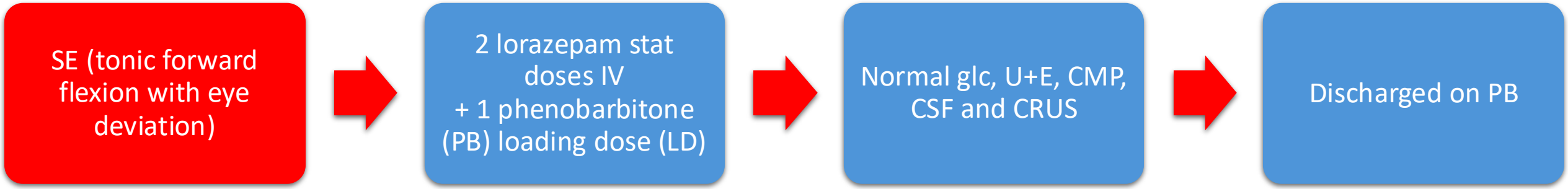
UNIVERSITY OF KWAZULU-NATAL ™
INYUVESI YAKWAZULU-NATALI

Malformations of Cortical Development

PANDA Webinar
13 May 2026
Author: Dr Kelly Stretch
Supervisor: Dr Lawrence Mubaiwa

Case 1

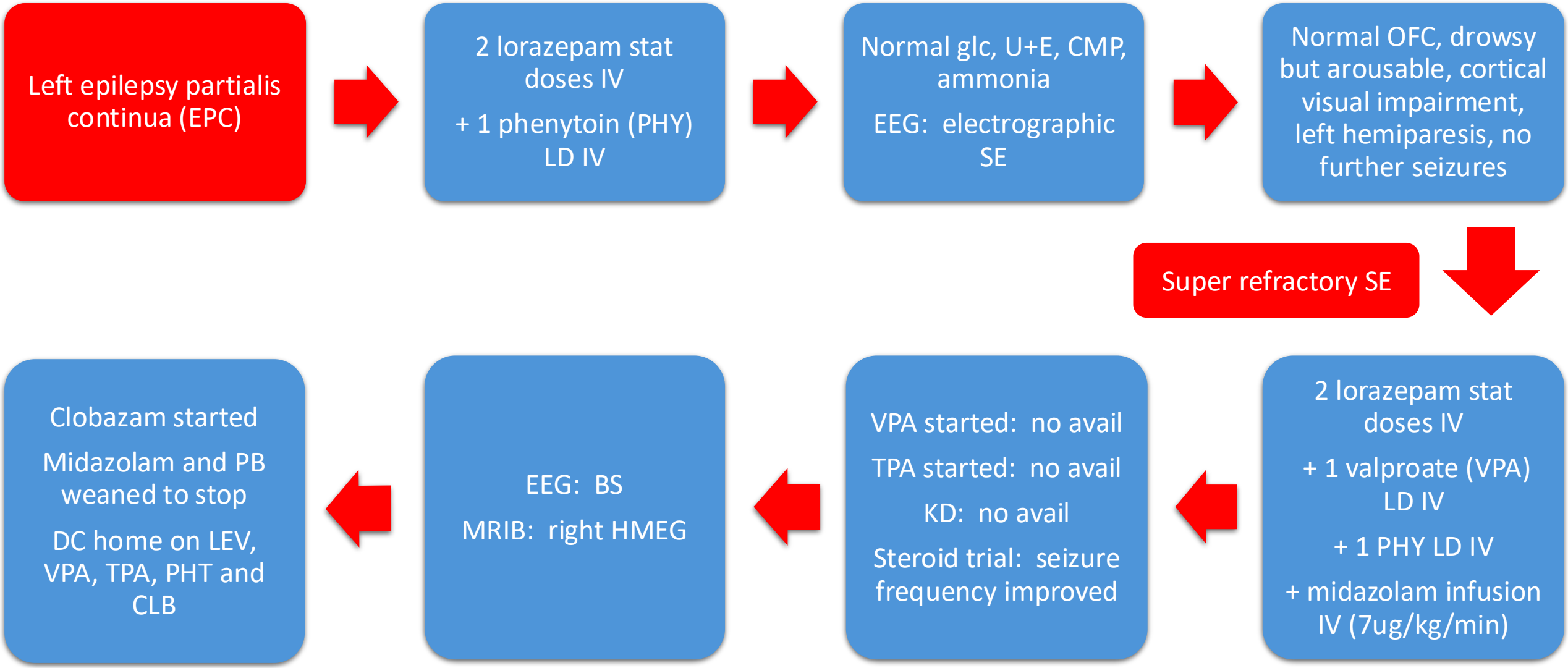
- Now 2 year old male with early infantile epileptic encephalopathy
- Birth hx: Term vertex delivery, AGA, BW 2.9kg, OFC 35cm, Apgars 8 and 9
- Family hx: nil of epilepsy or neurodevelopmental disorder
- Multiple admissions with status epilepticus (SE)
- D1 of life (regional hospital):



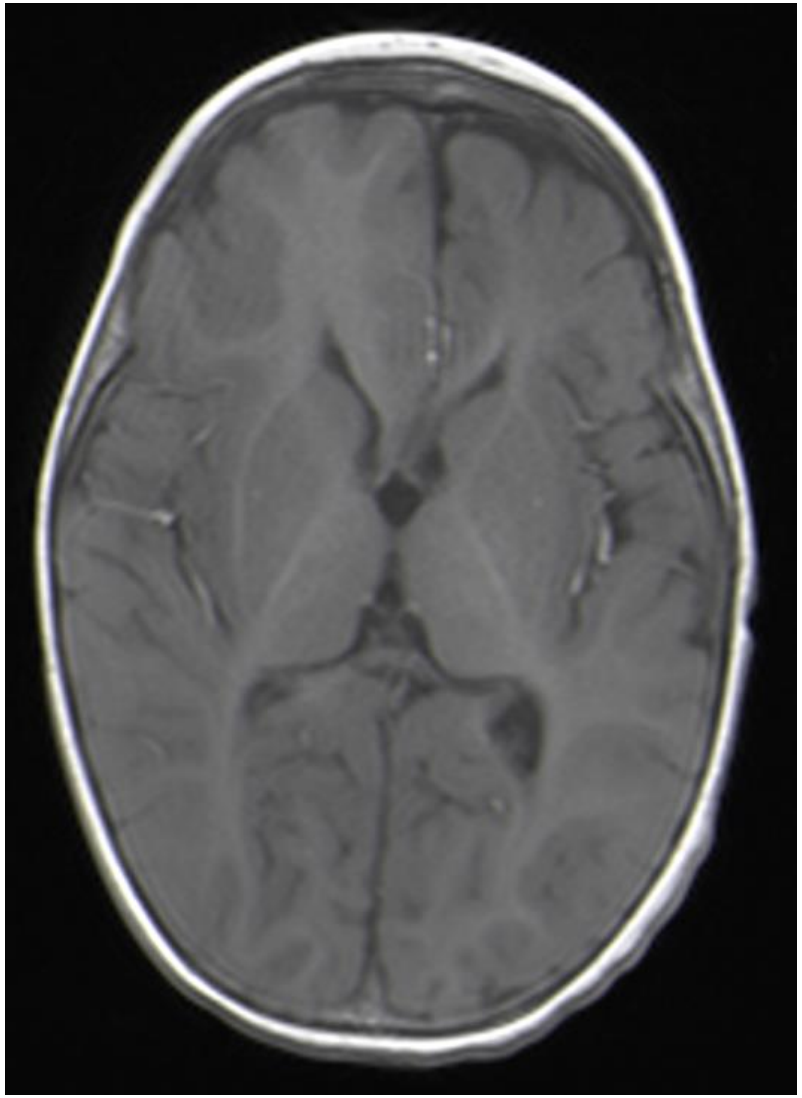
- Age 6 weeks of life (regional hospital): required phenytoin loading dose and midazolam infusion, CT brain NAD, urine organic and amino acids unremarkable, discharged home on PB and levetiracetam (LEV)

Case 1

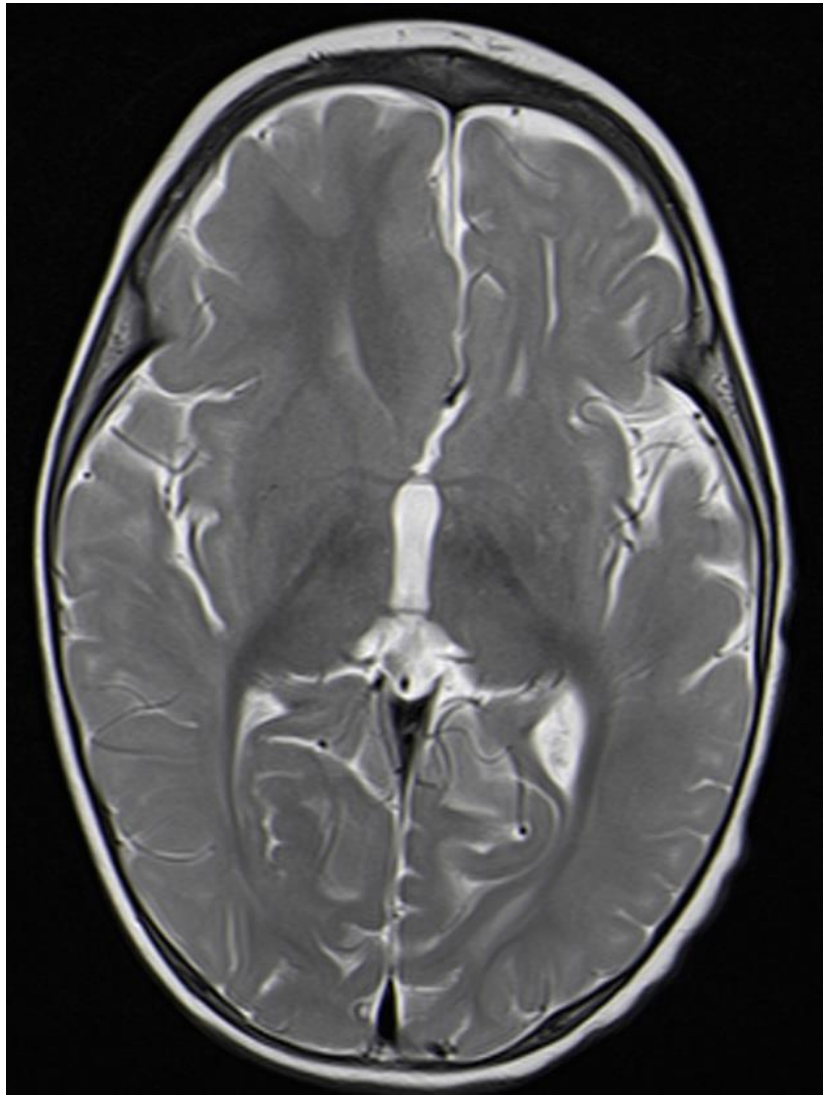
- Age 10 months (quaternary hospital):



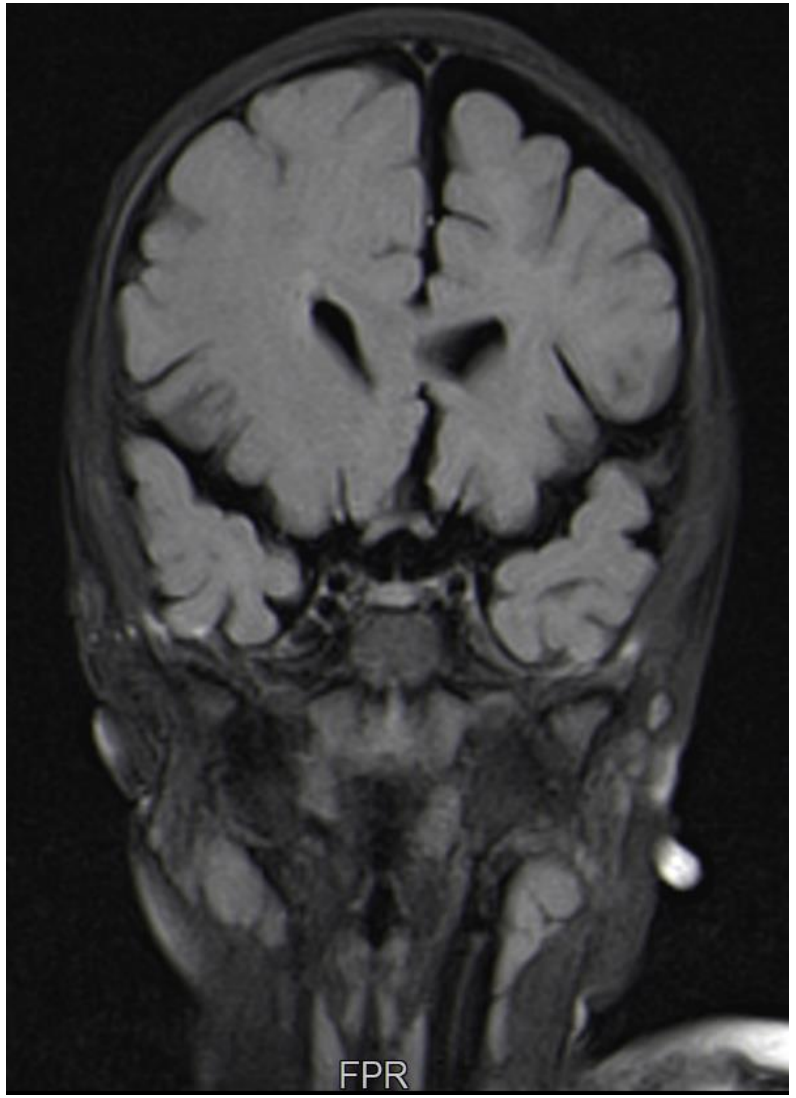
Case 1



MRIB, T1 sequence, axial view



MRIB, T2 sequence, axial view



MRIB, T2 FLAIR sequence, coronal view

Case 1

- Age 13 months (May 2025): readmission for workup for epilepsy surgery

LTEM:
higher amplitude epileptiform abnormalities and slowing over the right hemisphere

PET CT brain: hypometabolism noted in the right frontal and left temporal

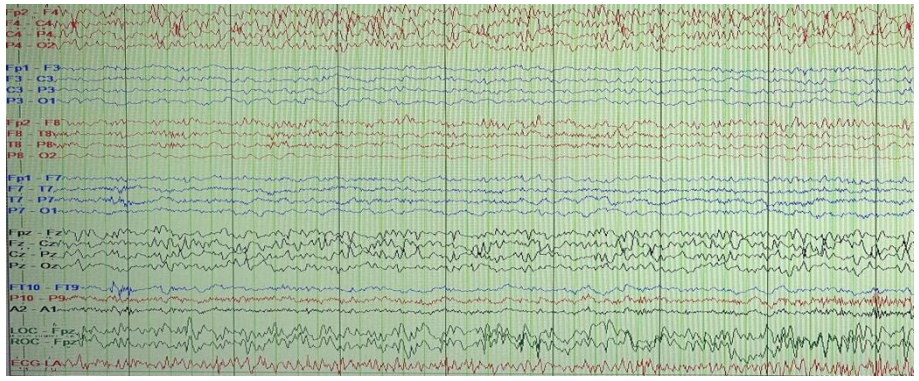
No clinical seizures for 1 month

CLB weaned to stop

PHT weaned to stop

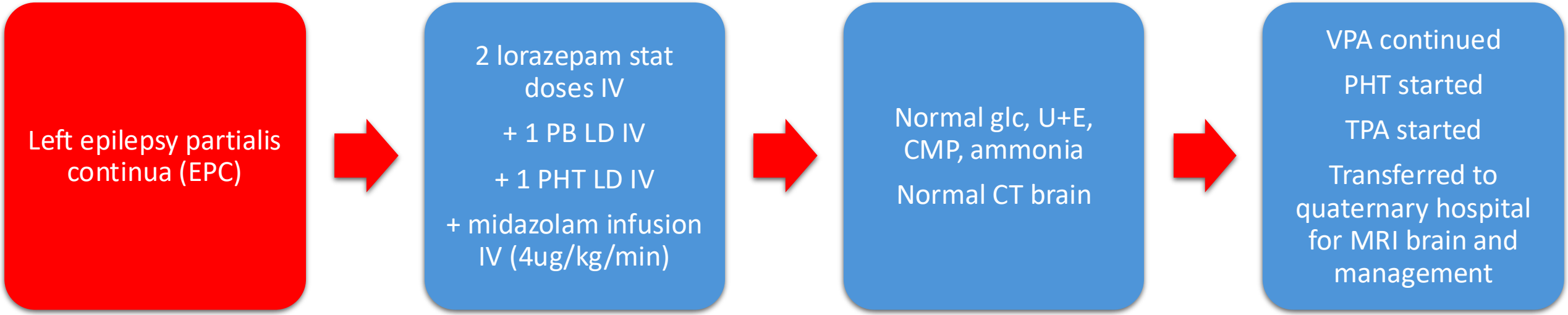
Discharged home on LEV, VPA, TPA

Seen in paed neurology clinic thrice: no clinical seizures, gaining milestones, left hemiparesis, decision made to hold off on epilepsy surgery



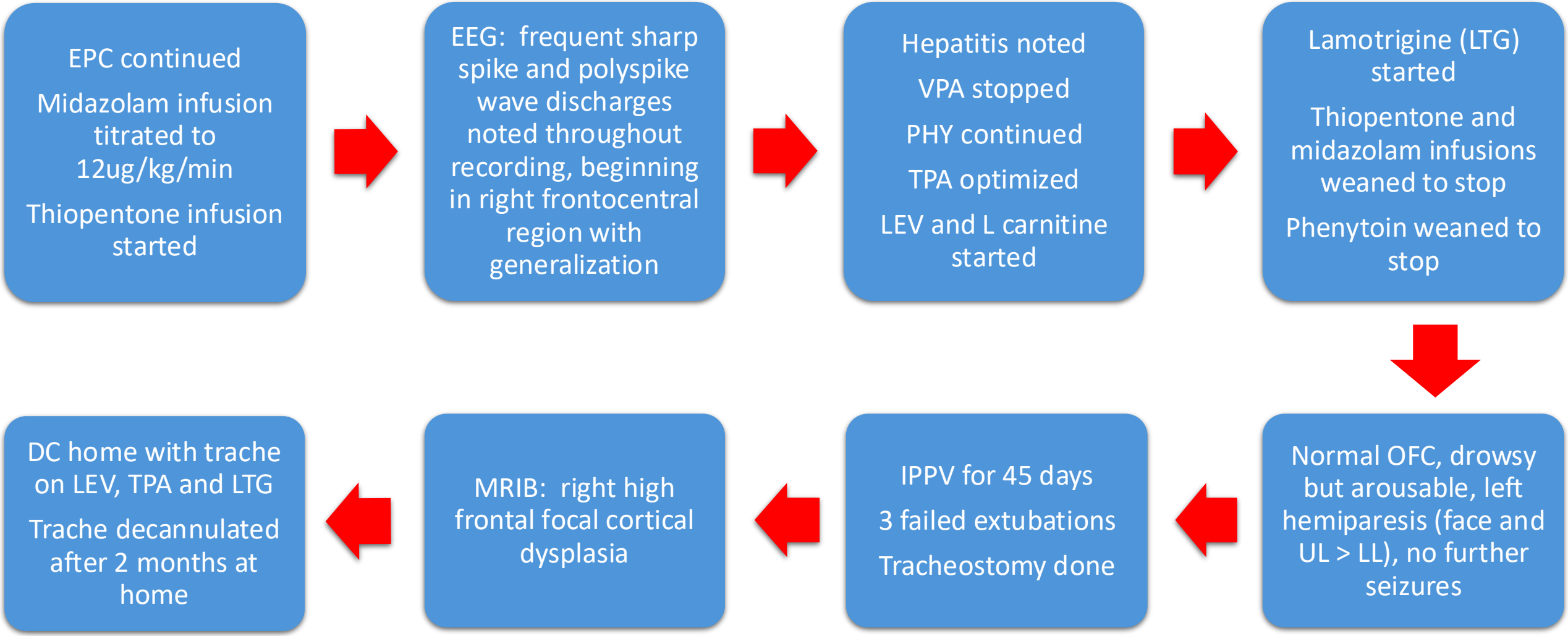
Case 2

- Now 11 year old male with left focal clonic drug resistant epilepsy and left hemiparesis
- Birth hx: Term vertex delivery, AGA, BW 3.2kg, OFC 36cm, Apgars 9 and 10
- Family hx: nil of epilepsy or neurodevelopmental disorder
- Multiple admissions with status epilepticus (SE)
- Age 1 year of life (regional hospital): no details of PICU admission, normal CT brain, discharged on VPA
- Age 3 years of life (regional hospital):

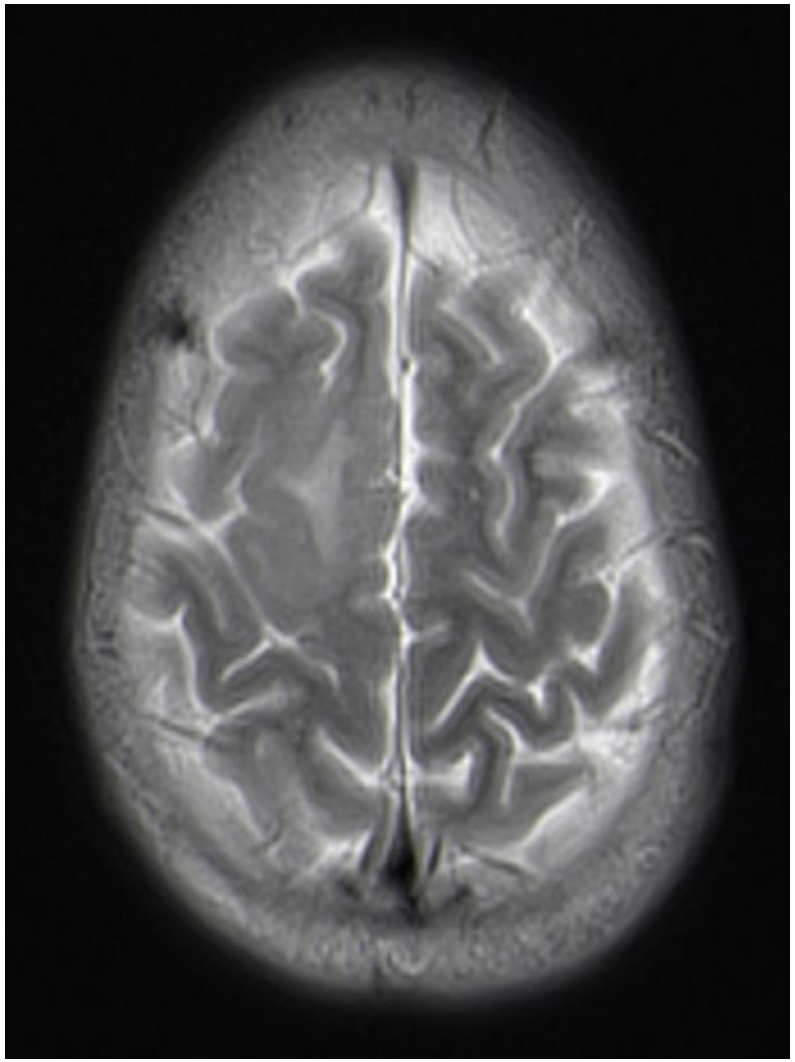


Case 2

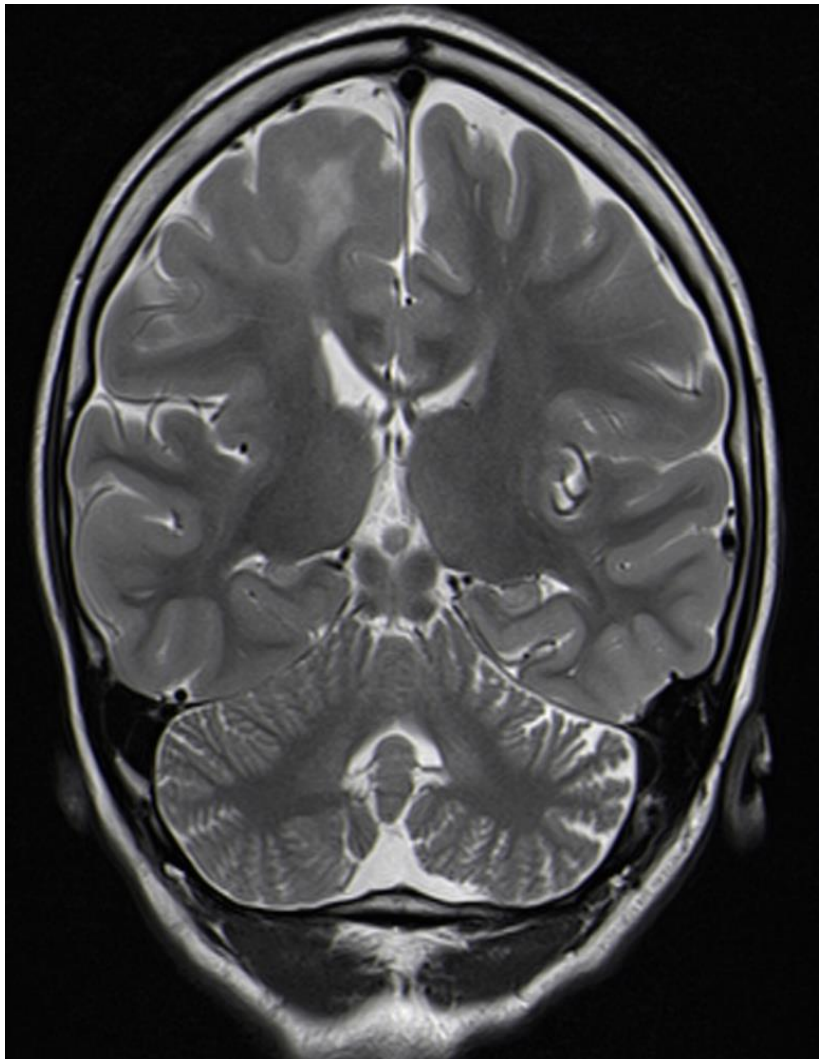
- Age 3 years of life (quaternary hospital):



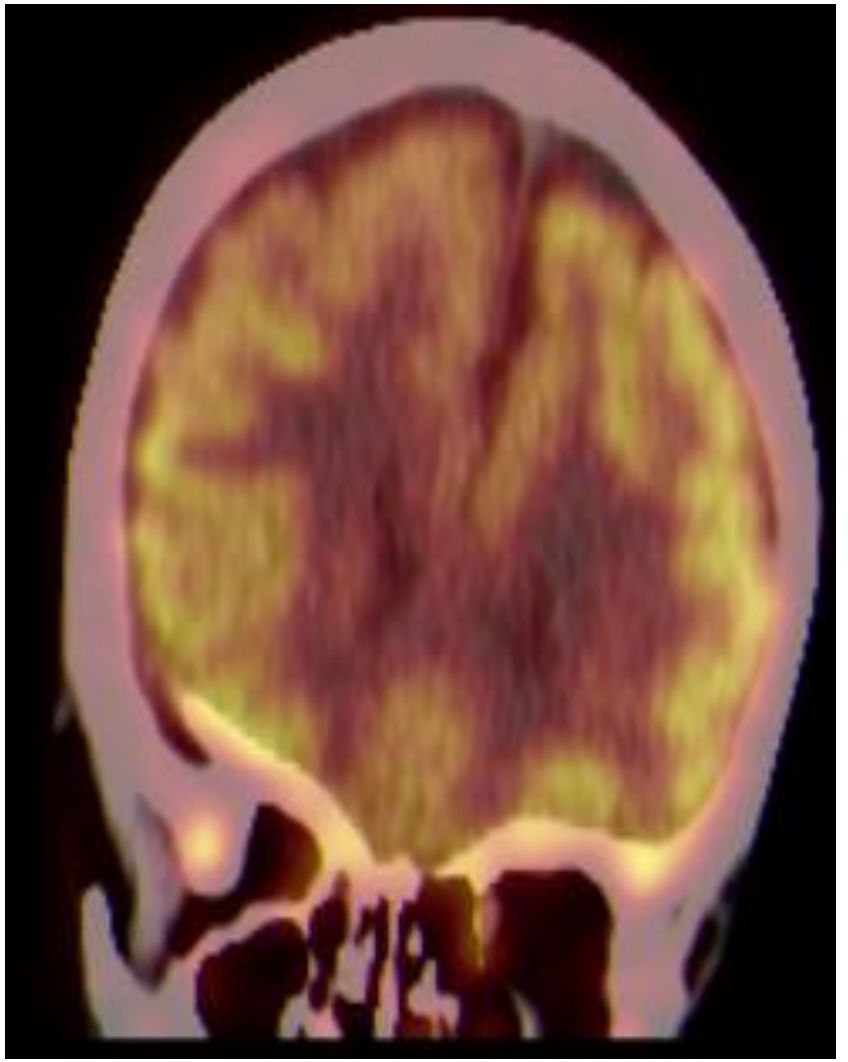
Case 2



MRIB, T2 sequence, axial view



MRIB, T2 sequence, coronal view



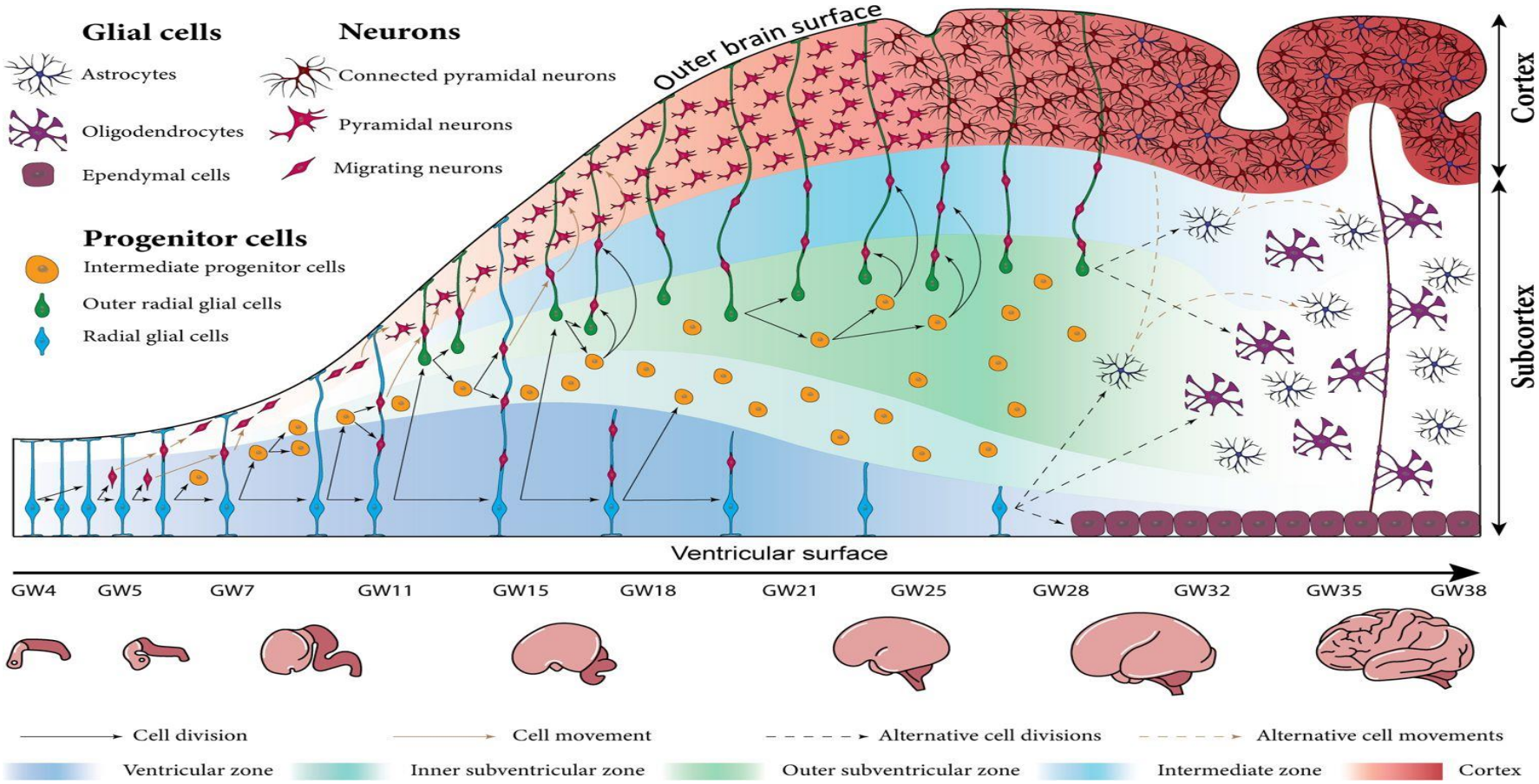
PET CT brain, coronal view

Case 2

- 4 admissions to quaternary hospital Paed Neurology ward with poor seizure control:
    1. Age 4 years 6 months: LEV, TPA and LTG doses optimized
    2. Age 4 years 8 months: LEV, TPA and LTG continued, PHY started
    3. Age 5 years 5 months (after PHY weaned to stop): LEV, TPA and LTG continued, PHY restarted, CBZ started
    4. Age 10 years: LEV, TPA, LTG, PHY and CBZ continued, VPA restarted to no avail, modified Aktins diet started to no avail, CLB started with some improvement in seizure frequency, workup for epilepsy surgery commenced
- Age 11 years (quaternary hospital): 2 short left focal clonic seizures per day. Investigations done:
    1. MRI brain: right high frontal focal cortical dysplasia
    2. PET CT brain: altered metabolism right frontal lobe
    3. EEG: right frontal focus with secondary generalization
- Underwent right frontal lobectomy in April 2026 with good recovery

Table of contents

Development of the cerebral cortex



4th to 24th week of gestation:

Neuronal proliferation

12th to 22nd week of gestation:

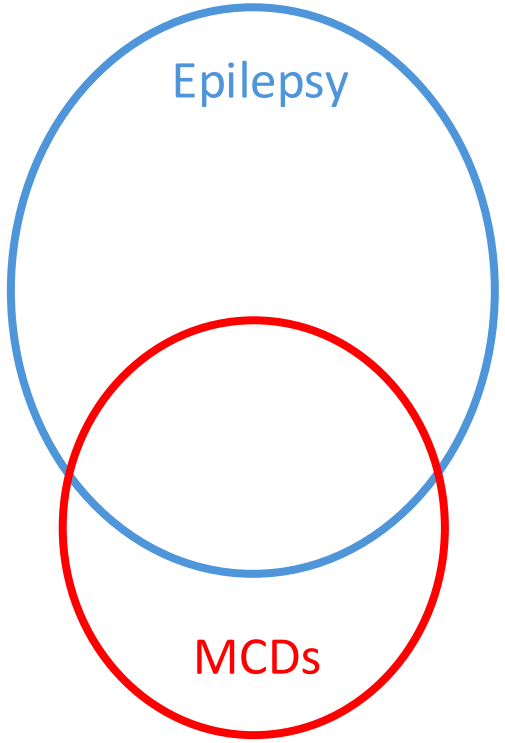
Neuronal migration

22nd week of gestation to 2 years of life:

Cortical organization

Introduction to MCDs

- A large spectrum of disorders resulting from disruption of normal cortical development
- Barkovich et al. in 1996 described MCDs to include disorders with abnormal cortical developmental in which the cortical ribbon itself appears normal – the classification of MCDs was revised in 2001, 2005 and 2012
- Disruption may result from any of the following aetiologies:
  1. Genetic
  2. Infective
  3. Vascular
  4. Metabolic
- Multiple biologic pathways have been associated with MCDs, including:
  1. MCD specific gene mutations
  2. Defects in messenger RNA splicing
  3. Defects in intracellular trafficking
  4. Defects in glycosylation



- Important causes of epilepsy, intellectual disability, neurological deficits and developmental delay
- A common cause of drug resistant epilepsy in children

Diagnosis of MCDs

- Thorough history (incl. seizure semiology) and exam (OFC, syndromic clinical features) is key to ax
- Brain biopsy is not always feasible - neuroimaging is the cornerstone of diagnosis and presurgical ax
- High resolution MRI brain is the primary imaging modality for detecting MCDs - In infants, MRI brain abnormalities may be better seen before or after myelination - T2 isointense stage may obscure MCDs

Recommendations for the use of structural magnetic resonance imaging in the care of patients with epilepsy: A consensus report from the International League Against Epilepsy Neuroimaging Task Force

2019 ILAE Task Force recommended the HARNESS-MRI 3D protocol at 3T to standardize best practice neuroimaging in children with epilepsy which includes a minimum of:

- Multiplanar 3T MRI for cortical architecture (7T MRI used for problem solving): thin sections, 3D volume acquisition, allows PET/SPECT fusion
- Need high spatial resolution and tissue contrast: T1 and 3D T2 FLAIR sequences in axial, coronal and sagittal views

Epilepsia. 2019;60:1054–1068

What's new on the front of MCDs?

The ILAE consensus classification of focal cortical dysplasia: An update proposed by an ad hoc task force of the ILAE diagnostic methods commission

2022 ILAE Task Force revised the prior classification of focal cortical dysplasia (FCD):

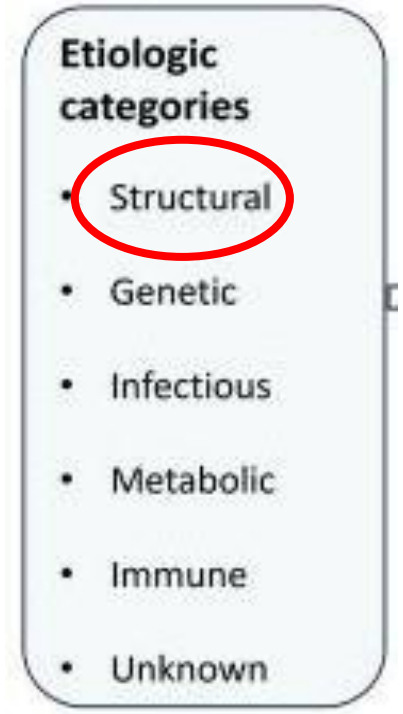
- To incorporate and update clinicopathologic and genetic information, with the aim to provide an objective classification scheme
- To introduce the concept of an integrated (layered) diagnosis

  Layer 1: Histopathologic assessment

  Layer 2: Molecular and genetic results

  Layer 3: Presurgical neuroimaging

  Layer 4: Integrated diagnosis



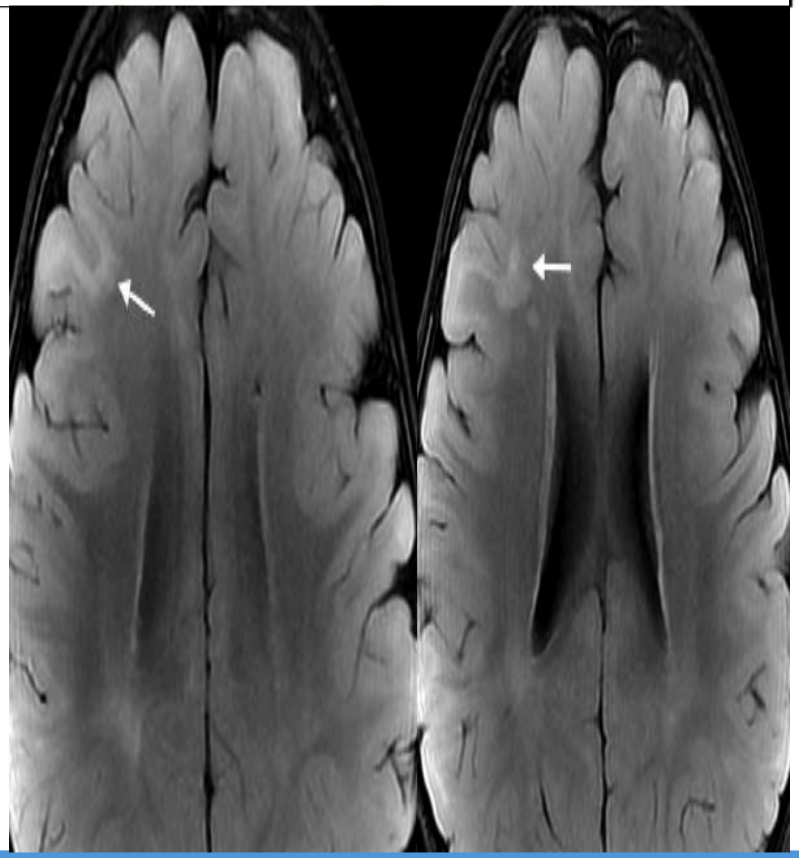
Epilepsia; 2022; 63:1899-1919

What's new on the front of MCDs?

Updates from the International League Against Epilepsy Classification of Epilepsy (2017) and Focal Cortical Dysplasias (2022): Imaging Phenotype and Genetic Characterization

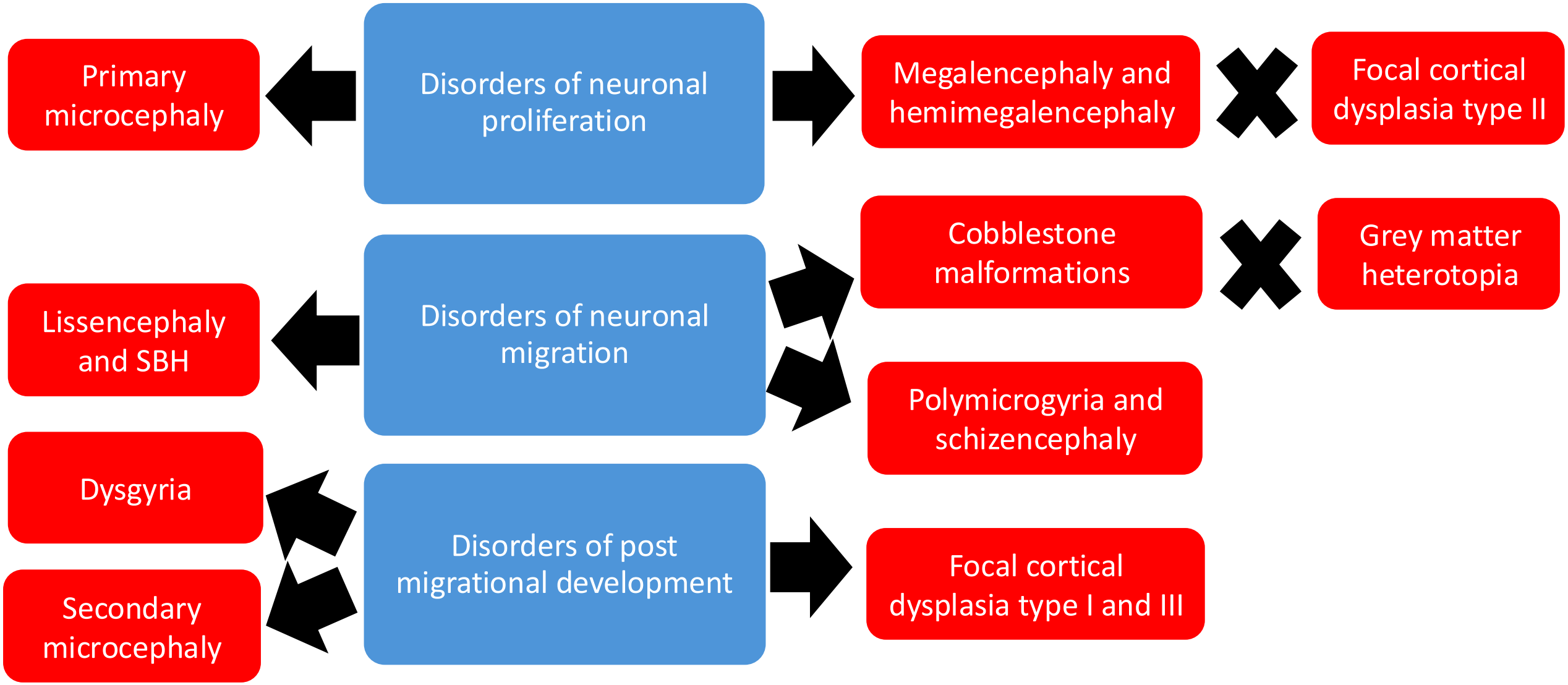
2024 ILAE Task Force has updated:

- FCD type II
- New entities identified such as mild malformations of cortical development (mMCDs) and malformations with oligodendroglial hyperplasia (MOGHEs)
- MOGHE: young children with seizure onset around 2 years of age, frontal lobe > temporal, strong association with SLC35A2 gene mutations, primarily WM abnormality and can have subtle cortical thickening, excellent outcome after resection



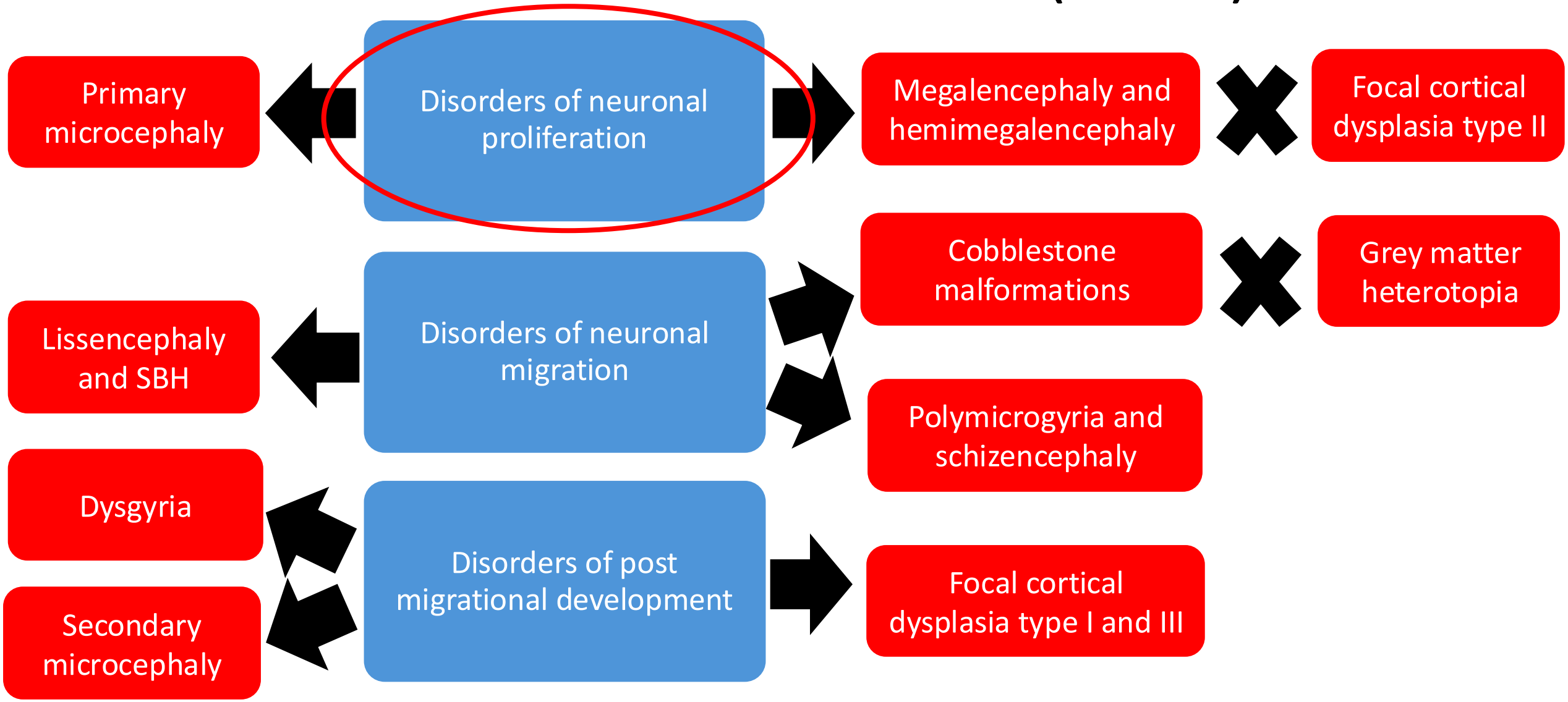
AJNR Am J Neuroradiol; Aug 2024; 45:991-999

Classification of MCDs (latest)



Severino M et al. Definitions and classification of malformations of cortical development: practical guidelines. Brain 2020;143(10):2874–2894.

Classification of MCDs (latest)



Severino M et al. Definitions and classification of malformations of cortical development: practical guidelines. Brain 2020;143(10):2874–2894.

Microcephaly

- Head circumference < -2 SD for age and sex
- Most common MCD resulting in developmental delay (15%)
- Present at birth (congenital) or develop post natally (acquired)
- Acquired microcephaly may have either static or progressive neurological symptoms
- CFs:
  1. Cognitive impairment in approximately 50% of children
  2. Epilepsy in approximately 40% of children,
  3. Cerebral palsy in approximately 20% of children, and
  4. Ophthalmologic abnormalities in 20 to 50% of children
- Ix:
  1. MRIB preferrable (normal or simplified gyral pattern with/out associated brain malformations)
  2. CTB preferred for calcifications and bone structure
  3. Other investigations as indicated by history, examination and neuroimaging
- Mx and prognosis: dependent on specific aetiology and phenotype of the child

Congenital microcephaly aetiolgies

Primary genetic microcephaly (AR)	Syndromic microcephaly	Antenatal vascular events	Congenital infection	Maternal teratogen use
• MCPH1 • ASPM • CDK4RAP2 • CENPJ	• Seckel syndrome • MOPD type 2 • Cornelia de Lange syndrome • DiGeorge syndrome	• Ischaemic stroke • Haemorrhagic stroke	• CMV • HIV • Toxoplasmosis • Rubella • HSV • Syphilis • Zika virus	• Alcohol • Hydantoin • Maternal PKU • Poorly controlled maternal DM

Abuelo, D; Microcephaly syndromes; Seminars in Paediatric Neurology 2007; 14: 118-127

Acquired microcephaly aetiolgies (static neurological symptoms)

Syndromic microcephaly	Vascular events	Infections	Teratogens	Deprivation
• Aicardi Goutieres syndrome • Miller Dieker syndrome	• HIE • TBI • Ischaemic stroke • Haemorrhagic stroke	• HIV encephalopathy • Viral encephalitis • TBM	• Lead poisoning • Chronic renal failure	• Malnutrition • Anaemia

Acquired microcephaly aetiolgies (progressive neurological symptoms)

Metabolic disorder	Degenerative disorders
• Propionic acidaemia • Phenylketonuria • Leigh like disease	• Rett syndrome • Rett like syndrome • Ataxia telangiectasia

Megalencephaly, hemimegalencephaly (HMEG) and focal cortical dysplasia (FCD)

- Megalencephaly refers to an increase in brain size and can be divided into the following categories:
  1. Developmental megalencephaly: disruption of signalling pathways that regulate brain cellular proliferation, differentiation, cell cycle regulation and survival
  2. Metabolic megalencephaly: brain infiltration of a toxic metabolite because of an inborn error of metabolism or a leukodystrophy
- Unilateral or bilateral, partial or complete
- Hemimegalencephaly (HMEG): unilateral complete megalencephaly involving (more or less) all of one cerebral hemisphere
- Focal cortical dysplasia (FCD): focal regions of abnormal cortex (defined histopathologically into FCD types I, II and III)
- The histopathology of HMEG is the essentially the same as FCD type II
- The histopathological features of FCD type IIb overlap with those of tubers in tuber sclerosis complex (TSC)

HMEG and FCD IIb

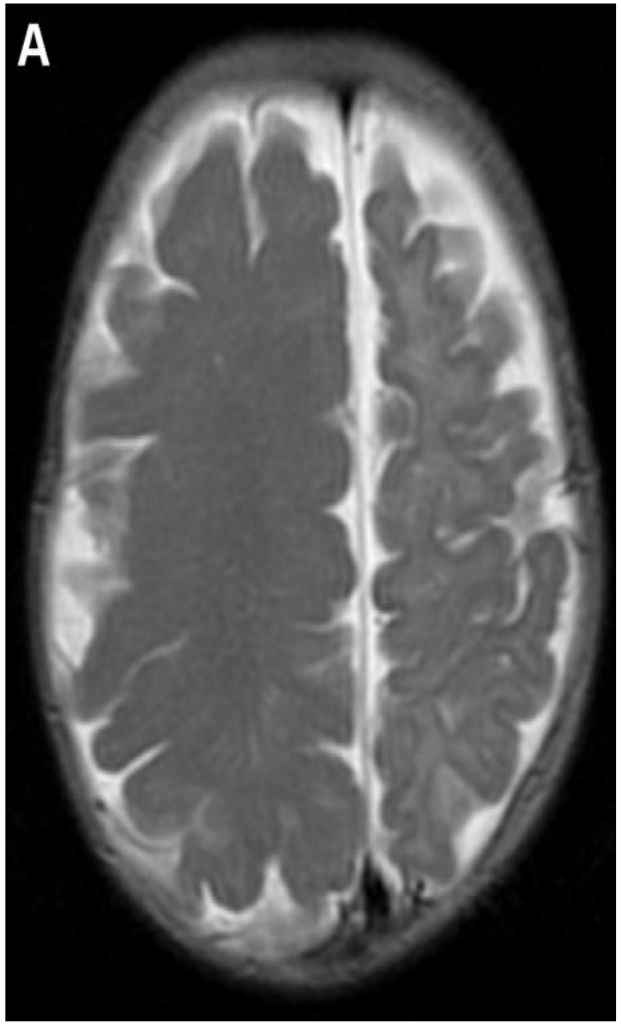
- HMEG and FCD typically occur as an isolated feature, but may occur with the following syndromes:
  1. Tuber sclerosis complex, Sturge Weber syndrome
  2. Hypomelanosis of Ito, linear naevus syndrome
- CFs:
  1. Epilepsy
  2. Cognitive impairment
  3. Neurodevelopmental delay
  4. Focal neurological clinical features
- Ix:
  1. CTB: FCD rarely visible
  2. MRIB: T1 sequence reveals poor grey and white matter differentiation, abnormalities in gyral pattern and thickened cortex; T2 and FLAIR sequences reveal hyperintensities in the base of the lesion and in the underlying white matter in a characteristic pattern ('base of sulcus sign' and 'transmantle sign')
  3. PET: highly sensitive for detecting MRI negative FCD
  4. EEG: Identifies epileptogenic foci

Table 4: Gene Defects Identified and Associated with Megalencephaly

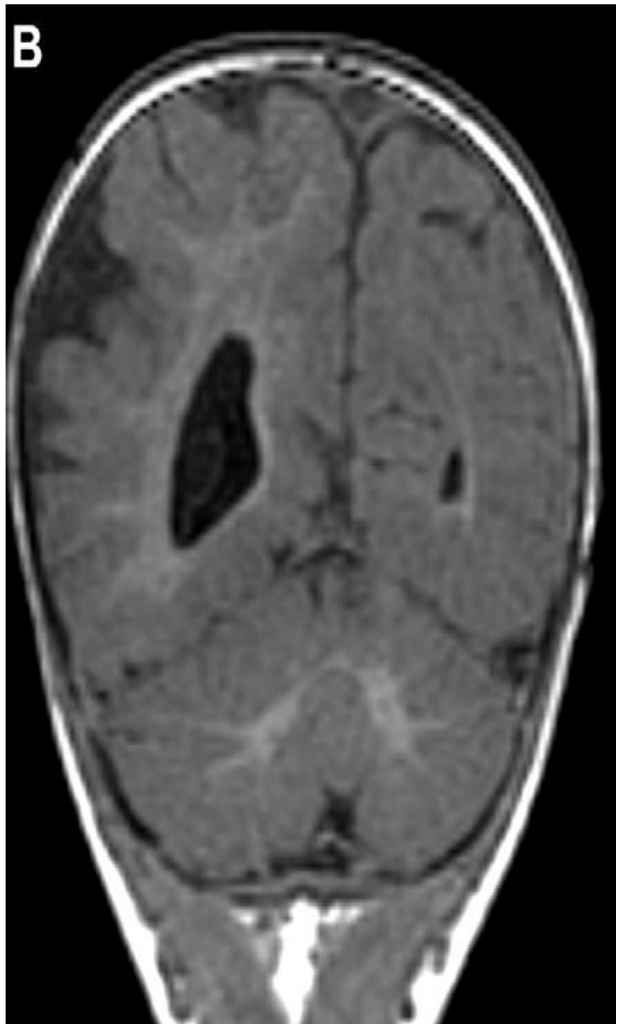
Gene mutation
PI3K–AKT–mTOR pathway
RAS–MAPK–ERK pathway
DNA methyltransferase
Transcription initiation regulators and tyrosine kinase receptor
Other findings
Isolated or syndromic megalencephaly, with somatic (body) overgrowth and/or other MCD, including PMG

Brunelli et al. Malformations of Cortical Development: Updated Imaging Review. Radiographics. 2024 Nov;44(11):e230239.

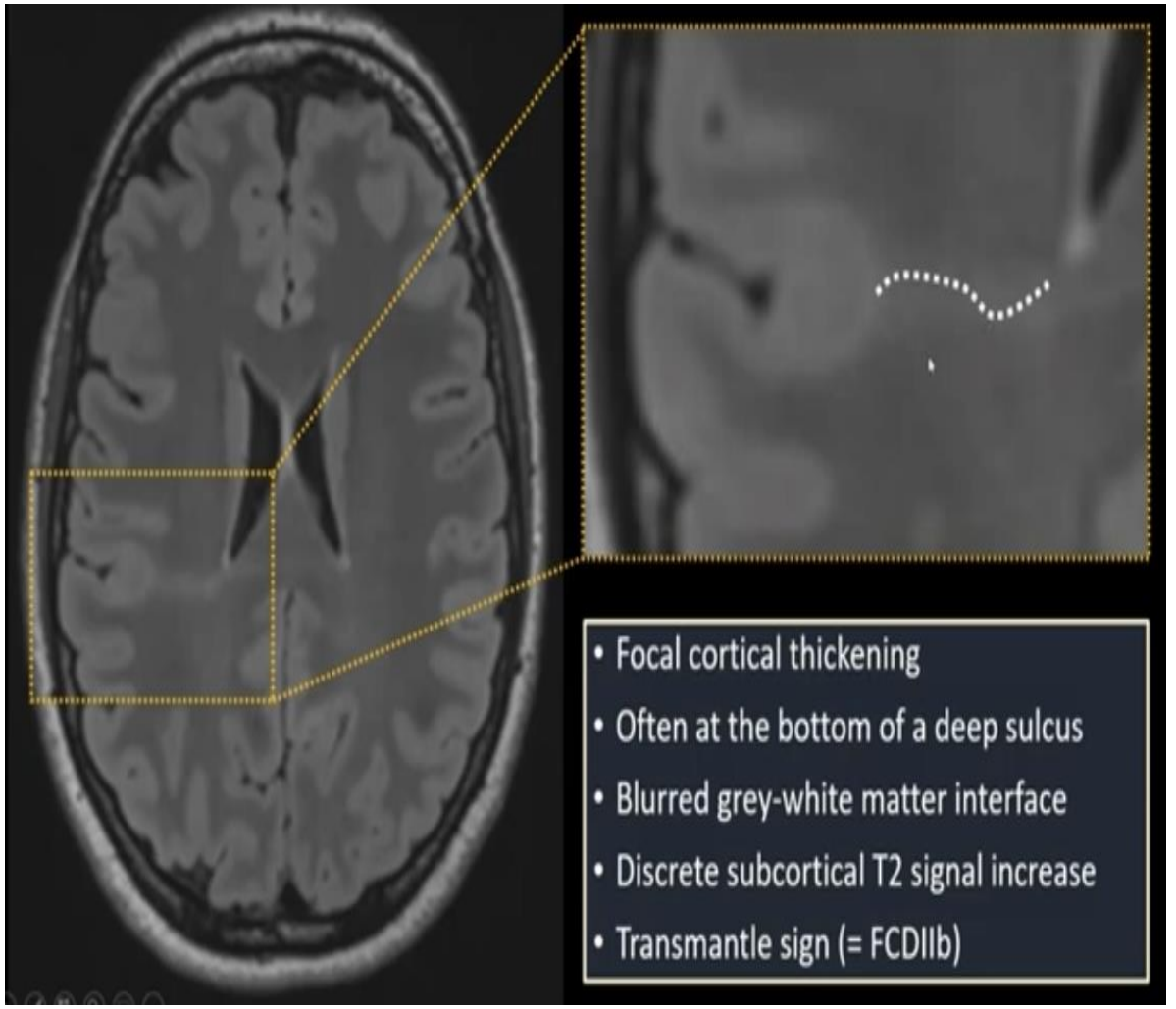
HMEG and FCDIIb



MRIB, T2 sequence, axial view



MRIB, T1 sequence, coronal view



MRIB, T2 FLAIR sequence, axial view

HMEG and FCD

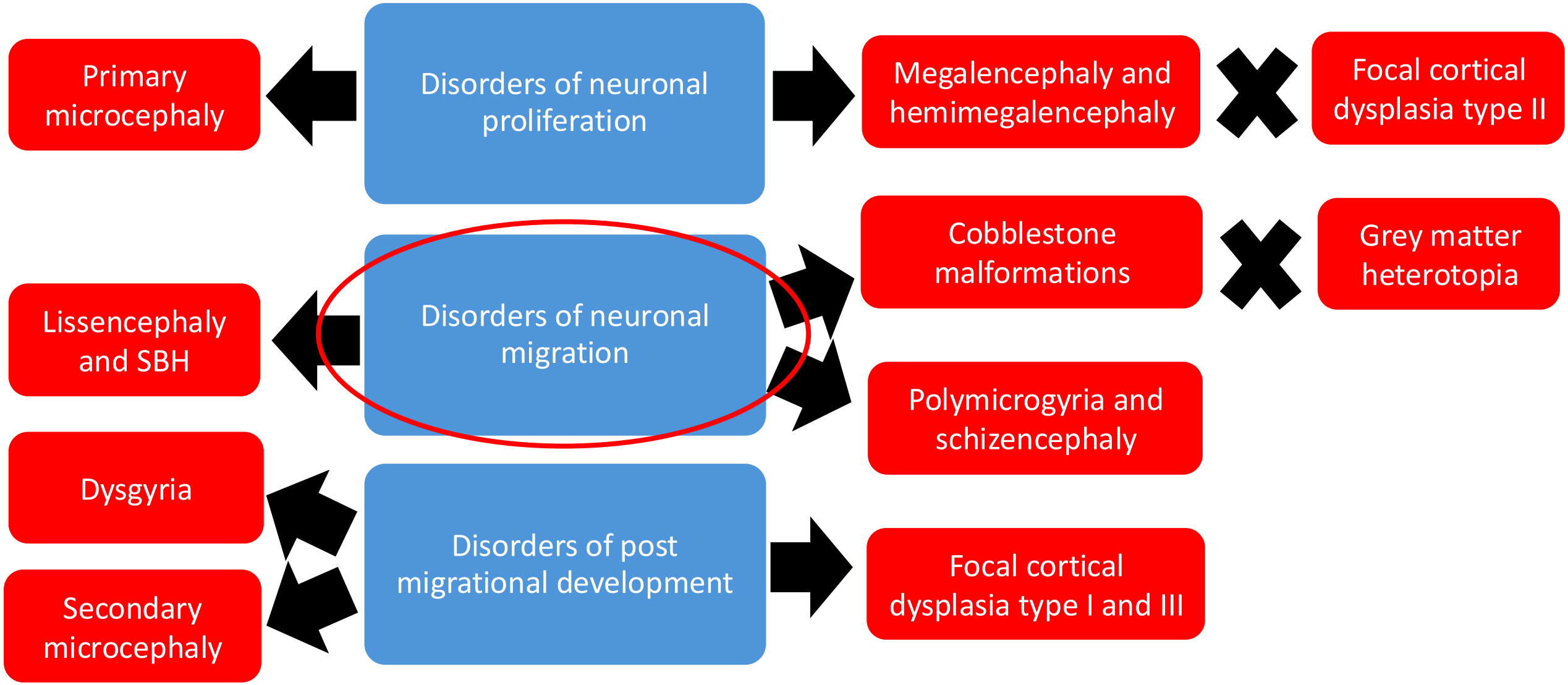
- Mx:
  1. MDT
  2. OT, PT, SLT
  3. Tx epilepsy
  4. Epilepsy surgery if lesion surgically accessible, the only epileptogenic focus, and not in an eloquent area of the brain

> A retrospective analysis published in 2010, analyzed seizure outcomes and quality of life in 83 children who underwent epilepsy surgery at a quaternary hospital in Wisconsin:
> - Seizure freedom in children was highest following temporal lobectomies (84.2%) and hemispherectomies (76.2%)
> - Hemispherectomy was more effective than multilobar resections
> - Cortical dysplasia cases did less well with a 57.5% seizure control
> - Qualify of life paralleled seizure outcome

  5. For those not candidates for epilepsy surgery
     - Ketogenic diet
     - mTOR inhibition
     - Neurostimulation techniques

Zupanc ML et al. Epilepsy Surgery Outcomes: Quality of Life and Seizure Control. Pediatr Neurol 2010;42:12.

Classification of MCDs (latest)



Severino M et al. Definitions and classification of malformations of cortical development: practical guidelines. Brain 2020;143(10):2874–2894.

Lissencephaly and subcortical band heterotopia

- Lissencephaly (LIS) refers to an abnormal gyral pattern
- Subcortical band heterotopia (SBH) refers to normal (or mildly simplified) gyral pattern associated with a variably thick layer of gray matter replacing the central and upper portions of white matter
- Both LIS and SBH result from of a genetic mutation in a gene involved in neuronal migration
- Most severe form of LIS is associated with Miller Dieker syndrome

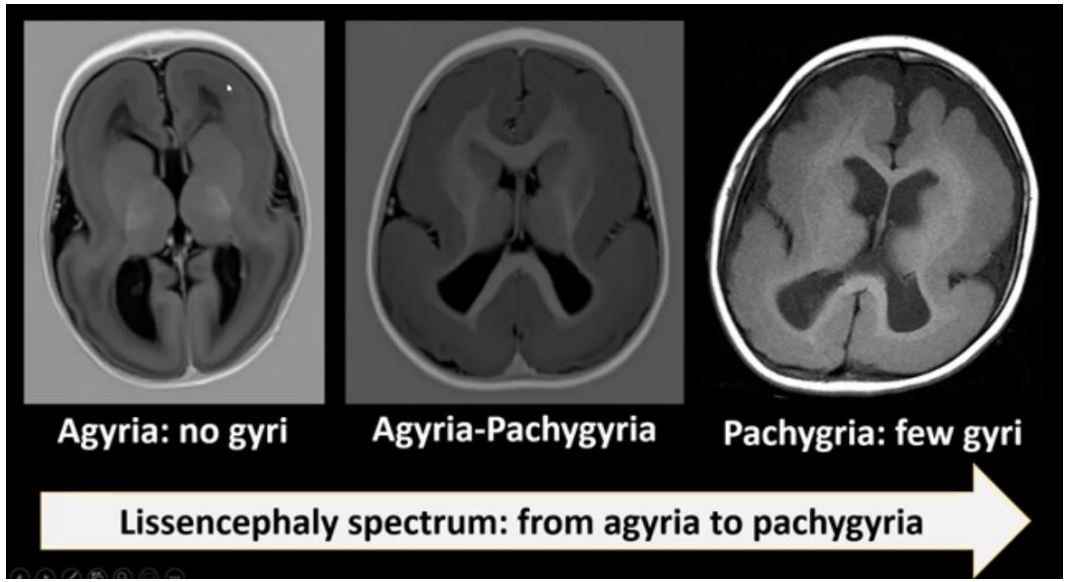
Table 5: Main Genes Associated with LIS

Gene Abnormality	Associated Phenotype
Mutation or deletion of *LIS1* (*PAFAH1B1*)	Isolated LIS syndrome or Miller-Dieker syndrome (spectrum of LIS with facial dysmorphism)
DCX (doublecortin protein) located in X chromosome	Classic LIS and SBH (affecting males more severely)
ARX	Temporal-predominant LIS variant or X-linked LIS with abnormal genitalia
RELN	LIS associated with cerebellar hypoplasia and hippocampal abnormalities
Tubulinopathy (*TUB*) gene mutation: *TUBA1A*, *TUBB2B*, *TUBB*, *TUBB3*, and *TUBA1A*	LIS with cerebellar hypoplasia, which can be associated with microcephaly or normal head size, thin cortex, or striking *TUB*-dysgyria

Brunelli et al. Malformations of Cortical Development: Updated Imaging Review. Radiographics. 2024 Nov;44(11):e230239.

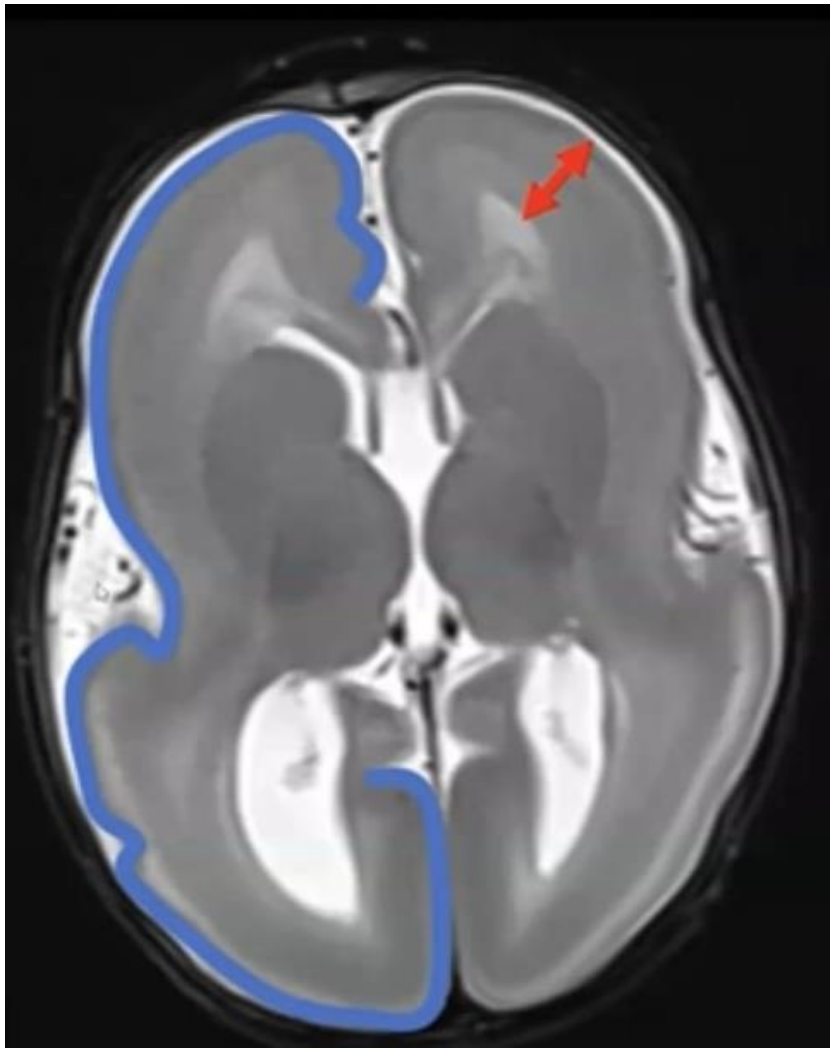
LIS and/or SBH

- CFs:
  1. Epilepsy
  2. Poor feeding
  3. Hypotonia
  4. Opisthotonus
- Ix:
  1. MRIB: preferrable and used to grade LIS
     - Grade 1 is agyria, figure of 8 (most severe form)
     - Grade 3 is mixed agyria and pachygyria
     - Grade 6 is SBH only (least severe form)
- Mx:
  1. MDT
  2. OT, PT, SLT
  3. Tx epilepsy



LIS

- Absent or minimal sulcation
- Thickened cortex (12-20mm thick)
- Shallow underdeveloped sylvian fissures
- Typical hourglass or figure of 8 shape
- Reduced white matter volume
- Often mild ventriculomegaly



MRIB, T2 sequence, axial view

Cobblestone malformations

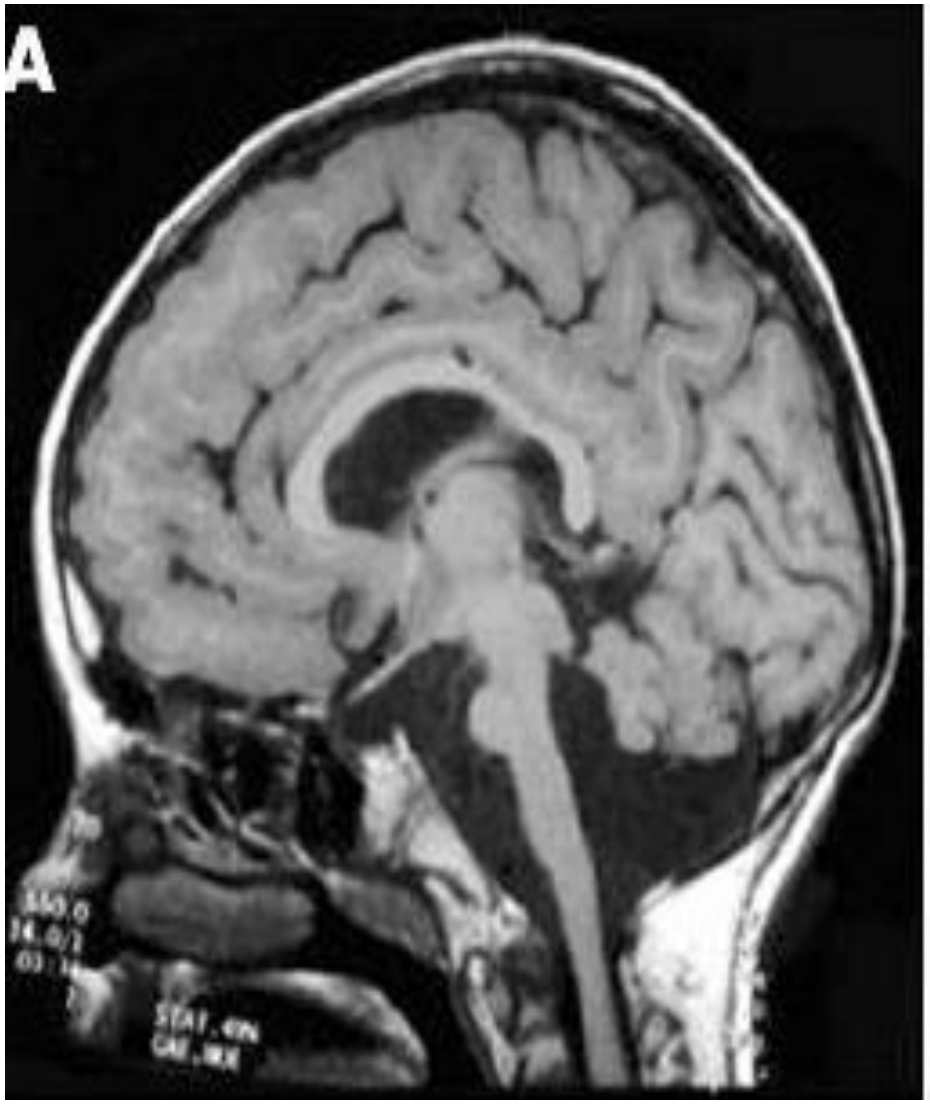
- Cobblestone malformations refer to a nodular appearance of the cerebral cortex
- Caused by mutations in genes involved in neuronal migration
- Dystroglycanopathies are the commonest aetiology of cobblestone malformations (AR)
- They result in impaired glycosylation of alpha dystroglycan, impaired integrity of the glial limitans and neuronal over migration
- They are divided into the following categories, from most severe form to least severe:

Walker Warburg syndrome	Muscle eye brain disease	Fukuyama congenital muscular dystrophy
• POMT1 or POMT2 gene mutation • Present in early life • Demise within a few months • Retinal dysplasia • Microphthalmia • Cataracts • Glaucoma • Congenital muscular dystrophy	• POMGnT1 gene mutation • Present in early life • Survive to later in their first decade • Retinal hypoplasia • Optic disc pallor • Cataracts • Glaucoma • Severe intellectual disability • Epilepsy • Congenital muscular dystrophy	• Fukutin gene mutation • Present in infancy with hypotonia • Moderate intellectual disability • Epilepsy • Congenital muscular dystrophy

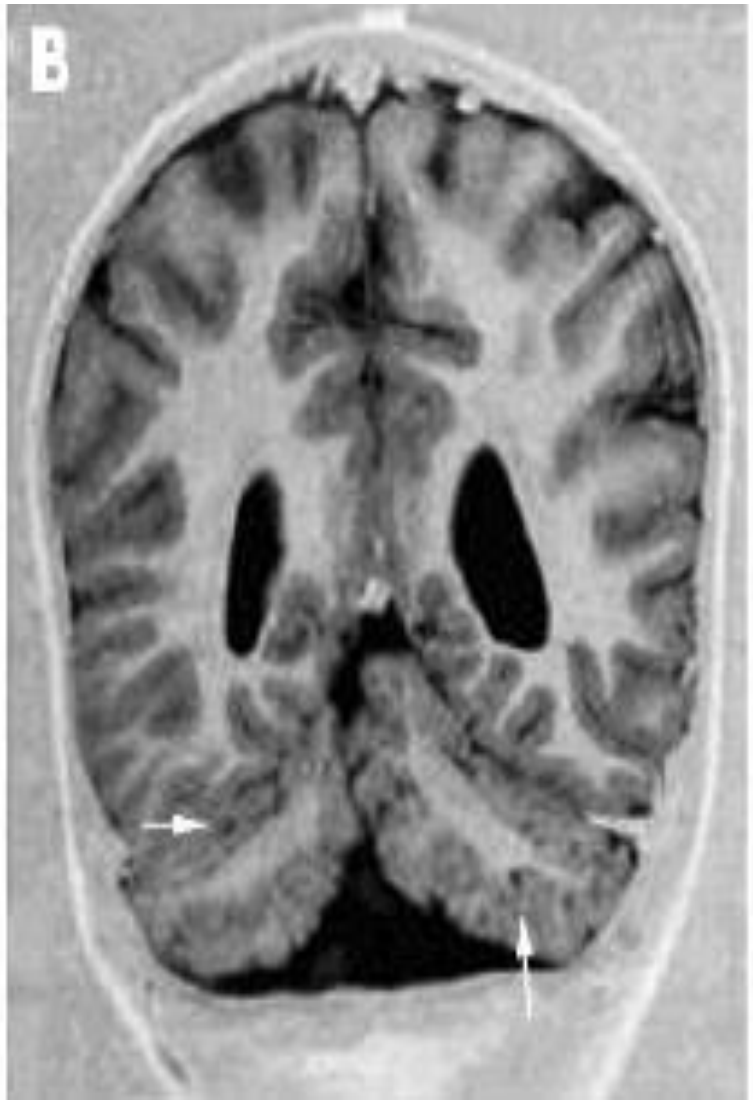
Dystroglycanopathies

- Ix:
  1. Elevated serum CK
  2. Muscle biopsy: hypoglycosylation of alpha dystroglycan and changes in keeping with a CMD
  3. MRIB for WWS and MEB:
     - Under sulcated cerebral surface
     - Mild to moderately thickened cerebral cortex
     - Jagged cortical white matter border with frequent vertical striations
     - Cerebellar vermian hypoplasia
     - Cerebellar agyria/polymicrogyria
     - Corpus callosum agenesis/hypogenesis
     - Most children with WWS have a hypoplastic Z-shaped brainstem and obstructive hydrocephalus secondary to aqueduct stenosis, 25% of children with WWS with an occipital encephalocoele
- Mx:
  1. MDT (ophthalmology therapies should be assessed on an individual basis owing to poor prognosis)
  2. OT, PT, SLT
  3. Tx epilepsy
  4. VPS for obstructive hydrocephalus

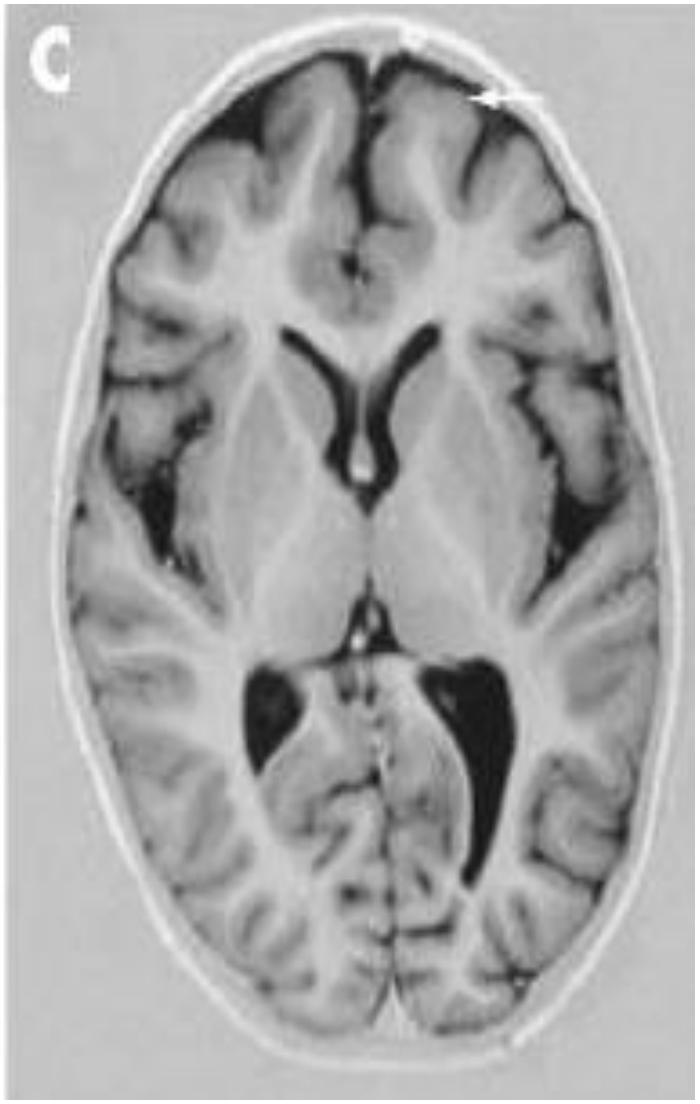
Dystroglycanopathies



MRIB, T1 sequence, sagittal view



MRIB, T1 sequence, coronal view



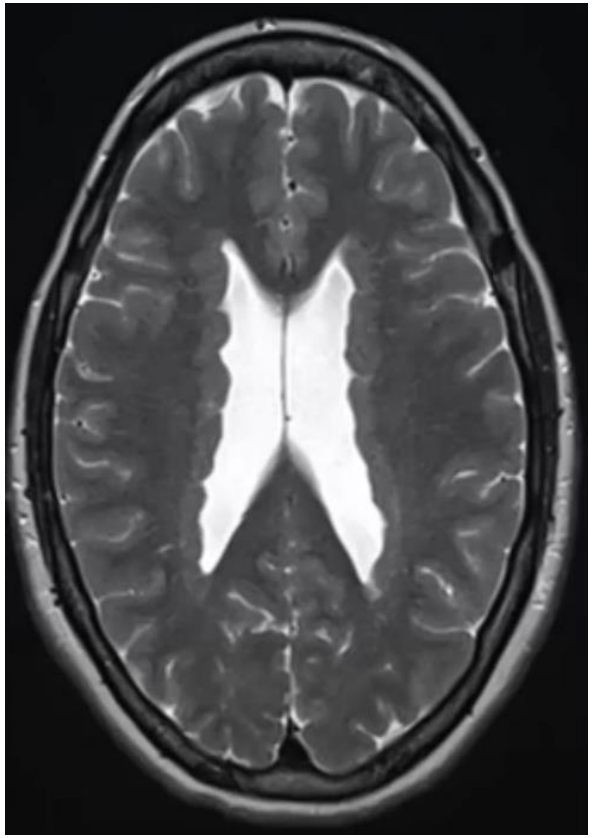
MRIB, T1 sequence, axial view

Grey matter heterotopias

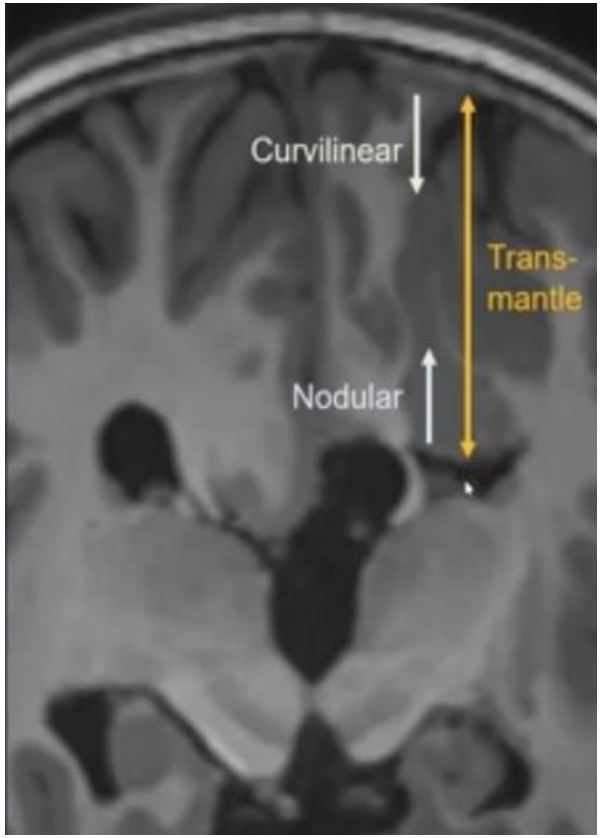
- Grey matter heterotopia refers to groups of neurons in abnormal locations
- Commonest subtype of grey matter heterotopia is periventricular nodular heterotopia (PNH)
- Subcortical nodular heterotopia (SNH) is a less common subtype, and is often associated with other MCDs
- PNH refers to nodular masses of grey matter that line the ventricular walls and protrude into the lumen
  1. If contiguous, PNH is caused by mutations in genes involved in neuronal migration such as filamin A (XLD)
  2. If singular, PNH is caused by as antenatal infections, vascular events, and irradiation
- CFs of PNH:
  1. Epilepsy in approximately 90% of children with PNH (most present in adolescence)
  2. Learning disabilities (usually normal intelligence)
- SNH refers to collections of grey matter dispersed in the white matter of the cerebral hemispheres and results from a genetic mutation involved in neuronal migration, or an antenatal vascular event
- CFs of SNH:
  1. Epilepsy (variable age of presentation)
  2. Intellectual disability (as a result of other MCDs)

Grey matter heterotopias

- Ix:
  1. MRIB:
     - PNH: nodular masses of grey matter that line the ventricular walls and protrude into the lumen
     - SNH: collections of grey matter dispersed in the white matter of the cerebral hemispheres (curvilinear, transmantle, nodular)



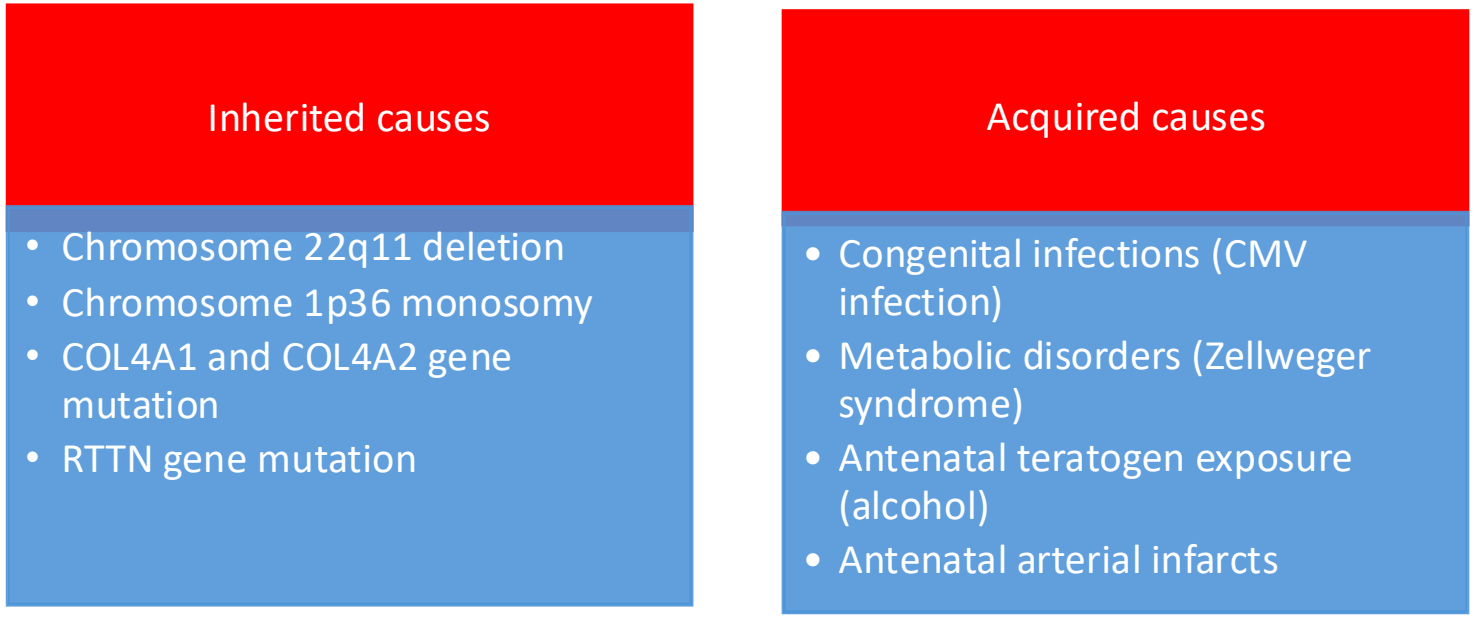
MRIB, T2 sequence, axial view



MRIB, T1 sequence, coronal view

Polymicrogyria (PMG)

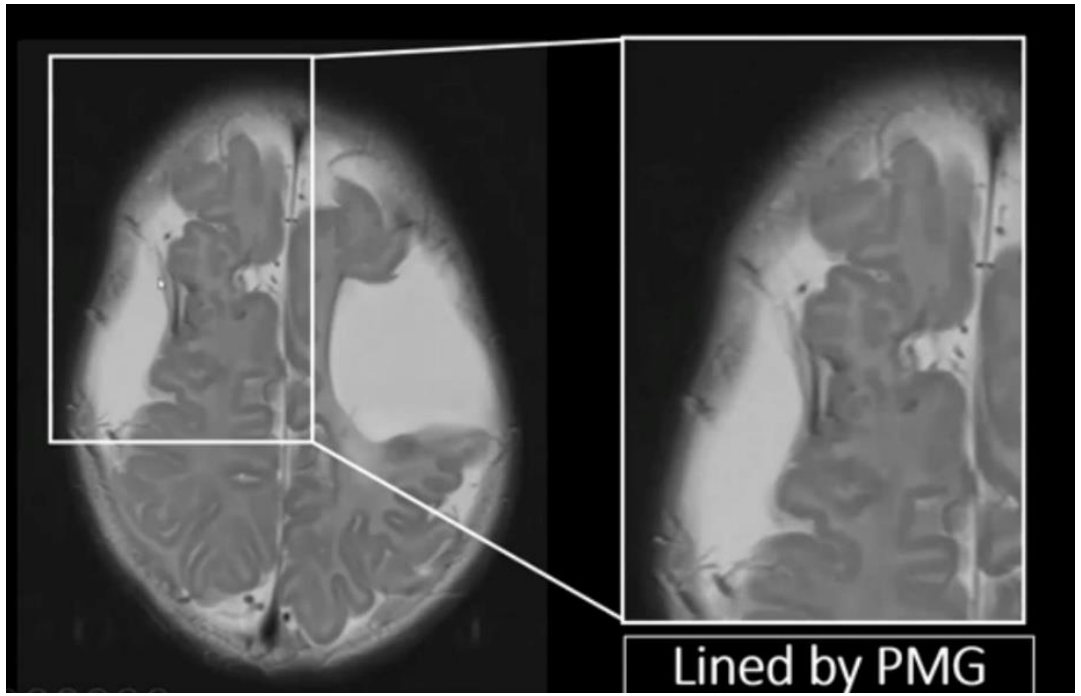
- Newly classified as a disorder of late neuronal migration
- Polymicrogyria (PMG) refers to an excessive number of small gyri separated by shallow sulci, giving the surface of the cortex its characteristic lumpy appearance
- PMG can be focal or diffuse, unilateral or bilateral, and with or without schizencephaly
- The aetiology of PMG includes both inherited and acquired causes



- CFs:
  1. Congenital bilateral perisylvian syndrome: pseudobulbar palsy, epilepsy and intellectual disability
  2. Frontoparietal polymicrogyria syndrome: spastic quadriparesis, speech delay, epilepsy and intellectual disability

PMG

- Ix:
    1. CTB: PMG frequently misdiagnosed as LIS
    2. MRIB:
        - Mildly thickened cortex (because of cortical overfolding)
        - Small, irregular gyri and an indistinct grey white matter junction
        - Occasionally associated with SCZ, grey matter heterotopia, corpus callosum abnormalities and cerebellar abnormalities



MRIB, T2 sequence, axial view

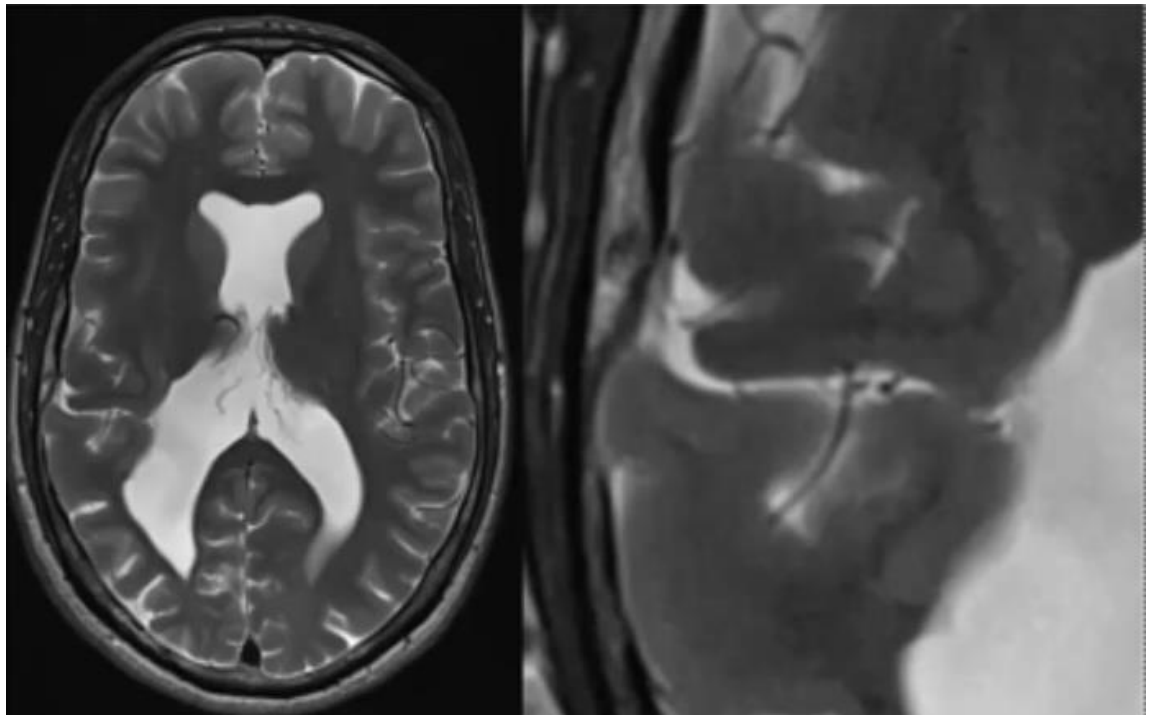
Schizencephaly (SCZ)

- Schizencephaly (SCZ) refers to a cleft extending from the cerebral cortex to the ventricle and is typically lined by polymicrogyric cortex
- SCZ can be unilateral or bilateral, and tends to involve the insular, precentral and post central regions of the cerebral cortex
- SCZ can be divided into open and closed lip forms depending on whether the cleft is fully patent and filled with CSF, or sealed by the abutting cortical margins
- Aetiology of SCZ is thought to be an early prenatal focal injury to the germinal matrix, or an infarct in the immature cerebrum with consequent liquefaction of injured tissue
- CFs:
    1. Closed lip SCZ: epilepsy and spastic hemiparesis
    2. Open lip SCZ: microcephaly, epilepsy, severe spastic hemiparesis and NDD

SCZ

- Ix:
  1. CTB: Sufficient to diagnose SCZ and determine whether it is open or closed
  2. MRIB: SCZ can be distinguished from a porencephalic cyst by the fact that the schizencephalic cleft is lined by grey matter instead of white matter with variable grades of gliosis

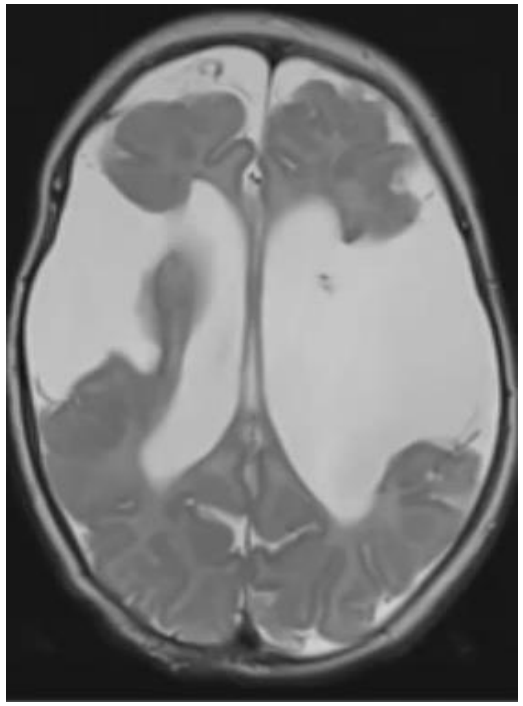
Type 1: closed lip
(no separation of cleft surfaces)



MRIB, T2 sequence, axial view

A CSF containing cleft from the pial to the ependymal surface lined by dysplastic cortical tissue

Type 2: open lip
(separation of cleft surfaces)



MRIB, T2 sequence, axial view

Summary and aim of proposed research

- MCDs encompass a large spectrum of disorders resulting from disruption of normal cortical development
- Clinical features vary from asymptomatic to epilepsy, intellectual disability, neurological deficits and neurodevelopmental delay
- MCDs are a common cause of drug resistant epilepsy in children (and may be potentially treatable)
- Epilepsy and neurodevelopmental disorders have a profound impact on the physical and cognitive health of children, and subsequently their ability to achieve employment
- The management of these children also provides a great burden on health systems
- Identification of the type of MCD allows one to formulate a more accurate treatment plan, prognosticate and provide genetic counselling
- Precise data on the global incidence of MCDs are limited due to variations in diagnostic capabilities and reporting practices
- For this reason, we aim to analyse the risk factors, clinical profile, radiological pattern and outcome between the subcategories of MCDs in children attending the IALCH Paediatric Neurology Clinic from January 2015 to December 2024

The research protocol

The clinical spectrum of malformations of cortical development in children attending a quaternary hospital in KwaZulu-Natal over a decade

Author: Dr Kelly Stretch

Supervisor: Dr Lawrence Mubaiwa

Objectives

Describe the radiological patterns of MCDs in the participant population and organize them into subcategories

Quantify the number of children with MCDs in each subcategory

Describe and compare the following in each subcategory:

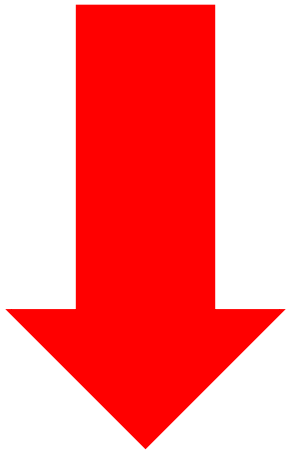
- Birth and demographic information
- Neurological examination and comorbidities
- Results of special investigations
- Treatment required

Methods

- Study design: retrospective cross-sectional study
- Setting: IALCH Paediatric Neurology Clinic
- Participant selection: all children with a diagnosis of MCD confirmed on neuroimaging
- Data source: retrospective audit the folders of children with a diagnosis of a MCD from the Meditech database at IALCH
- Data capture: participants will be captured in a study register in Microsoft Word and provided a study number. Study numbers will be populated into a sheet in Microsoft Excel, and their information will be recorded
- Measurements: will be recorded in Excel (birth and demographic information, neurological examination and comorbidities, results of special investigations, treatment required)
- Data analysis:
  - Data will be analysed using the statistical package for social sciences version 15.0 software package (SPSS, Inc., Chicago)
  - Means and percentages will be used for numerical variables, and Chi square and Fisher exact tests will be used for categorical variables in group comparisons
  - Results will be evaluated with a confidence interval of 95%, p value < 0.05 will be considered statistically significant

Ethical considerations, timeline and progress

- Ethical considerations:
  - In this study, no patient identifiers will be used - data are therefore anonymous
  - No patient contact will occur and therefore individual patient consent is not necessary
- Timeline: January 2015 to December 2024



- Progress:
  - Ethical approval gained from BREC
  - Permission to conduct research obtained from IALCH medical manager and KZN-DoH
  - Data to be collected, analysed and write up completed

‘If I have seen further (than others), it is by standing on the shoulders of giants’

Isaac Newton