continua for years!

Catastrophic Epilepsy in Childhood

Girl Hemimegalencephaly; Epilepsy surgery 7½ months of age

- 18 months of age: close to 100% seiz red.
  AED: VGB + VPA
- Accelerating development
- PAD: Severe CD
Congenital bilateral perisylvian syndrome: a study of 31 patients: MRI
Kuzniecki et al., Lancet 1993;341:608-612

- Bilateral perisylvian involvement
- Opercular region alone
- Out to parietal and sup temp regions
- Polymicrogyria
- No nodular heterotopia
- Symmetrical >80%

Classification Scheme for Malformations of Cortical Development
Barkovich et al., Neuroped 1996;27:59-63

- III. Unnormal cortical organisation
  - A. Generalized
    - PMG, Polymicrogyria
  - B. Focal or Multifocal
    - PMG/Schizencefaly
      - Bilat. Symmetrical PMG
      - Bilat. perisylvian PMG
    - Asymmetrical
      - Schizencefaly with a mixture Schizencefaly/PMG
    - Focal or multifocal cortical dysplasia without balloongcells
    - Microdysgenesis

cont.
Perisylvian Syndrome

Congenital bilateral perisylvian syndrome: a study of 31 patients

*Kuzniecki et al., Lancet 1993;341:608-612*

31 patients

- Reduced tongue-mobility 100%
- Severe dysarthria, nasal speech 97%
- Epilepsy 81%
- Mild/moderate MR 75%
  - Delayed motor development 75%
  - Delayed speech development 100%
- Dysphagia 81%
- Absent gag reflex 75%
- Drowling 71%
- Symptom pyramidal tract 71%
- Presenting: Difficulties feeding especially when introduced solid food.
Congenital bilat perisylvian syndrome
Associated malformations 30%

- Arthrogryposis multiplex 4%
- Pes planovalgus 6%
- Mild pyramidal tract sympt 60%
- Quadriparesis 3%

The epileptic spectrum in the congenital bilateral perisylvian syndrome: Epilepsi
Kuzniecki et al., Neurol 1994;44:379-385

- Onset: 1m- 14 year, 7/27 onset < 5 år.
- 4/27 infantil spasms (one presenting)
  - 3/4 responded to ACTH. Seizfree until 6 years of age
- 6 different epilepsy pattern:
  - 19/26 atonic and tonic drop attacs
  - 16/26 absences and/or short atonic
  - 9/26 GTCS.
  - 21/26 short tonic/atonic or atyp absences
  - 7/26 partial seizures
    - 3/7 without sec generalization
    - 4/7 clonic seiz in lips with sec propagation to face + sec gen.
### The epileptic spectrum in the congenital bilateral perisylvian syndrome. Epilepsy

**Kuzniecki et al., Neurol 1994;44:379-385**

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<tr>
<th>EEG</th>
<th>Treatment</th>
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<tr>
<td>• Normal background 50%</td>
<td>• AED: to all with epilepsy</td>
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<tr>
<td>• Bilat synkron spike-wave act 10/26</td>
<td>• Polytherapy 17/27,</td>
</tr>
<tr>
<td>• Bilat slow spike-wave act or multifocal</td>
<td>– 10 2 AED,</td>
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<tr>
<td>centro-temporo-parieto act 7/26</td>
<td>– 7 3 AED.</td>
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• 7/26 callosotomy
• Ketogenic diet

### Familial Perisylvian Polymicrogyria: A New Familial Syndrome of Cortical Maldevelopment

**Guerreiro et al., Ann Neurol 2000;48:39-48**

• 12 families, 42 patients, 10 centers
• Clinical heterogeneous group
  – abnormal tongue movements
  – dysarthria
• Genetically heterogeneous
  – X-linked inh 10 families
Epilepsy has many etiologies. It is associated with developmental arrest, cognitive impairment, and negative social outcome.

Remember epilepsy surgery.

However many epilepsies are compatible with normal well-being.

Johan Lundgren
Lund
Sweden