2018 paediatric epilepsy syndromes

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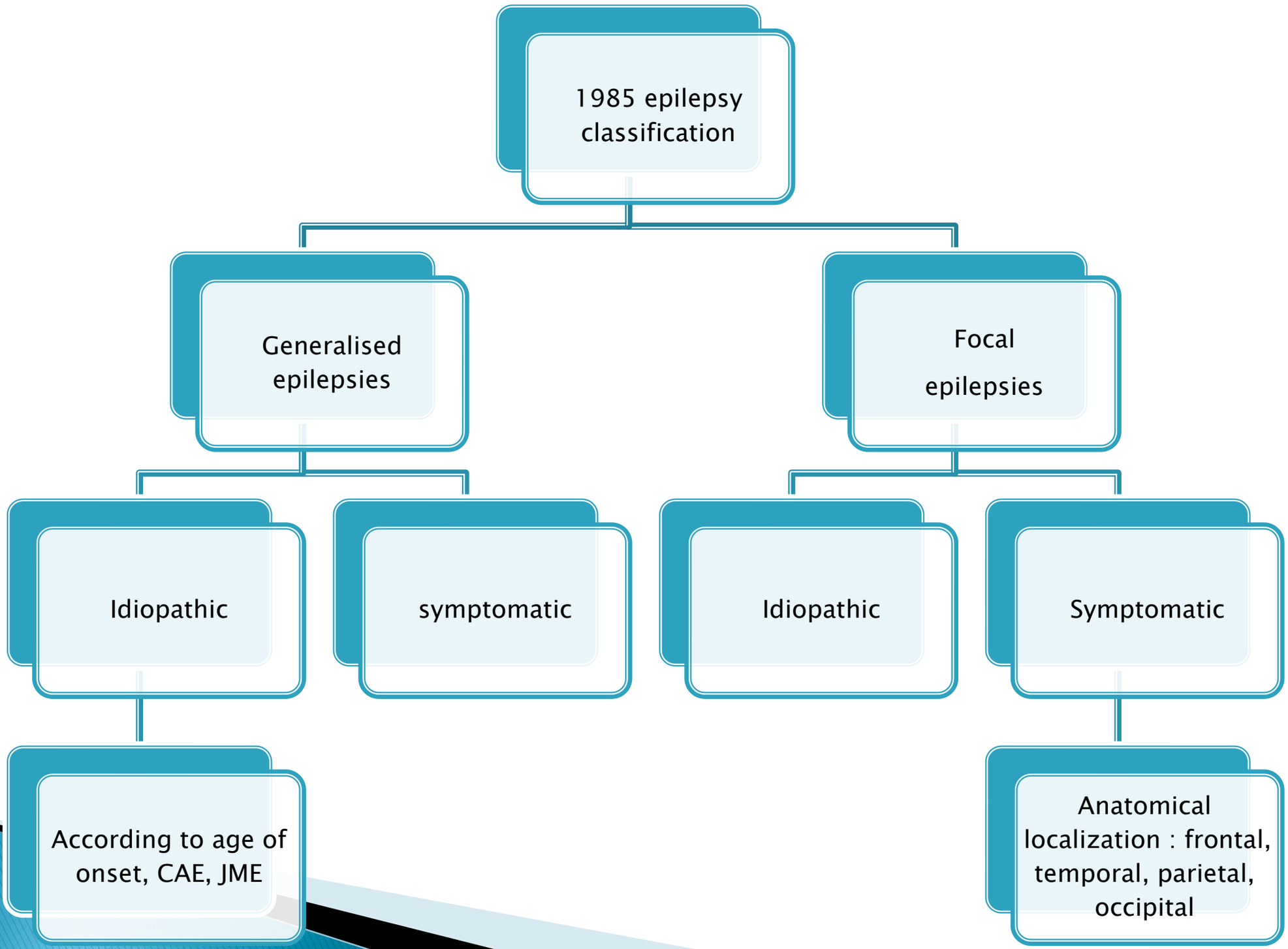
ILAE classification of seizures and epilepsy

Seizure and epilepsy classification

- International League against epilepsy (ILAE)
- New proposals for revision have provoked a lot of debate.
- Difficulties in following the rationales and arguments behind the changes and revisions

1985 and 1989 classifications of epilepsies and epilepsy syndromes



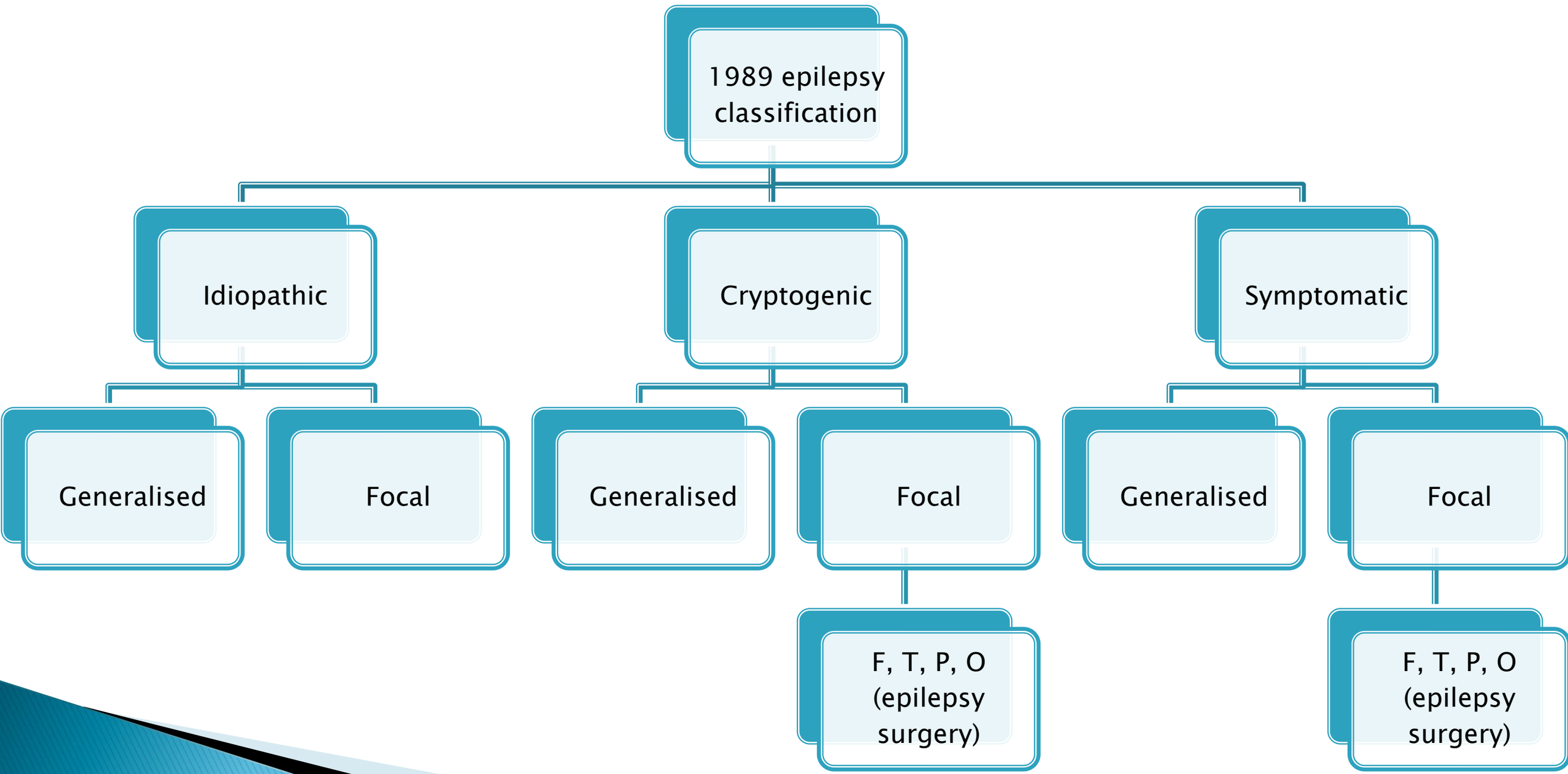
1985 classification of epilepsies and epilepsy syndromes

- Idiopathic = no identifiable etiologies, potentially genetic causes
- Symptomatic = consequence due to a known disorder or CNS lesion, such as tumour, infection, trauma

1989 classification of epilepsies and epilepsy syndromes

- Idiopathic = no identifiable etiologies, potentially genetic causes
- Symptomatic = consequence due to a known disorder or CNS lesion, such as tumour, infection, trauma
- Cryptogenic = remote symptomatic or presumed symptomatic, though cause not identified, normal MR imaging of brain

1985 and 1989 classifications of epilepsies and epilepsy syndromes



Change in subsequent 20 years

- ICS (1981) and ICE (1989) well accepted
- 2001 – adding a 5 axes diagnostic scheme : (1) ictal phenomenology, (2) seizure type, (3) epilepsy syndrome, (4) etiology, (5) impairment
- 2006: unchanged dichotomy scheme of generalised and focal seizures and epilepsies, updated list of epileptic syndromes
- Wanted to discard the term “generalised seizure” as no seizures are generalised according to electrophysiology and must arise or originate from a focal point in the brain
- Increase in use of interictal EEG, ictal EEG, simultaneous video ictal recording, invasive monitoring, brain mapping

2006 classification Engel et al

TABLE 2. *Epilepsy syndromes by age of onset and related conditions*

- Neonatal period
  - Benign familial neonatal seizures (BFNS)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- Infancy
  - Migrating partial seizures of infancy
  - West syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Benign infantile seizures
  - Dravet syndrome
  - Myoclonic encephalopathy in nonprogressive disorders
- Childhood
  - Early onset benign childhood occipital epilepsy (Panayiotopoulos type)
  - Epilepsy with myoclonic astatic seizures
  - Benign childhood epilepsy with centrotemporal spikes (BCECTS)
  - Late onset childhood occipital epilepsy (Gastaut type)
  - Epilepsy with myoclonic absences
  - Lennox-Gastaut syndrome (LGS)
  - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) including Landau-Kleffner syndrome (LKS)
  - Childhood absence epilepsy (CAE)
- Adolescence
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Progressive myoclonus epilepsies (PME)
- Less Specific Age Relationship
  - Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
  - Familial temporal lobe epilepsies
  - Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
  - Rasmussen syndrome
  - Gelastic seizures with hypothalamic hamartoma
- Special epilepsy conditions
  - Symptomatic focal epilepsies not otherwise specified
  - Epilepsy with generalized tonic-clonic seizures only
  - Reflex epilepsies
  - Febrile seizures plus (FS+)
  - Familial focal epilepsy with variable foci
- Conditions with epileptic seizures that do not require a diagnosis of epilepsy
  - Benign neonatal seizures (BNS)
  - Febrile seizures (FS)

2010 concepts of organization of seizures and epilepsies

- Organisation = flexibility in categorising epilepsies
- 2 main points in the proposal
  - Redefinition of generalised and focal seizures
  - Reorganization of epilepsies
- Advances in imaging and functional imaging, genetic, metabolic investigations, pathological diagnosis and confirmation

2010 concepts of organization of seizures and epilepsies

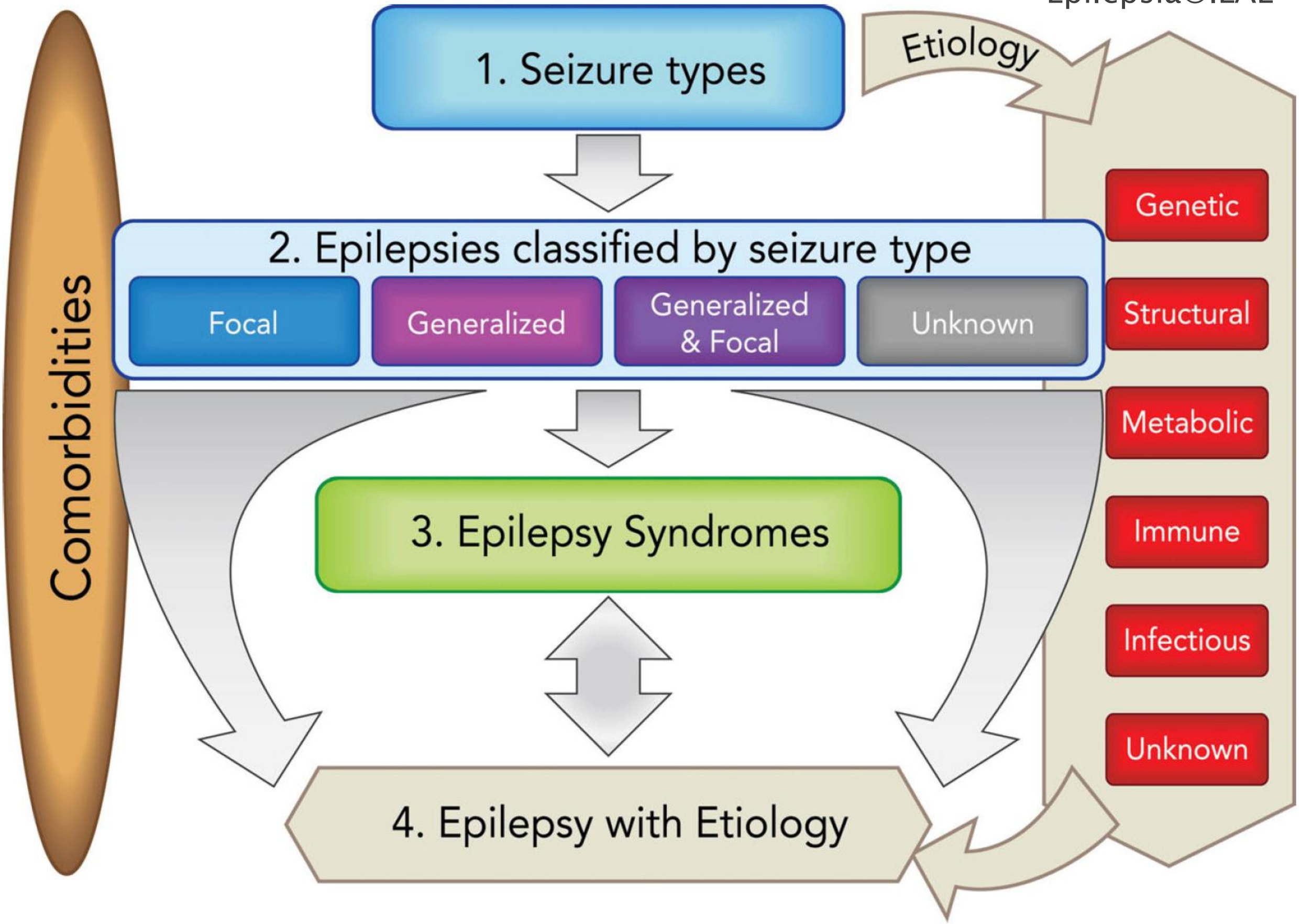
- Reorganization of epilepsies
  - Concept of epileptic syndromes retained
  - To discard terms of idiopathic, symptomatic, cryptogenic syndromes
  - More specific terms : genetic, structural, metabolic, unknown
  - Constellation = electroclinical syndromes with specific associations with radiological or pathological findings

- Electroclinical syndromes arranged by age at onset[a]
  - Neonatal period
    - Benign familial neonatal epilepsy (BFNE)
    - Early myoclonic encephalopathy (EME)
    - Ohtahara syndrome
  - Infancy
    - Epilepsy of infancy with migrating focal seizures
    - West syndrome
    - Myoclonic epilepsy in infancy (MEI)
    - Benign infantile epilepsy
    - Benign familial infantile epilepsy
    - Dravet syndrome
    - Myoclonic encephalopathy in nonprogressive disorders
  - Childhood
    - Febrile seizures plus (FS+) (can start in infancy)
    - Panayiotopoulos syndrome
    - Epilepsy with myoclonic atonic (previously astatic) seizures
    - Benign epilepsy with centrotemporal spikes (BECTS)
    - Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
    - Late onset childhood occipital epilepsy (Gastaut type)
    - Epilepsy with myoclonic absences
    - Lennox-Gastaut syndrome
    - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]
    - Landau-Kleffner syndrome (LKS)
    - Childhood absence epilepsy (CAE)
  - Adolescence – Adult
    - Juvenile absence epilepsy (JAE)
    - Juvenile myoclonic epilepsy (JME)
    - Epilepsy with generalized tonic–clonic seizures alone
    - Progressive myoclonus epilepsies (PME)
    - Autosomal dominant epilepsy with auditory features (ADEAF)
    - Other familial temporal lobe epilepsies
  - Less specific age relationship
    - Familial focal epilepsy with variable foci (childhood to adult)
    - Reflex epilepsies
- Distinctive constellations
  - Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
  - Rasmussen syndrome
  - Gelastic seizures with hypothalamic hamartoma
  - Hemiconvulsion–hemiplegia–epilepsy
  - Epilepsies that *do not* fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)
- Epilepsies attributed to and organized by structural-metabolic causes
  - Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
  - Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
  - Tumor
  - Infection
  - Trauma
  - Angioma
  - Perinatal insults
  - Stroke
  - Etc.
- Epilepsies of unknown cause
- Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
  - Benign neonatal seizures (BNS)
  - Febrile seizures (FS)

2010 organisation-constellation of electroclinical syndromes

2017 Framework for classification of epilepsies.

Epilepsia©ILAE



Epilepsy syndrome

- An epilepsy syndrome = a cluster of features
  - seizure types,
  - Specific EEG findings, and
  - imaging features that tend to occur together.
- age-dependent features such as age at onset and remission (where applicable), seizure triggers, diurnal variation.
- May have distinctive comorbidities such as intellectual and psychiatric dysfunction
- Associated etiologic, prognostic, and treatment implications, purpose of guiding management
- many well recognized syndromes, such as childhood absence epilepsy, West syndrome, and Dravet syndrome

Idiopathic Generalized Epilepsies (IGE)

- common subgroup
- The IGEs encompass four well-established
- epilepsy syndromes:
  - Childhood Absence Epilepsy,
  - Juvenile Absence Epilepsy,
  - Juvenile Myoclonic Epilepsy
  - Generalized Tonic– Clonic Seizures Alone (formerly known as Generalized Tonic– Clonic Seizures on Awakening but modified in recognition that seizures can occur at any time of day).
- Presumed genetic, but not monogenic (with inherited or de novo pathogenic variants), likely complex (polygenic with or without environmental factors) inheritance.

Self-limited focal epilepsies

- several self-limited focal epilepsies, typically beginning in childhood.
- The most common is self-limited epilepsy with centrotemporal spikes, formerly called " benign epilepsy with centrotemporal spikes."
- Others included the self-limited occipital epilepsies of childhood, with the early-onset form described by
- Panayiotopoulos and the late-onset form by Gastaut.
- Other self-limited frontal lobe, temporal, and parietal
- lobe epilepsies have been described with some beginning in adolescence and even adult life.

Etiology

- a first epileptic seizure -> the clinician should be aiming to determine the etiology
- A range of etiologic groups has been recognized, with emphasis on those that have implications for treatment (e.g. TSC and mTOR inhibitor).
- Often the first investigation carried out involves neuroimaging, ideally MRI where available.
- The etiologic groups are
  - structural,
  - genetic,
  - infectious,
  - metabolic,
  - immune,
  - and unknown.

Structural etiology

- Structural etiologies
  - Acquired (such as stroke, trauma, and infection, HIE),
  - or genetic (such as malformations of cortical development)
- Identification of a subtle structural lesion requires appropriate MRI studies using specific epilepsy protocols.
- well-recognized associations within the epilepsies
  - mesial temporal lobe seizures with hippocampal sclerosis
  - gelastic seizures with hypothalamic hamartoma,
  - Rasmussen syndrome and hemiconvulsion-hemiplegia-epilepsy.
- Recognition of these associations -> to ensure careful examination for specific structural abnormality -> the need for consideration for epilepsy surgery should the patient fail medical therapy.
- The underlying basis for a structural abnormality may be genetic or acquired, or both.
  - For example, polymicrogyria may be secondary to mutations in genes such as GPR56 , or acquired, secondary to intrauterine cytomegalovirus infection.

    Tuberous sclerosis complex - caused by mutations in genes TSC1 and TSC2 encoding hamartin and tuberin

Genetic etiology - genetic epilepsy

- family history of an autosomal dominant disorder.
  - For example, in the syndrome of Benign Familial Neonatal Epilepsy, most families have mutations of one of the potassium channel genes, KCNQ2 or KCNQ3
- Molecular genetics has led to identification of the causative mutation in a large number of epilepsy genes, most frequently arising de novo, in 30– 50% of infants with severe developmental and epileptic encephalopathies.
- The best known example is Dravet syndrome in which > 80% of patients have a pathogenic variant of SCN1A .
- known genetic abnormalities causing both severe and mild epilepsies (phenotypic heterogeneity)
  - such as SCN1A mutations, associated with Dravet syndrome and Genetic Epilepsy with Febrile Seizures Plus (GEFS+), FS
- Genetic heterogeneity

FS specturm

FS	Dravet	FIRES
Channelopathies	>80% SCN1A	Presumed genetic

Infectious etiology

- Not seizures occurring in the setting of acute infection such as meningitis or encephalitis.
- Epilepsy associated with neurocysticercosis, tuberculosis, HIV, cerebral malaria, subacute sclerosing panencephalitis, cerebral toxoplasmosis, and congenital infections such as Zika virus and cytomegalovirus.
- An infectious etiology carries specific treatment implications.
- Postinfectious development of epilepsy, such as viral encephalitis leading to seizures in the aftermath of the acute infection (HSV).

Metabolic etiology – **Metabolic epilepsy**

- such as porphyria, uremia, aminoacidopathies, or pyridoxine-dependent seizures.
- In many cases, metabolic disorders will have a genetic defect.
- some may be acquired such as cerebral folate deficiency.
- The identification of specific metabolic causes of epilepsy is extremely important due to implications for specific therapies and potential prevention of intellectual impairment.

Immune etiology – Immune epilepsy

- where there is evidence of autoimmune- mediated central nervous system inflammation.
- Examples include anti-NMDA (N -methyl-D - aspartate)
- receptor encephalitis and anti-LGI1 encephalitis.
- Treatment implications with targeted immunotherapies.

Approach to patients with recognisable clinical syndromes – anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis*

Diagnosis can be made when all 3 of the following criteria have been met:

1. Rapid onset (<3 months) of at least 4 of 6 following major groups of symptoms (or 3 + a systemic teratoma):
   - Abnormal (psychiatric) behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation
2. At least one of the following laboratory study results:
   - Abnormal EEG (focal or diff use slow or disorganised activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands
3. Reasonable exclusion of other disorders

Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the 6 groups of symptoms and IgG anti-GluN1 antibodies, esp CSF, after reasonable exclusion of other disorders

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms.

Position paper. Lancet Neurol. 2016 Apr;15(4):391-40

Unknown etiology

- not possible to make a specific diagnosis apart from the basic electroclinical semiology such as frontal lobe epilepsy.

Comorbidities

- such as learning, psychological, and behavioral problems.
- range in type and severity, from subtle learning difficulties to intellectual disability, to psychiatric features such as autism spectrum disorders and depression
- In the more severe epilepsies, a complex range of comorbidities may be seen, including motor deficits such as cerebral palsy or deterioration in gait, movement disorders, scoliosis, sleep, and gastrointestinal disorders.
- presence of comorbidities be considered for every patient with epilepsy at each stage of classification, enabling early identification, diagnosis, and appropriate management.

Developmental and epileptic encephalopathies

- where the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g.,focal cortical malformation -> IS ->developmental regression).
- the abundant epileptiform activity interferes with development resulting in cognitive slowing and often regression, and sometimes is associated with psychiatric and behavioral conse**quences -> amelioration of the epileptiform activity may have the potential to improve the developmental consequences.**
- **Many epilepsy syndromes associated with encephalopathy have) genetic etiology, such as West syndrome (marked genetic heterogeneity, and Epileptic encephalopathy with continuous spike and-wave during sleep (CSWS), where the first genes have begun to emerge.**
- the terms " developmental and epileptic encephalopathy" may be subsumed by using the name of the underlying condition, such as "STXBP1 encephalopathy" or"KCNQ2 encephalopathy."
- **such syndromes may have an acquired cause such as HIE or stroke, or may be associated with a malformation of cortical development that may also have a genetic or acquired etiology.**

To conclude …

- The concept of epileptic syndromes with EEG features, typical age of onset, -> prognostic and treatment implications
- An expanding list of epileptic syndromes: related to advances in imaging and functional imaging -> metabolic -> genetic