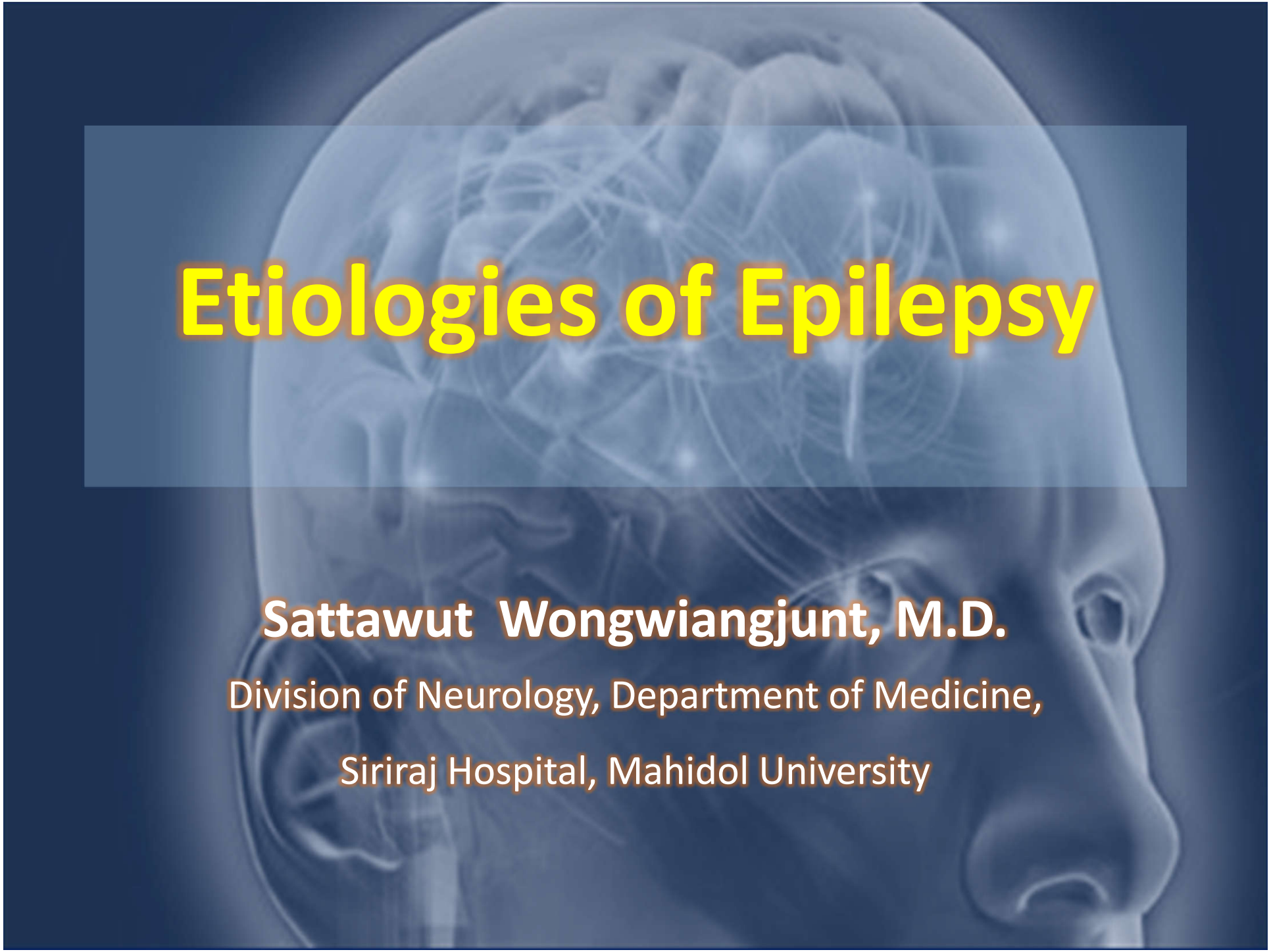

Etiologies of Epilepsy
Sattawut Wongwiangjunt, M.D.
Division of Neurology, Department of Medicine,
Siriraj Hospital, Mahidol University

Classification of EPILEPSY

Classification of Epilepsy: etiology

Idiopathic

Presumed to be genetic

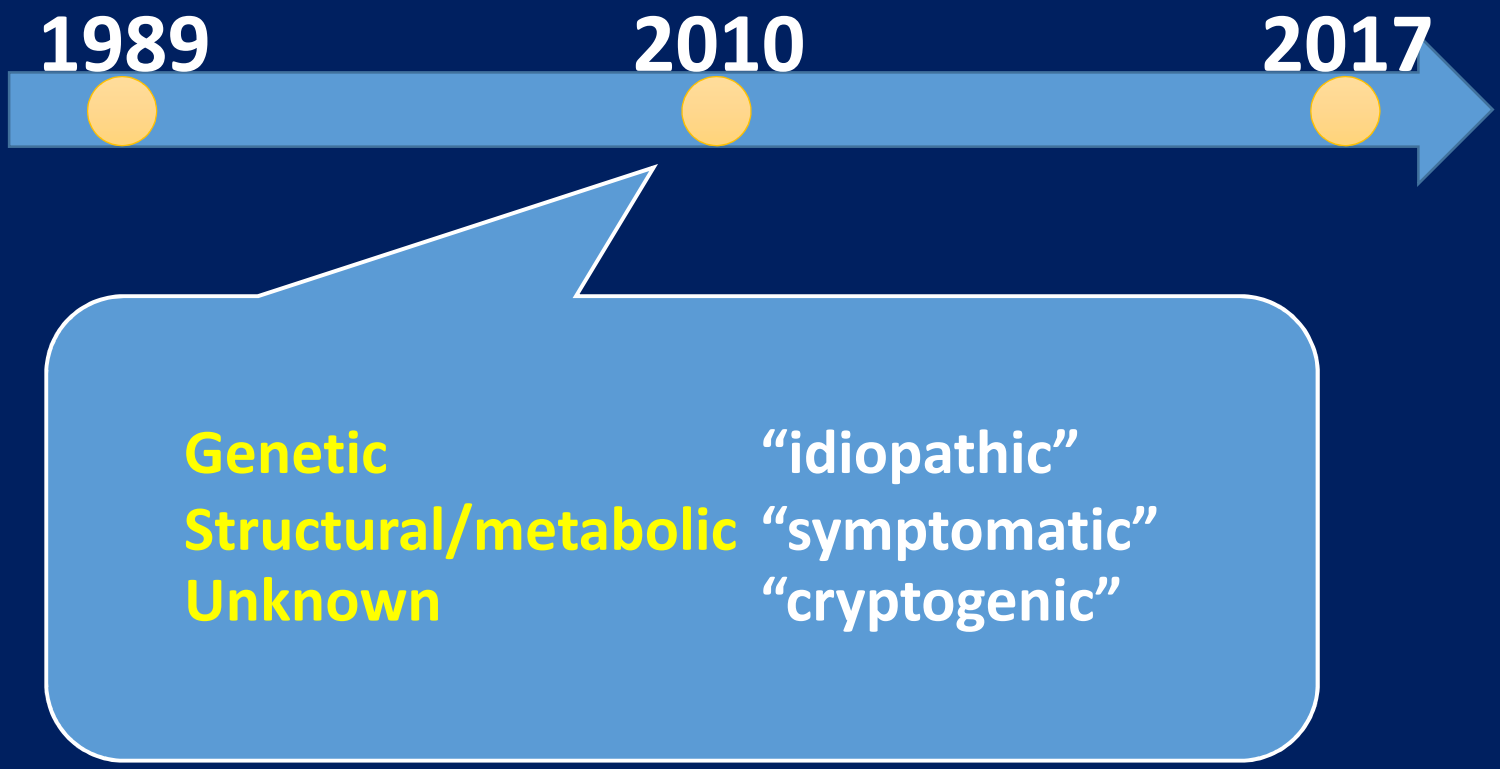
Cryptogenic

Presumed to be symptomatic but are of unknown cause in specific patients

Symptomatic

Structural lesion

Classification of Epilepsy: etiology



ILAE Classification of the Epilepsies 2017

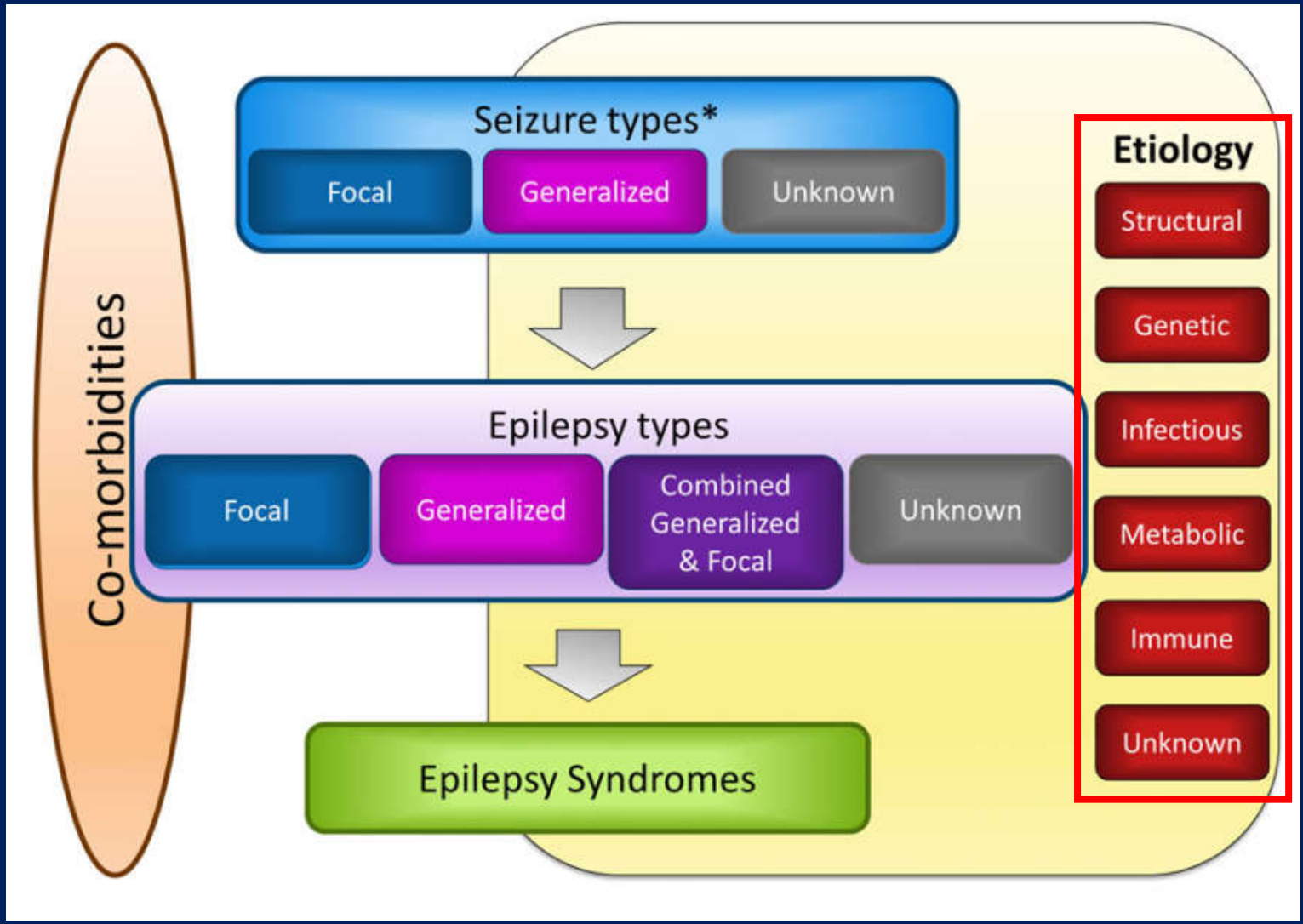
Dr. Ingrid E. Scheffer chairs the ILAE Task Force on the Classification of the Epilepsies.

ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

[1,2,3]Ingrid E. Scheffer, [1]Samuel Berkovic, [4]Giuseppe Capovilla, [5]Mary B. Connolly, [6]Jacqueline French, [7]Laura Guilhoto, [8,9]Edouard Hirsch, [10]Satish Jain, [11]Gary W. Mathern, [12]Solomon L. Moshé, [13]Douglas R. Nordli, [14]Emilio Perucca, [15]Torbjörn Tomson, [16]Samuel Wiebe, [17]Yue-Hua Zhang, and [18,19]Sameer M. Zuberi

Epilepsia, **(*):1–10, 2017
doi: 10.1111/epi.13709

ILAE Classification of the Epilepsies 2017



6 groups of etiologies (short version)

1. Genetic etiology
2. Structural etiology
3. Metabolic etiology
4. Immune etiology
5. Infectious etiology
6. Unknown etiology

6 groups of etiologies (expanded version)

1. **Genetic**
   - Chromosome abn
   - Gene abn
2. **Structural**
   - Malf of cortical development
   - Vascular malf
   - Hippocampal sclerosis
   - Hypoxic-ischemic
   - Traumatic
   - Tumors
3. **Metabolic**
4. **Immune**
   - Rasmusen syndrome
   - Ab mediated
5. **Infectious**
6. **Unknown**
   - Febrile infection related epilepsy syndrome

Genetic etiology

- The concept → the epilepsy is the direct result of a known or presumed genetic defect.
- “Genetic" ≠ “Inherited“ (might be de novo mutation)
- Important genetic etiologies for epilepsy
  - Chromosome abnormality
  - Gene abnormality

Chromosome Abnormality

- 15q13.3 MICRODELETION SYNDROME
- 18q- SYNDROME
- INV-DUP (15) OR IDIC (15)
- DEL 1p36
- ANGELMAN SYNDROME
- DOWN SYNDROME (TRISOMY 21)
- KLEINFELTERS SYNDROME (XXY)
- MILLER DIEKER SYNDROME (DEL 17p)
- PALLISTER KILLIAN SYNDROME (TETRASOMY 12p)
- RING 14 (r14) SYNDROME
- RING 20 (r20) SYNDROME
- TRISOMY 12p
- WOLF-HIRSCHHORN SYNDROME (DEL 4p)

https://www.epilepsydiagnosis.org/aetiology/chromosomal-abnormalities-overview.html

Gene Abnormality

- AKT3
- ARFGEF2
- ARHGEF9
- ARX
- CACNA1A
- CACNB4
- CDKL5
- CHD2
- CHRNA2
- CHRNA4
- CHRNB2
- CLCN2
- COL4A1
- DCX
- DEPDC5
- EFHC1
- FKRP
- FKTN
- FLNA
- FMR1 (FRAGILE X SYNDROME)
- FOXG1
- GABRA1
- GABRD
- GABRG2
- GLI3
- GNAQ
- GRIN2A
- KCNQ2
- KCNQ3
- KCNT1
- LARGE
- LGI1
- LIS1
- MECP2
- NPRL3
- PCDH19
- PIK3CA
- PIK3R2
- PLCB1
- PNKP
- POMT1
- POMT2
- PRRT2
- RELN
- SCN1A
- SCN1B
- SCN2A
- SLC2A1
- SLC25A22
- SPTAN1
- STXBP1
- TBC1D24
- TCF4 (PITT HOPKIN SYNDROME)
- TSC1
- TSC2
- TUBA1A
- WDR62

https://www.epilepsydiagnosis.org/aetiology/gene-abnormalities-overview.html

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5. **Infectious**
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Malf = malformation

Structural etiology

- Acquired or genetic origin
- Neuroimaging: required at least 1.5T MRI – dedicated epilepsy protocol
- Common structural brain abnormalities
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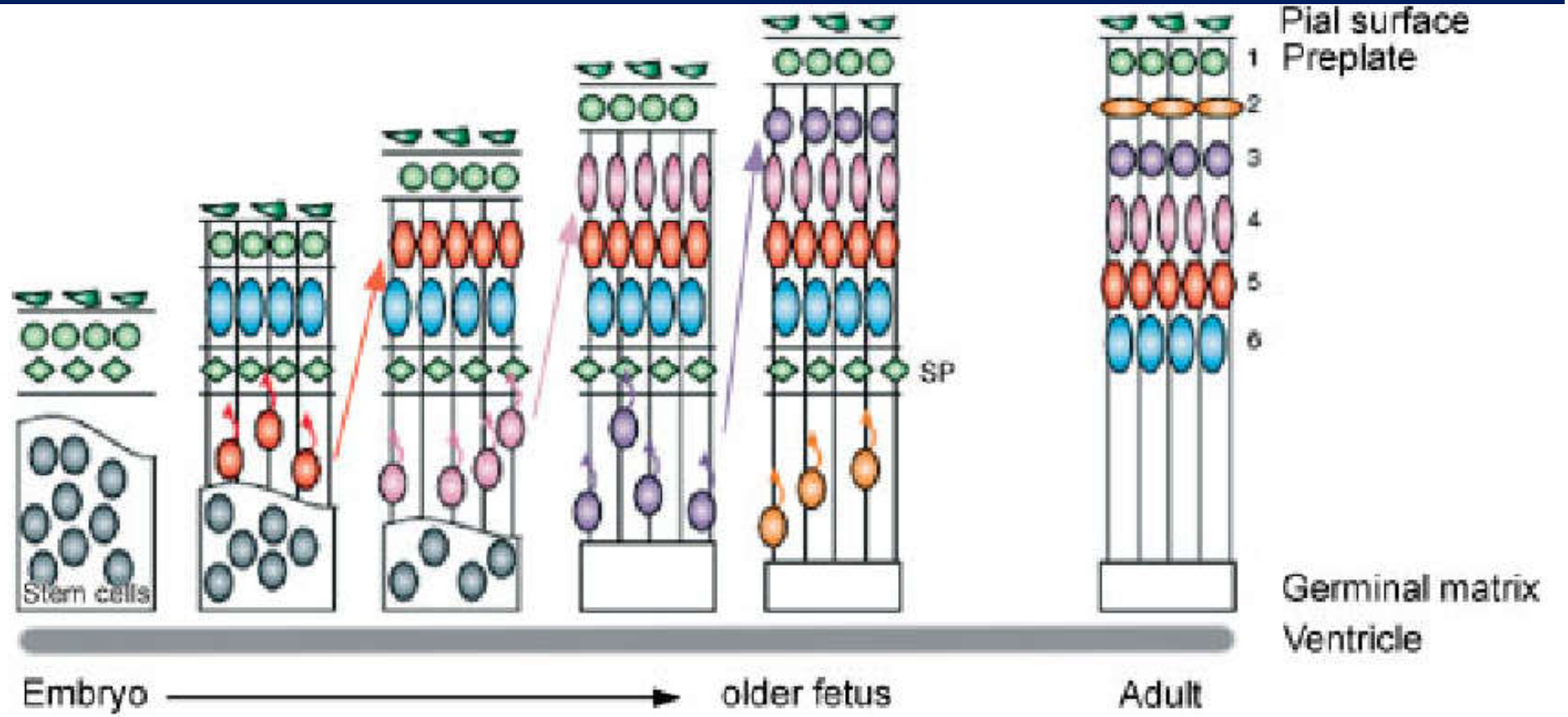
Malformation of cortical development



The **precursor cells** of the cerebral cortex are initially formed in the **periventricular region**, and **then migrate** to their correct location to form the normal.

Prenatal diagnosis 2009 DOI: 10.1002/pd.2211

Cortical malformation abnormality

- Gene > acquired (hypoxemia during intrauterine)
- Important cortical malformation
  - Focal cortical dysplasia
  - Tuberous sclerosis
  - Lissencephaly
  - Subcortical band heterotopia
  - Grey matter heterotopia
  - Polymicrogyria
  - Hemimegalencephaly
  - Schizencephaly

Focal Cortical Dysplasia (FCD)

- →localized regions of malformed cerebral cortex.
- Classification by pathology

FCD Type I	FCD Type II	FCD Type III
Type IA	Type IIA	Type IIIA
FCD with abnormal radial cortical lamination	FCD with dysmorphic neurons	Cortical dyslamination associated with HS
Type IB	Type IIB	Type IIIB
FCD with abnormal tangential cortical lamination	FCD with dysmorphic neurons and balloon cells	Cortical dyslamination associted with glial and glioneuronal tumor
Type IC		Type IIIC
FCD with abnormal radial and tangential lamination		Cortical dyslamination adjacent to vascular malformation

J Epilepsy Res. 2013;3(2):43-47

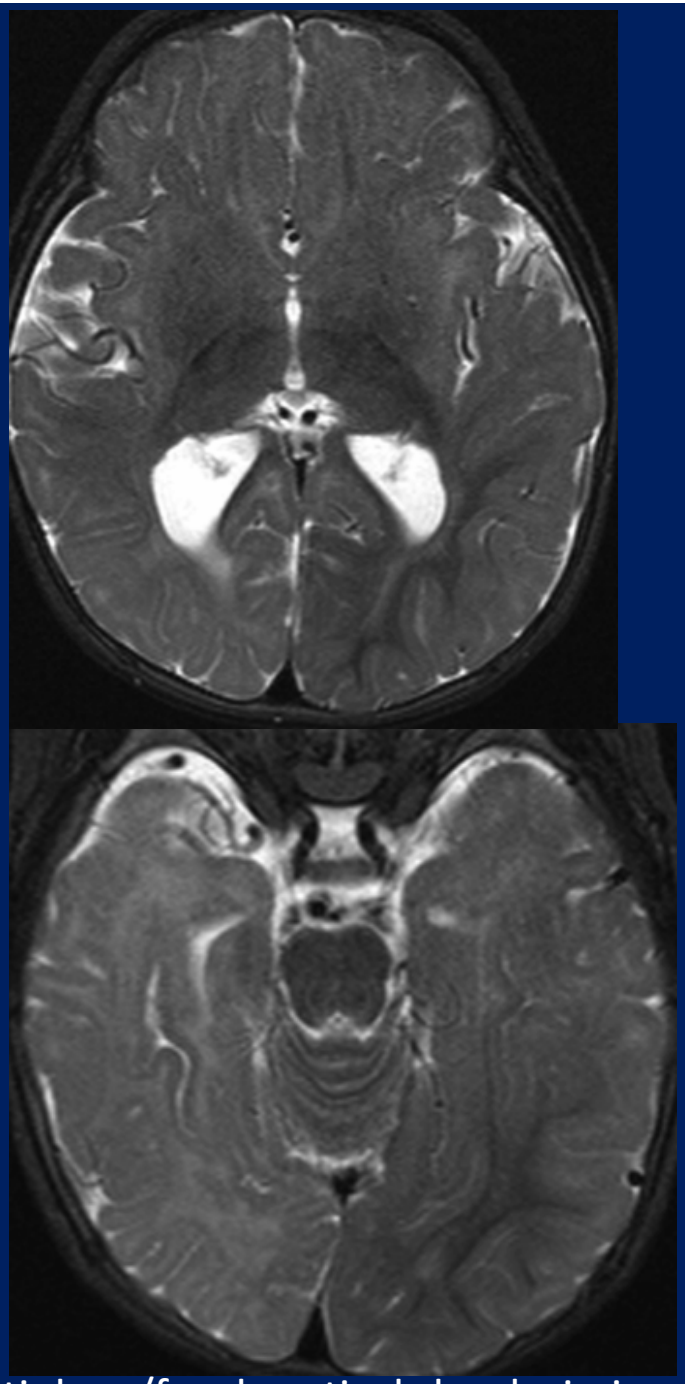
FCD: Clinical context

- SZ: depends of extent and location and co-occurring structural abnormality
- Usually do not affect intellectual, unless it is large.
- SZ onset can be at any age
  - 2/3 onset by 5 years
  - most patients by 16 years.
- SZ usually difficult to control.

MRI: FCD type I

- Atrophy - regional loss of subcortical white matter
- T2: ↑ signal in WM

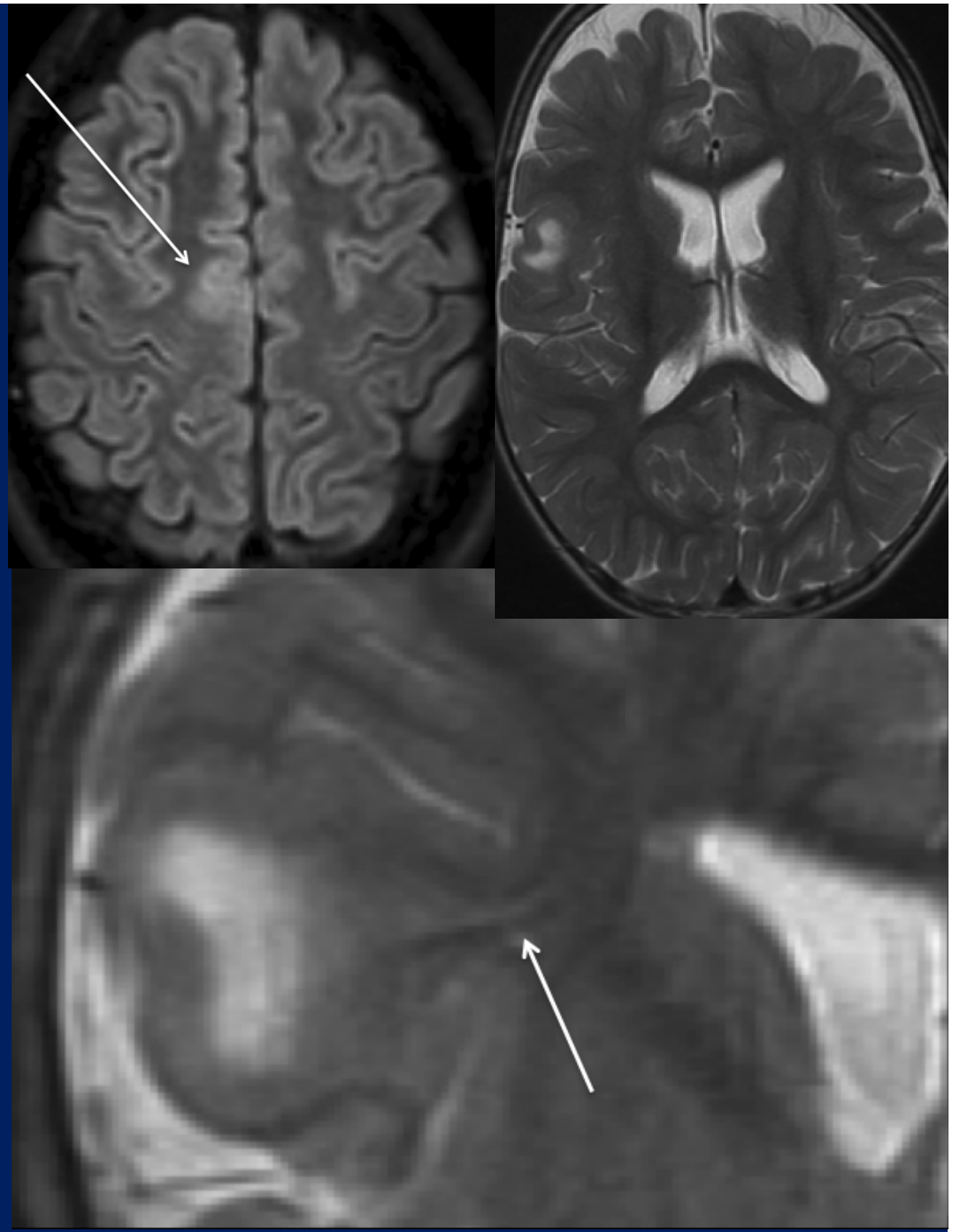
  T1: ↓ signal in WM
- FCD type Ia → temporal lobes and may be asso w/ hippocampal atrophy
- FCD type Ib →extratemporal lobes



https://www.epilepsydiagnosis.org/aetiology/focal-cortical-dysplasia-imaging.html

MRI: FCD type II

- ↑cortical thickness, w/ abn sulcal / gyral
- Blurring of the GW junc
- T2:↑ signal in WM
  T1:↓ signal
- T2: A radially-oriented linear or conical **transmantle** stripe tapering to the lateral ventricle
- FCD type II are most commonly found in the frontal lobes



https://www.epilepsydiagnosis.org/aetiology/focal-cortical-dysplasia-imaging.html

Tuberous sclerosis

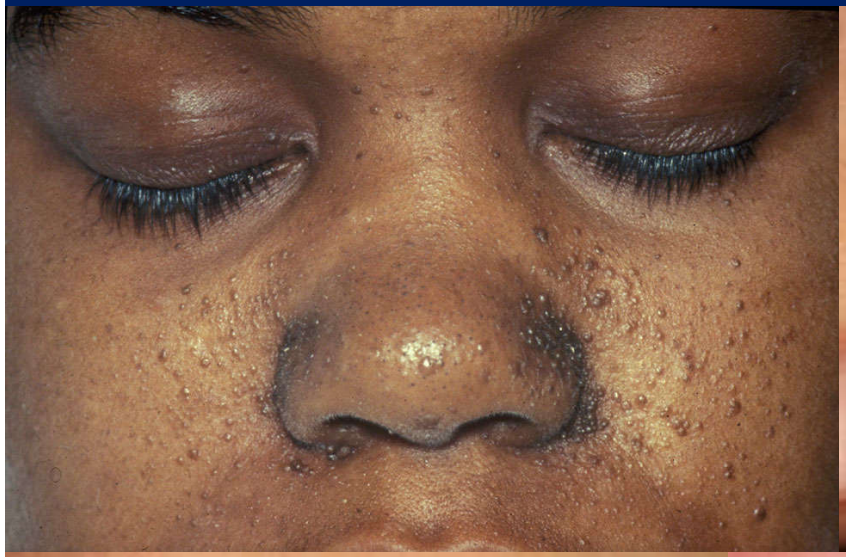
- Criteria diagnosis

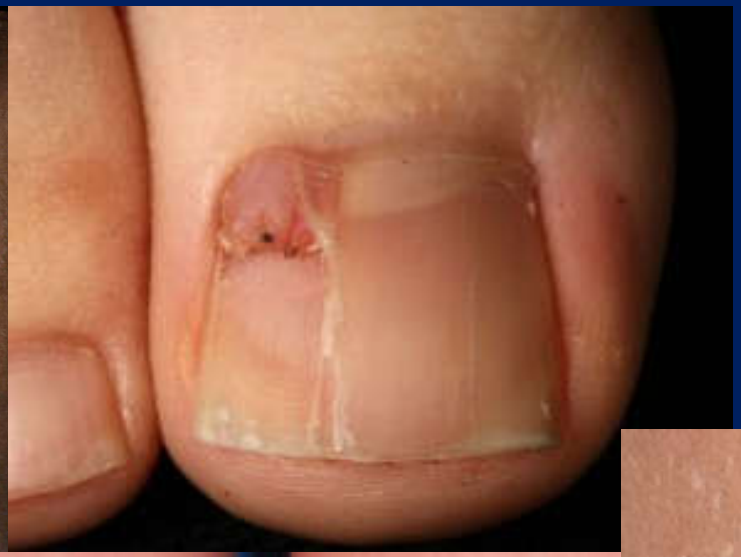
Major Features	Minor Features
≥ 3 hypomelanotic macules	"Confetti" skin lesions
≥ 3 angiofibromas	≥ 3 dental enamel pits
≥ 2 ungual fibromas	≥ 2 intraloral fibromas
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasia	Nonrenal hamartoma
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomymatosis	
Angiomyolipomas	

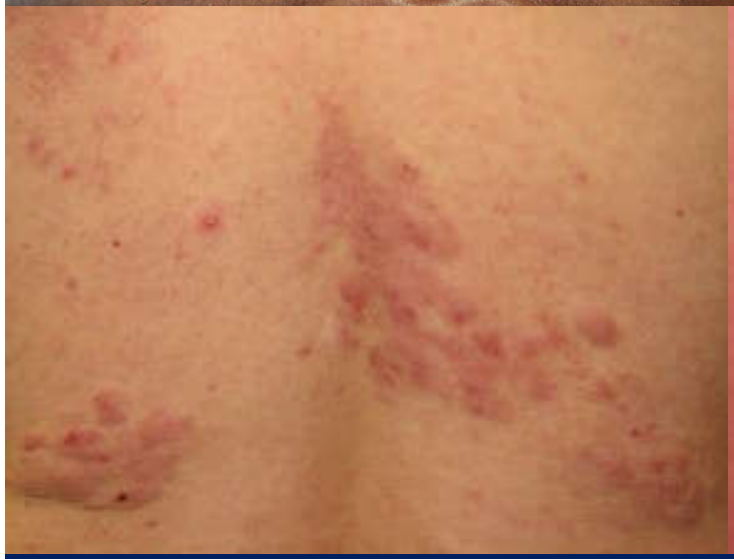
Definite: 2 major or 1 major + 2 minor
Possible: 1 major or 2 minor

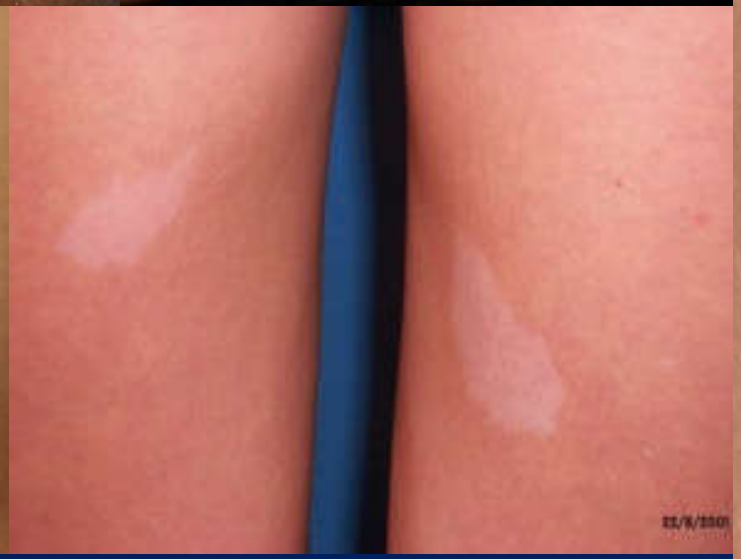
Identify TSC1 or TSC2 DNA mutation in normal tissue

Tuberous sclerosis: skin lesion

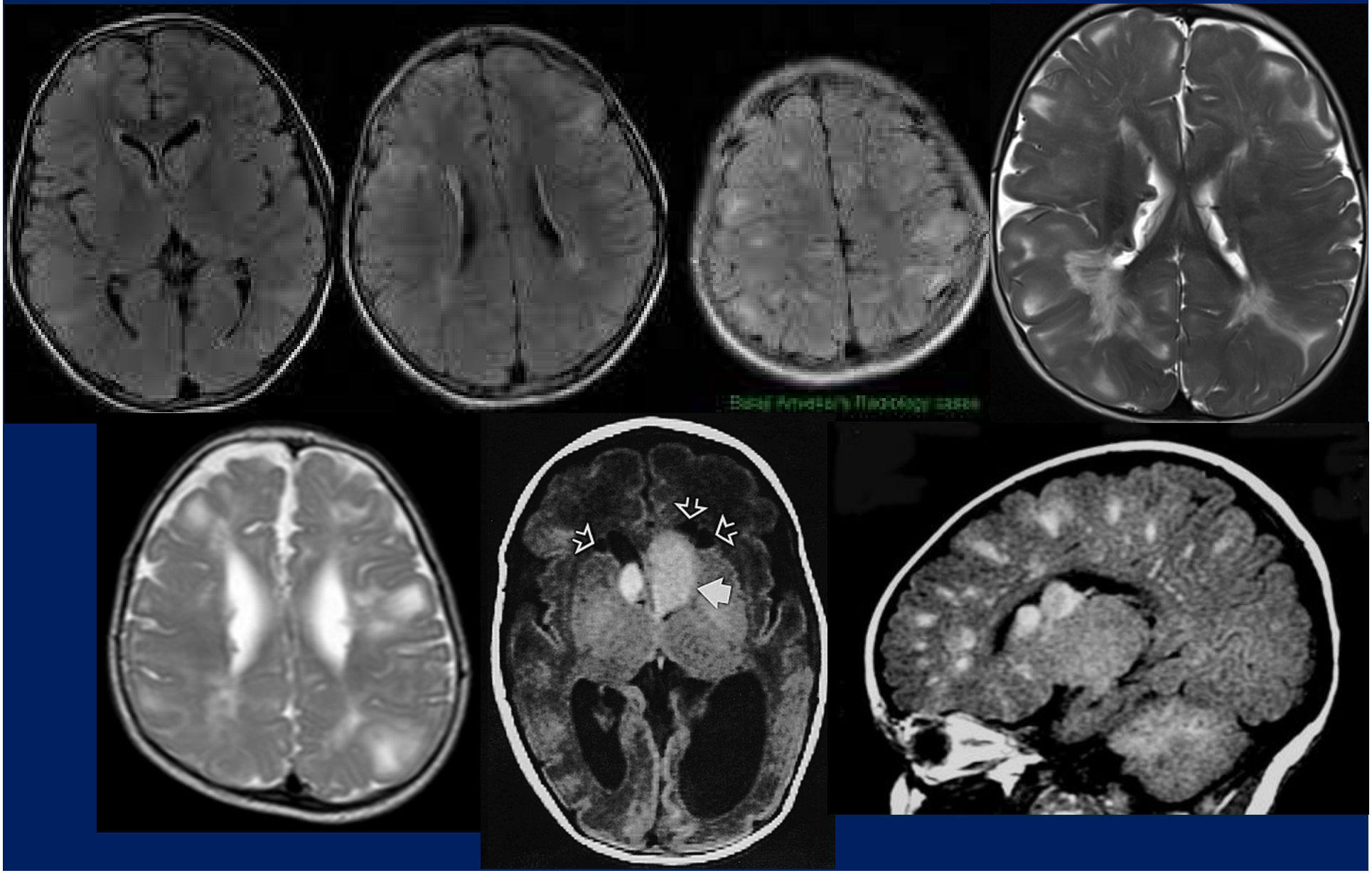




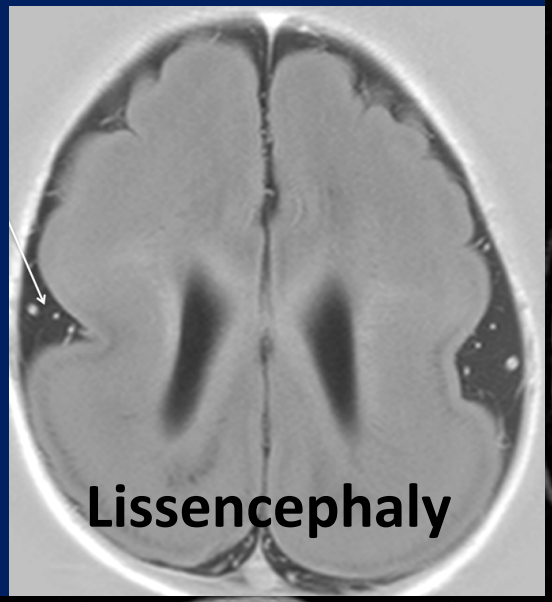


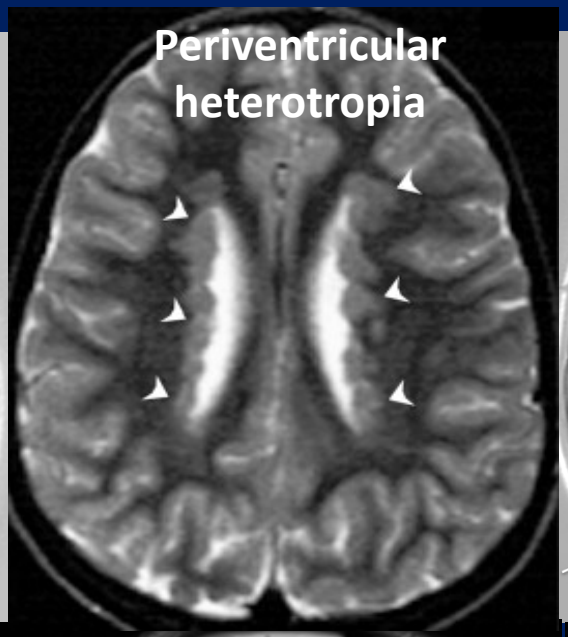


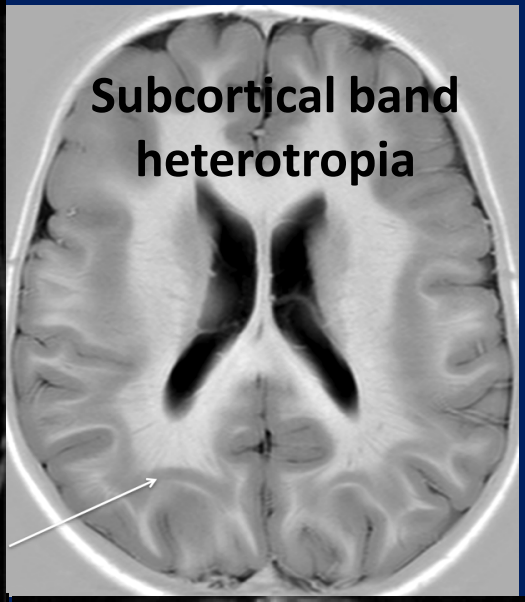
Tuberous sclerosis: MRI

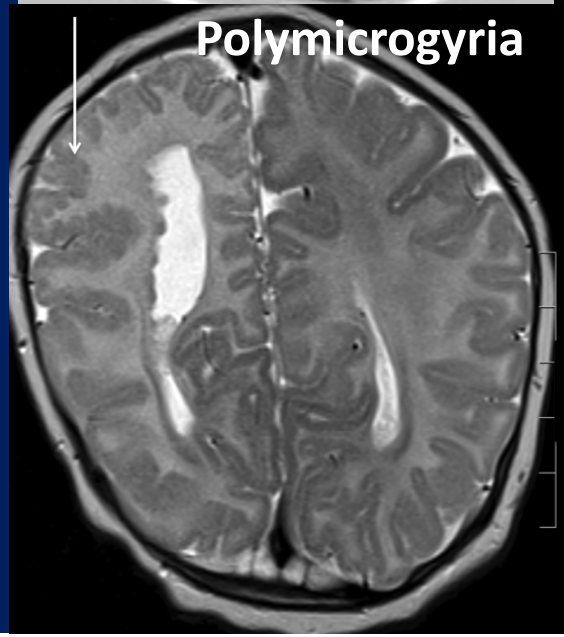


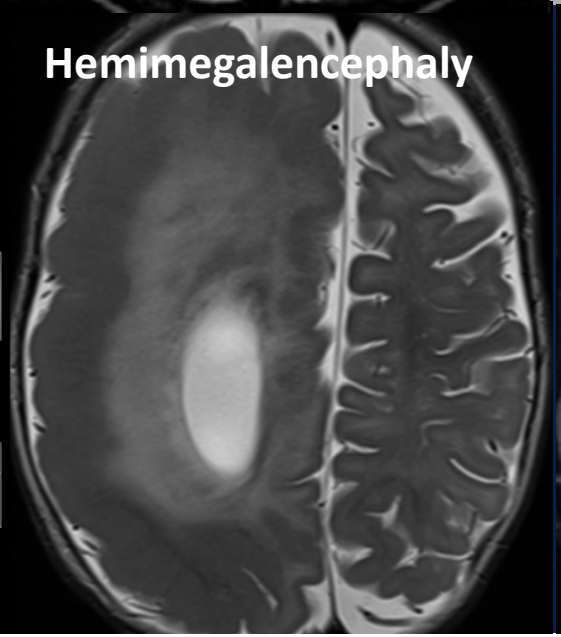
Other cortical malformation

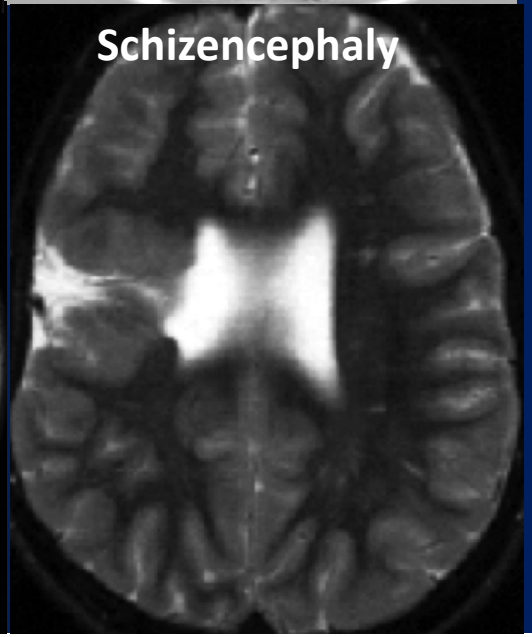










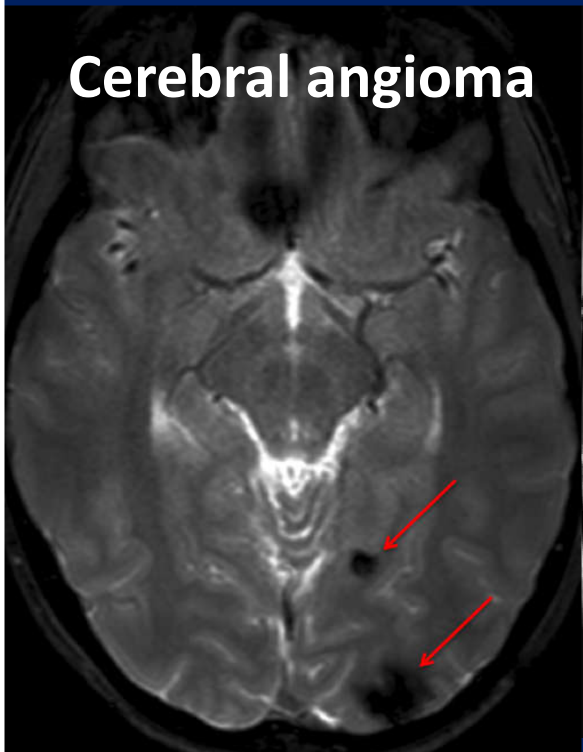


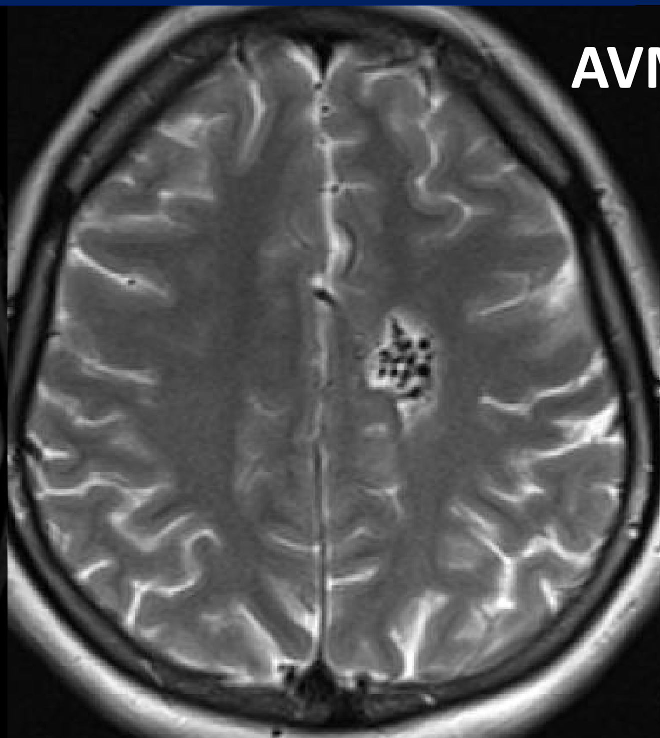
Structural etiology

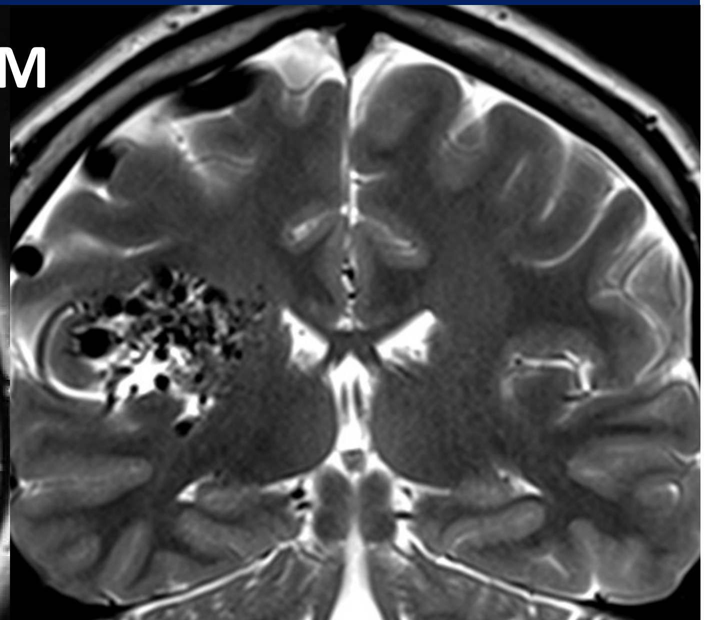
- Acquired or genetic origin
- Neuroimaging: required at least 1.5T MRI – dedicated epilepsy protocol
- Common structural brain abnormalities
  1. Malformation of cortical development
  2. Vascular malformation
  3. Hippocampal sclerosis
  4. Hypoxic-ischemic
  5. Traumatic
  6. Tumors

Vascular Malformation

- Cerebral angioma
- Sturge-Weber syndrome
- Arteriovenous malformation



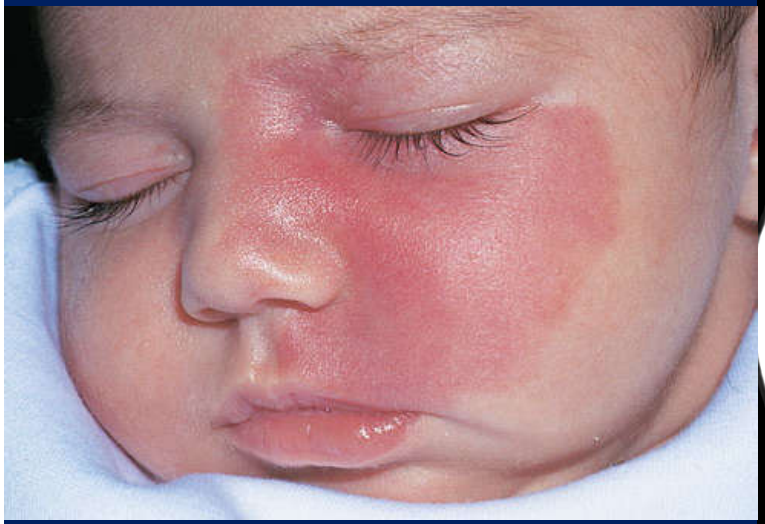


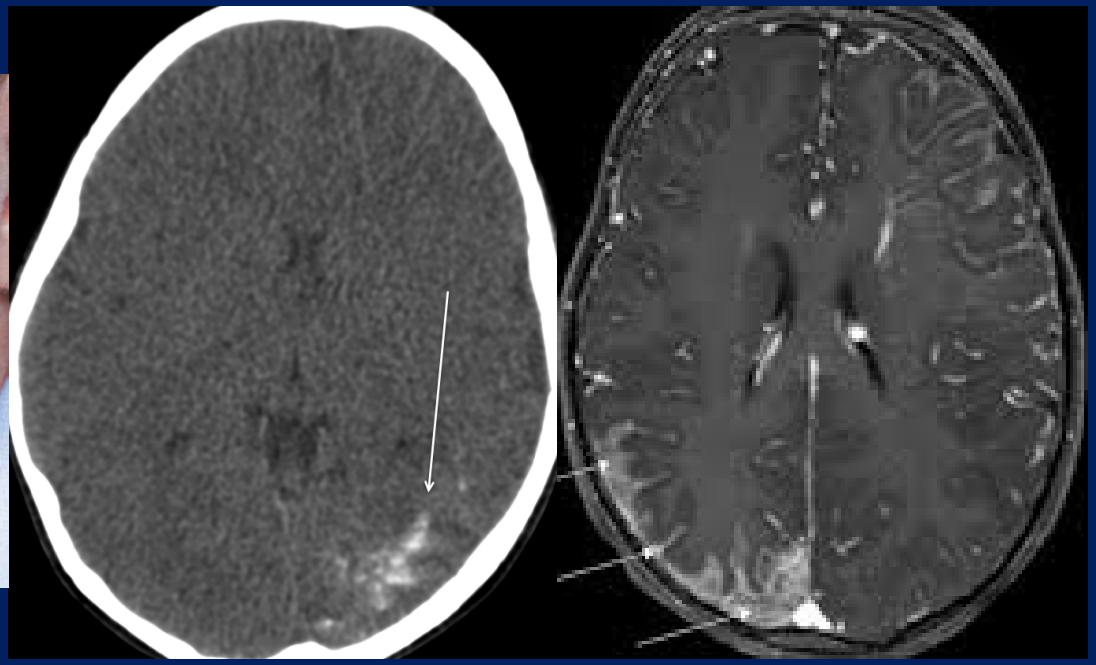


'bag of worms' - tangled vessels composed of feeding arteries, nidus and draining veins.

Sturge-Weber syndrome

- Clinical context
  - a facial port-wine stain (absent in 15%)
  - leptomeningeal angioma ipsilateral to the side of the port-wine stain, over occipital and posterior parietal regions predominantly
  - ocular (choroidal, scleral) angioma (in 30%)





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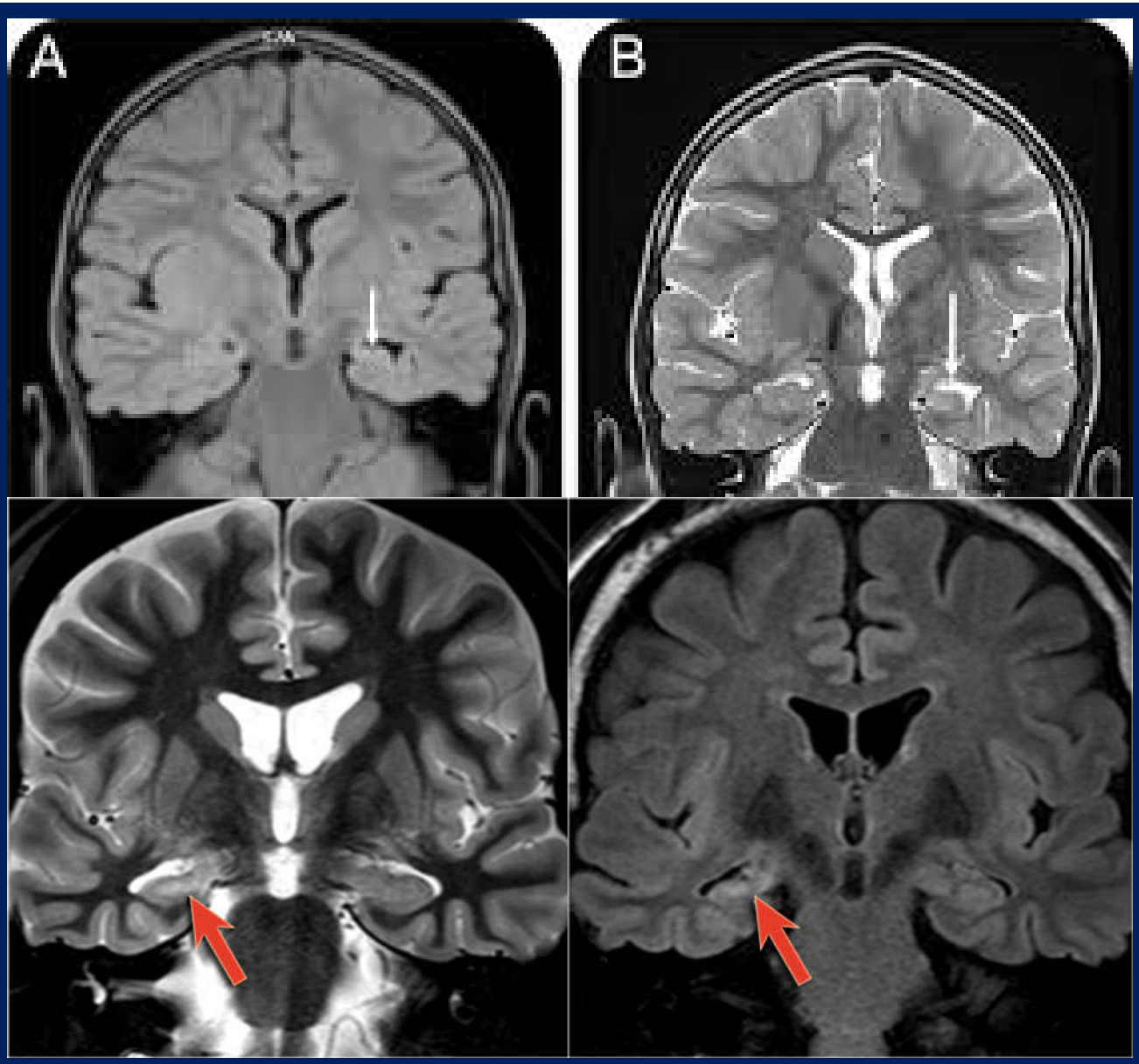
Hippocampal Sclerosis

- HS is characterized pathologically by loss of neurons and gliosis in the hippocampus.
- It is an acquired abnormality: as a consequence of seizures, especially prolonged febrile seizures.
- Up to 1/3 have 'dual pathology’; malformations of cortical development and vascular malformations.

HS: Clinical context

- Seizures with mesial temporal features
- Typically resistant to medication
- May be cognitive deficits
  - verbal memory impairment in dominant side
  - visual memory impairment in non dominant side
- 25% of have a history of febrile seizures, esp prolonged febrile seizures.



- hippocampal atrophy
- hippocampal signal change (high T2 and FLAIR signal)

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Tumor

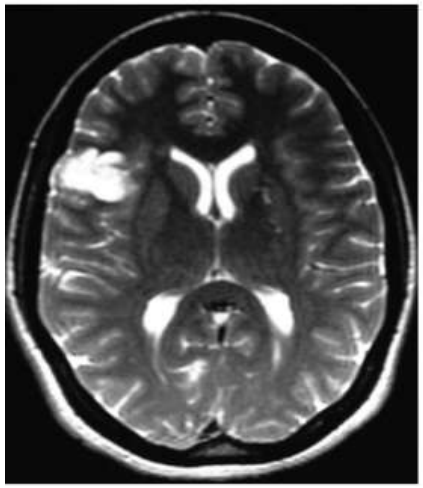
- Epileptogenic tumors → benign lesions that do not usually change over time but asso w/ drug resistant epilepsy
  - Dysembryoplastic Neuroepithelial Tumors (DNET)
  - Gangliogliomas

DNET

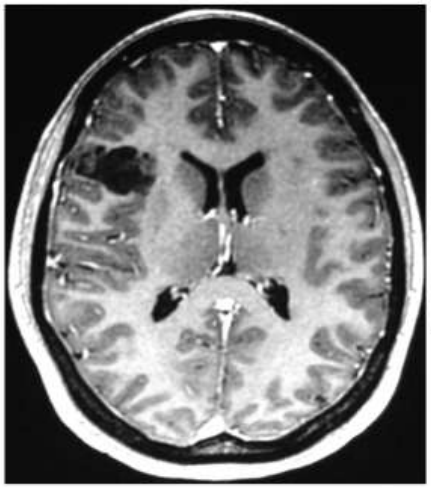
- DNET is a glioneuronal tumor that is cortically based
- Multinodular and/or multicystic appearance.
- Commonly found in the temporal lobes
- Can co-occur with adjacent FCD

- Clinical context
- SZ depends on location and other co-occurring abn
- SZ onset at any age; mostly in childhood

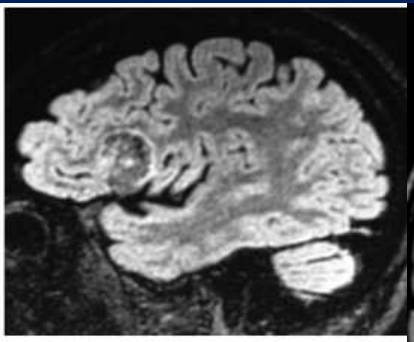
MRI



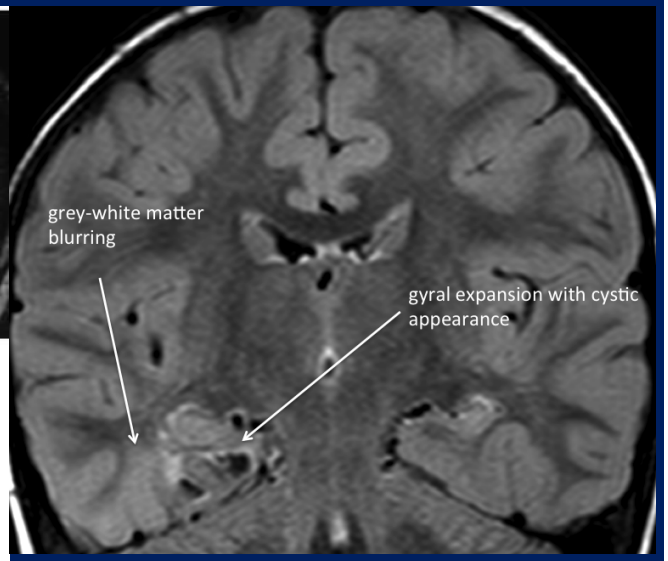
T2



T1



FLAIR



- Cortical lesions; no mass effect or peri-tumoral edema
- Typically with a 'bubbly appearance' due to their multicystic nature
- FLAIR: 'bright rim sign’
- Calcification (~30%)
- can co-occur with FCD (adjacent to the DNET) and/or HS

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Metabolic Etiology

- Metabolic d/o have genetic in origin.
- Metabolic epilepsies → distinct metabolic abn

  - Biotinidase and holocarboxylase synthase def
  - Cerebral folate def
  - Creatine disorders
  - Folinic acid responsive seizures
  - Glucose transporter 1 (GLUT1) def
  - Mitochondrial disorders
  - Peroxisomal Disorders
  - Pyridoxine dependent epilepsy/PNPO deficiency

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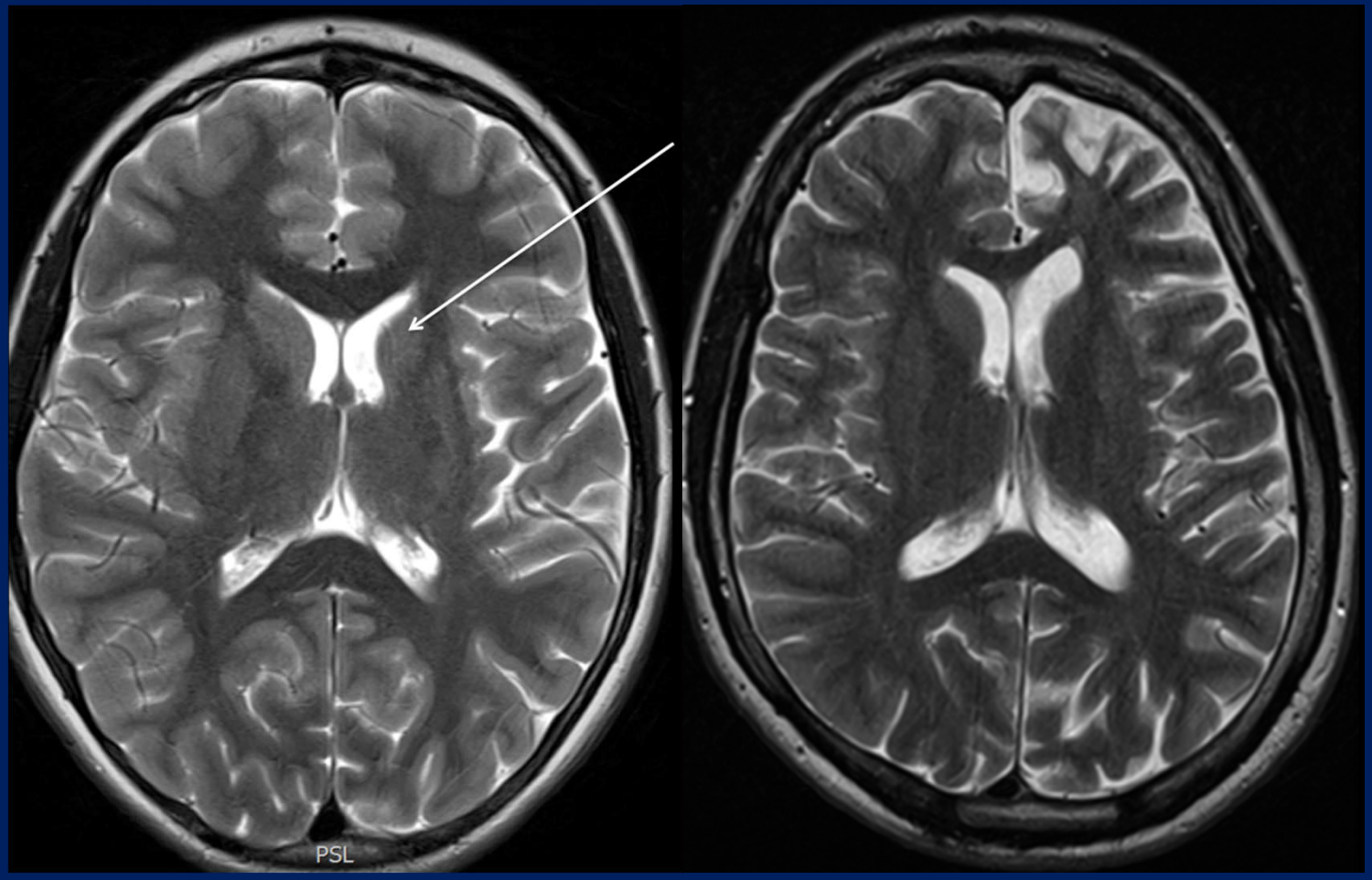
Immune Etiology

- Immune epilepsies -- a distinct immune-mediated etiology with evidence of CNS inflammation
- Important to recognize as outcome may be optimized with targeted immunotherapies.
  - Rasmussen syndrome
  - Antibody mediated etiologies

Rasmussen Syndrome

- Intractable focal sz (focal motor, esp **epilepsia partialis continua**) & progressive hemiparesis
- Onset peak 5-6 years old (1-10) with normal birth and development
- 3 stages to the illness
  1. **Prodromal phase:** infrequent sz and no hemiparesis
  2. **Acute phase:** frequent sz and development of hemiparesis
  3. **Residual stage:** permanent stable hemiparesis

- On imaging, progressive hemiatrophy



Antibody mediated etiologies

- ANTI-NMDA RECEPTOR ENCEPHALITIS
- VOLTAGE-GATED POTASSIUM CHANNEL Ab (LGI1 or CASPR2)
- GAD65 Ab
- GABA-B RECEPTOR Ab
- AMPA RECEPTOR Ab
- STEROID-RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH THYROID DISEASE
- CELIAC DISEASE, EPILEPSY AND CEREBRAL CALCIFICATION SYNDROME

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Infectious etiology

- Bacterial meningitis or meningoencephalitis
- Viral encephalitis
- Cerebral malaria
- Cerebral toxoplasmosis
- CMV
- HIV
- Neurocysticercosis
- Tuberculosis

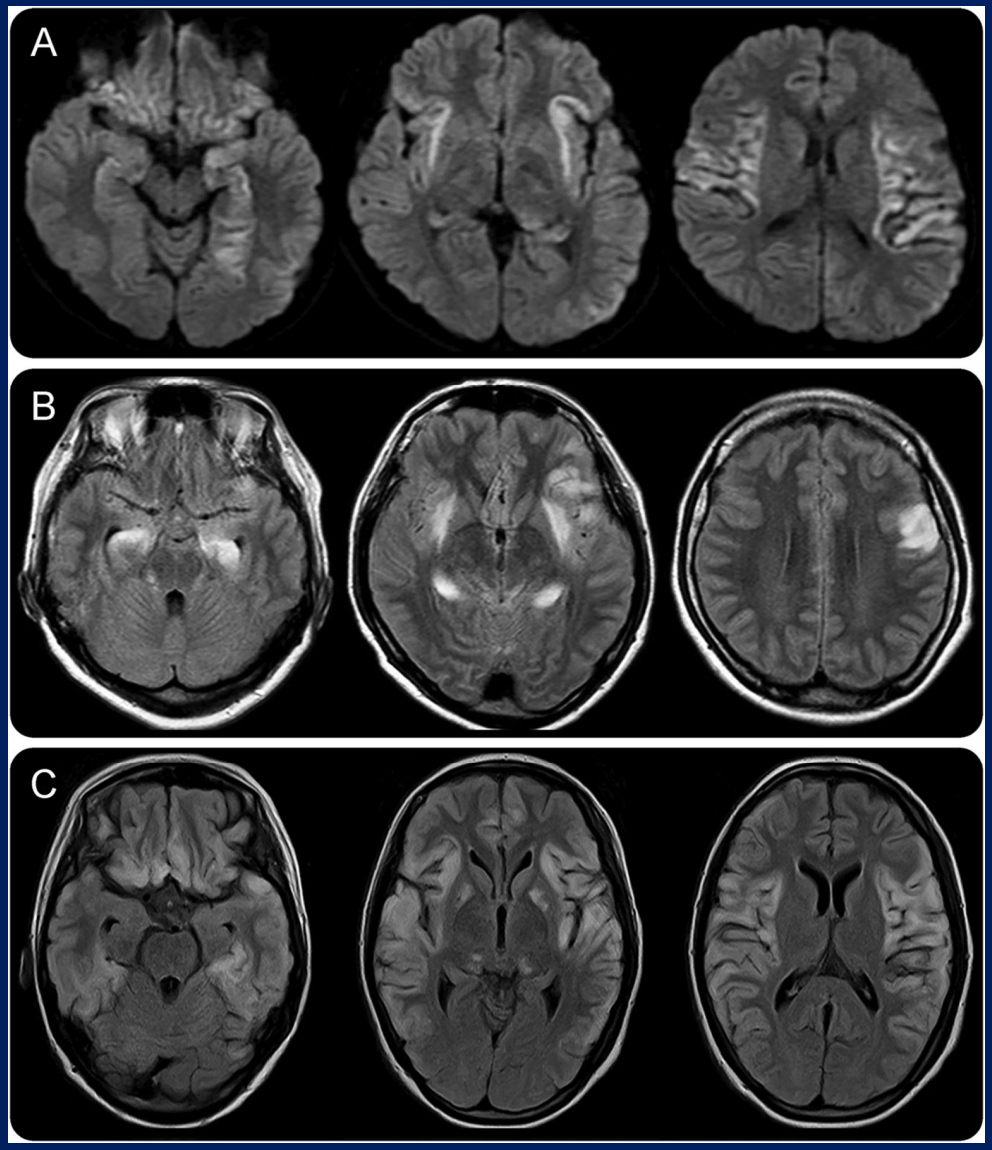
Febrile Infection Related Epilepsy Syndrome (FIRES)

- Previously known
  - fever induced refractory epilepsy
  - Devastating Epileptic Encephalopathy in School aged Children (DESC)
  - Acute Encephalitis with Refractory Repetitive Partial Seizures (AERRPS)
- It is severe post-infectious neurological d/o → intractable status epilepticus in a normal child (or less commonly adult) after a febrile illness.

FIRES

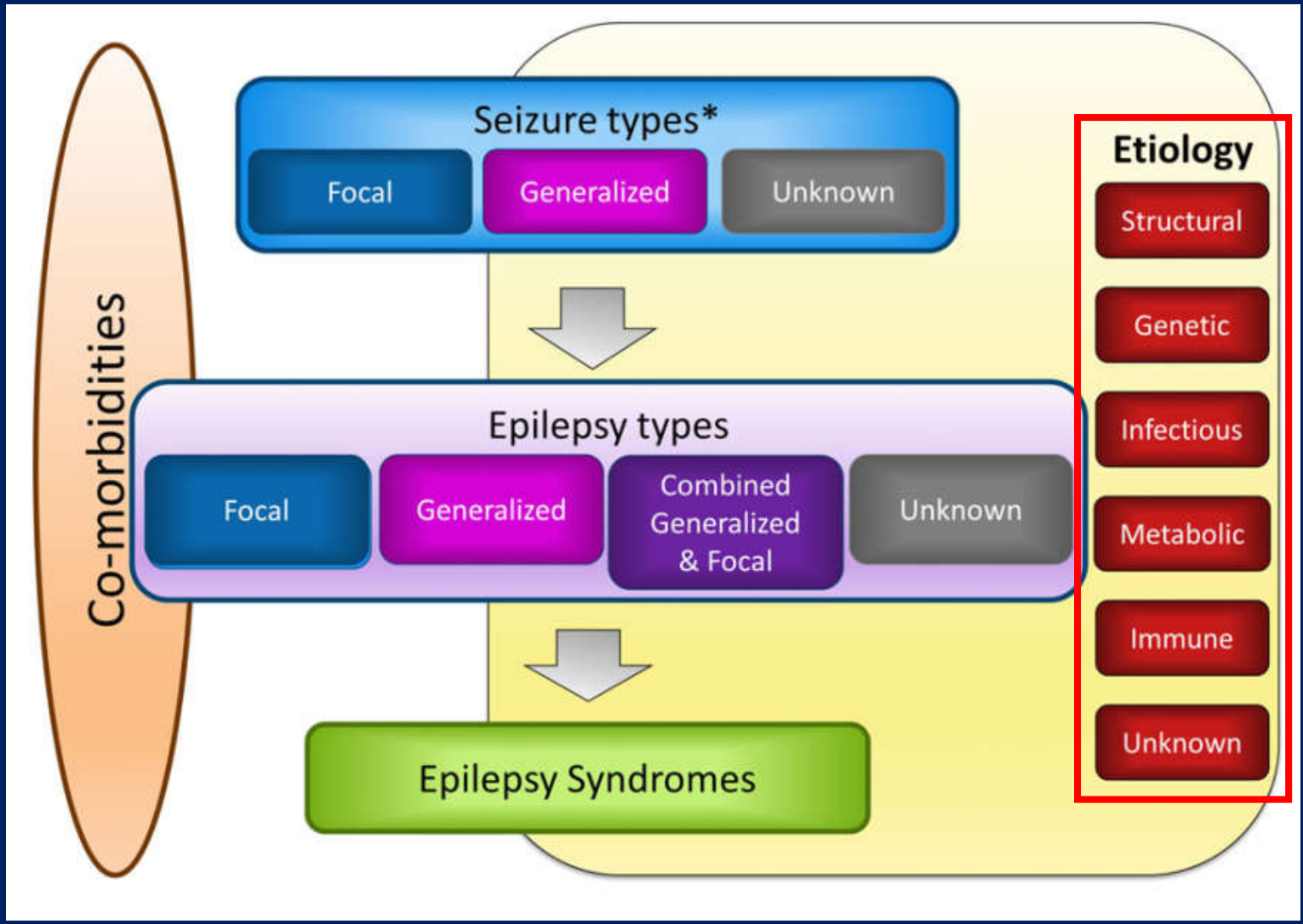
- Onset peak 8 years old (2-17), (slightly) male predominant
- A febrile URI/GI illness 1-14 days (median 4 days) before SZ onset.
- SZ rapidly progress to refractory status epilepticus.
- high mortality.
- Pathogenesis – unknown
- Extensive w/u immune Ab and infection – Negative
- Limited response to immunotherapies: high dose steroids, immunoglobulin or plasma exchange.

FIRES: imaging



- bi-temporal or peri-insular hyperintensities
- Over time, diffuse cerebral atrophy is seen, often with T2 hyperintensities in the temporal regions.

Take Home Message



6 groups of etiologies (expanded version)

1. **Genetic**
   - Chromosome abn
   - Gene abn
2. **Structural**
   - Malf of cortical development
   - Vascular malf
   - Hippocampal sclerosis
   - Hypoxic-ischemic
   - Traumatic
   - Tumors
3. **Metabolic**
4. **Immune**
   - Rasmusen syndrome
   - Ab mediated
5. **Infectious**
6. **Unknown**
   - Febrile infection related epilepsy syndrome

Malf = malformation