Classification of Epilepsies & Epilepsy Syndromes: Evolution of Concepts

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Scientific Advances since 1960s

- Genomic technology
- Molecular Genetics
- Computational capabilities
- Neurophysiology
- Neuroscience
- Developmental Neurobiology

- Neuroimaging
  - Structural
  - Functional

- Therapeutic options

1968: “Earthrise”
Apollo 8
ILAE Classifications of Epilepsy and Seizures

- 1969 – Gastaut – Proposals - seizures & epilepsies
- 1970 – Gastaut – Classification - seizures
- 1970 – Merlis – Classification - epilepsies
- 1981 – Commission – Classification – seizures
- 1985 – Commission – Classification - epilepsies
- 1989 – Commission – Classification - epilepsies
- 1993 – Commission – epidemiological standards
- 2001 – Blume – Glossary of ictal semiology
- 2001 – Engel – Proposed diagnostic scheme
- 2005 – Fisher – Definition of seizure and epilepsy

All in Epilepsia

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What is a classification and what should it do?

- A classification is a system for representing knowledge about items that are then placed within that system so as to reflect key characteristics.
- Teach (G. D. Jackson, 2011).
Classifications or Classification Systems

The tree of life

Periodic table of the elements
Purpose of the International Classification of Seizures and Epilepsies

- “To provide a common international terminology and classification – a precondition for comparability of results in research and therapy and for meaningful exchange of ideas”
Purpose of the International Classification of Seizures and Epilepsies

- “To provide a common international terminology and classification – a precondition for comparability of results in research and therapy and for meaningful exchange of ideas”

- Largely for clinical (treatment) purposes

- Research into causes and mechanisms was not a dominant focus
ILAE Epilepsy Syndromes (1989)

1.1. Localization-related: idiopathic
- Benign childhood epilepsy with centrotemporal spikes
- Childhood epilepsy with occipital paroxysms

2.1. Generalized epilepsy: idiopathic
- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- GTC upon awakening

2.2. Generalized: cryptogenic/symptomatic
- West’s syndrome (infantile spasms)
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic-astatic seizures
- Epilepsy with myoclonic absences

2.3. Generalized: symptomatic
- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy

3.1. Epilepsy with both focal and generalized
- neonatal seizures
- severe myoclonic epilepsy in infancy
- Landau-Kleffner syndrome

4. Special syndromes
- febrile seizures
Terms and Concepts

- Terminology:
  - Words should say what they mean, mean what they say
  - Based on relevant, useful, valid concepts
  - Use should be transparent
- Old terms are **barriers** to patient care:
  - Idiopathic-symptomatic-cryptogenic
  - Generalized epilepsy – focal epilepsy
  - Complex partial – simple partial
Terminology for etiology

- **Idiopathic** – “There is no underlying cause other than a possible hereditary predisposition. Idiopathic epilepsies are defined by age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic etiology.”

- **Symptomatic** epilepsies and syndromes are considered the consequence of a known or suspected disorder of the central nervous system (CNS).

- **Cryptogenic** refers to a disorder whose cause is hidden or occult. Cryptogenic epilepsies are presumed to be symptomatic, but the etiology is not known.

  - Commission Report, Epilepsia, 1989
“Idiopathic” & “Symptomatic” vague, “sloppy” connotations

- **Idiopathic:**
  - “Benign, easily treated”
  - **Instead: say what you mean**
    - Self-limited
      - The epilepsy often resolves on its own in time
    - Pharmacoresponsive
      - The seizures have a high likelihood of coming under complete control with AEDs

- **Symptomatic**
  - Bad outcome
    - Seizures
      - Cognitive-developmental
  - **Instead: Say what you mean**
    - Pharmacoresistant
    - Surgically remediable
    - Risk of developmental impairment
- Say what you mean

**Epilepsy based on Etiology**

- Genetic
- Structural/metabolic
- Unknown cause
Genetics of Epilepsies

Majority of cases: Complex inheritance
Complexities of classification
Many genes, currently unknown
Modified by environmental factors

Rare families: Simple inheritance
Multiple single gene disorders
? genes relevant to majority of cases

? < 5% families
Genetic Epilepsies

- **Voltage-gated ion channel subunits**
  - Sodium - GEFS\(^+\), Dravet, infantile seizures
  - Potassium - neonatal seizures, absence epilepsy
  - Chloride - generalized epilepsies
  - Calcium - absence epilepsy, generalized epilepsies

- **Ligand-gated ion channel subunits**
  - Nicotinic receptors - frontal lobe epilepsy (ADNFLE)
  - GABA receptors - GEFS\(^+\), absence epilepsy, juvenile myoclonic epilepsy

- **Non-ion channel genes**
  - LGI1 - temporal lobe epilepsy

- **Other genes** - \textit{BRD2}, \textit{ATP1A2}, \textit{KCNA1}, \textit{ME2}, \textit{EFHC1}, \textit{CRH}, \textit{KCNMA1}
Constance
Absence
Onset 6 yr

Kathryn
Absence
Onset 6 yr

Twins of William Lennox, 1950
Twins with Generalized Epilepsy

- Casewise concordance in GE for identical (MZ) twins
  - MZ 0.8  DZ 0.2  (n= 46; Berkovic et al)
  - MZ 0.8  DZ 0.0  (n= 23; Lennox series reanalyzed)

- All concordant pairs share the same syndrome

Twins with JME, studied by William Lennox
Structural/metabolic Epilepsies

- Malformation of cortical development
  - Focal cortical dysplasia
  - Lissencephaly
  - hemimegalencephaly
- Neurocutaneous syndromes
  - Tuberous sclerosis complex
  - Sturge-Weber syndrome
- Acquired epilepsy
  - Tumor
  - Infection/trauma
  - Perinatal insults/stroke
Distinctive Constellations

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Gelastic seizures with hypothalamic harmatoma
- Rasmussen syndrome
- Hemiconvulsion-Hemiplegia-Epilepsy
Electroclinical Epilepsy Syndromes

- Age of onset
- Development & examination
- Seizure type
- EEG pattern
- Prognosis
1989 Classification of the Epilepsies
Poor man’s “diagnosis” of epilepsies....

1. Partialization-related
   1.1 Idiopathic
      Specific syndromes
   1.2 Symptomatic
      Specific syndromes
   1.3 Cryptogenic
      Specific syndromes

2. Generalized
   2.1 Idiopathic
      Specific syndromes
   2.2 Cryptogenic/symptomatic
      Specific syndromes
   2.3 Symptomatic
      Specific syndromes

3. Undetermined
   3.1 With both partial and generalized features
      Specific syndromes
   3.2 Without unequivocal partial or generalized features
      = "unclassified"
## Electro-clinical syndromes arranged by age at onset

### Neonatal period
- Benign neonatal convulsions (BFNE)
- Early myoclonic encephalopathy (EME)
- Ohtahara syndrome

### Infancy
- Epilepsy of infancy with migrating partial seizures
- West’s syndrome
- Myoclonic epilepsy in infancy
- Benign infantile epilepsy
- Benign familial infantile epilepsy
- Dravet syndrome
- Myoclonic encephalopathy in nonprogressive disorders

### Childhood
- Febrile seizures plus (FS+)
- Panayiotopoulos syndrome
- Myoclonic atonic epilepsy
- Benign epilepsy with centotemporal spikes (BECTS)
- Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Myoclonic absence epilepsy
- Lennox-Gastaut syndrome
- Epileptic encephalopathy with continuous spike-and–wave during sleep (CSWS)
- Landau-Kleffner syndrome (LKS)
- Childhood absence epilepsy (CAE)

### Adolescence - Adult
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with GTC seizures alone
- Progressive myoclonus epilepsies (PME)
- Autosomal dominant partial epilepsy with auditory features (ADPEAF)
Think Epilepsy Syndrome!

- Age: 3 year old
- Development/Exam: normal
- Seizure types:
  - Sudden fall backward, eyes up.
  - Single GTC
- EEG:
  - Diffuse bursts of irregular spike/polyspike wave
  - Focal left predominant central temporal spikes, activated by sleep
- “localization-related” treated with OXC
- Unable to walk because of frequent falls.
Atonic Seizure
Myoclonic Atonic Epilepsy (MAE) of Doose

- Onset: peak 2-5 years
- Psychomotor development: normal at seizure onset
- Seizure types:
  - Myoclonic-astatic (fall, head drops)
  - Myoclonic, absence, GTC
  - Vibratory tonic seizures (late in course)
- EEG:
  - Irregular spike/polyspike wave
  - Prominent mid-central theta rhythms (4-7 Hz)
- Prognosis: variable
Age of onset (yrs)

5 10 15

Childhood Absence Epilepsy

Generalized Tonic-Clonic seizures Alone

Juvenile Myoclonic Epilepsy

Juvenile Absence Epilepsy

Adapted from Janz 1991
Seizures

Generalized
Originating and rapidly engaging bilaterally distributed networks

Focal
Originating consistently within one hemisphere either discretely localized or widely distributed

Epileptic spasm
<table>
<thead>
<tr>
<th>Generalized</th>
<th>Focal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic-clonic (in any combination)</td>
<td>Without impairment of consciousness</td>
</tr>
<tr>
<td>clonic</td>
<td>With observable signs</td>
</tr>
<tr>
<td>Tonic</td>
<td>Focal motor</td>
</tr>
<tr>
<td>Atonic</td>
<td>autonomic</td>
</tr>
<tr>
<td>Absence</td>
<td>Subjective sensory or psychic phenomena</td>
</tr>
<tr>
<td></td>
<td>aura</td>
</tr>
<tr>
<td></td>
<td>With impairment of consciousness or awareness</td>
</tr>
<tr>
<td>typical</td>
<td>Evolving to a bilateral convulsive seizure</td>
</tr>
<tr>
<td>atypical</td>
<td></td>
</tr>
<tr>
<td>Absence with special features:</td>
<td></td>
</tr>
<tr>
<td>Myoclonic absence</td>
<td></td>
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<tr>
<td>eyelid myoclonia</td>
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<tr>
<td>Myoclonic</td>
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<td>Myoclonic</td>
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<tr>
<td>Myoclonic atonic</td>
<td></td>
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<tr>
<td>Myoclonic tonic</td>
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</tbody>
</table>
Tonic Seizure
Terminology for Seizures

- **Focal Seizure Types**
  - Complex Partial
  - Simple Partial
  - Secondarily Generalized

- **Generalized Seizure Types**
  - Tonic-clonic (in any combination)
  - Absence
    - Typical
    - Atypical
    - Absence with special features
      - Myoclonic absence
      - Eyelid myoclonia
  - Myoclonic
    - Myoclonic
    - Myoclonic atonic
    - Myoclonic tonic

Reduce array of highly diverse ictal events into 3 artificial, often arbitrary categories
Focal Seizures

Subjective (auras)

Objective

Autonomic (specific observations)
Dyscognitive (specific observations)

Motor

Elementary (specific observations)
Complex – automotor (specific observations)
Negative (specific observations)

Blume et al. Glossary of ictal semiology, Epilepsia 2001
More barriers: Focal and Generalized Epilepsies

- Red herring - distraction
- Clinical relevance?
  - West & CAE are generalized
  - BECTS and gelastic seizures w/hypothalamic hamartoma are focal

- Missed opportunities, inappropriate treatment
- Surgical implications:
  - Focal implied potentially surgical
    - Inappropriate use of surgery: Dravet, ADNFLE
  - Generalized implied not surgical
    - Failure to refer: West, LGS

- Separate manifestations (seizures) from underlying process and cause (epilepsies)
Ideally: a classification should…

- Teach the features that are essential about the epilepsies to be classified.

- Essential to …
  - Diagnosis
  - Evaluation
  - Treatment
  - Long-term outcomes, counseling

- Organize information in a clear, accessible way.

- Teach and help physicians and others to diagnose and care for patients effectively
Are we ready for a Periodic Table or Tree of the Epilepsies?
Classification can be a barrier

Don’t Classify!

Diagnosis!

Look to guidelines!