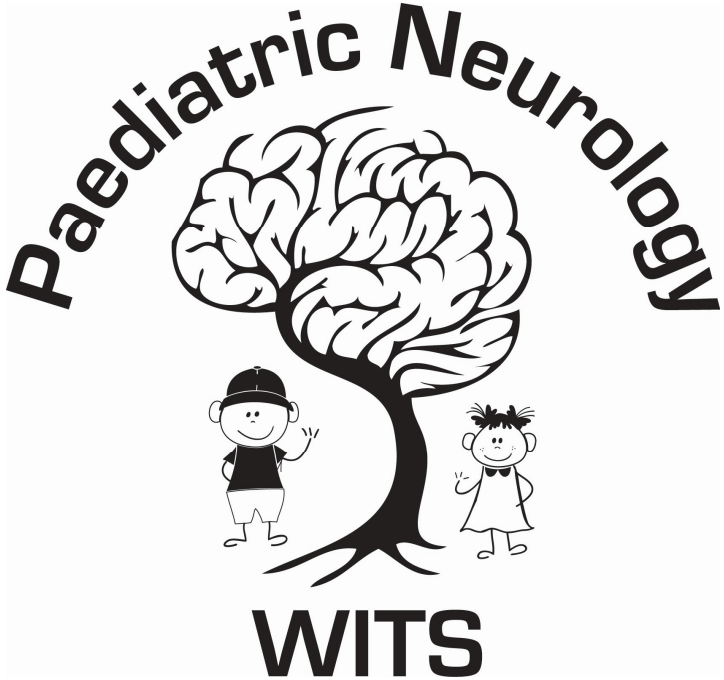
Lost along the way –
an approach to neuromigrational disorders



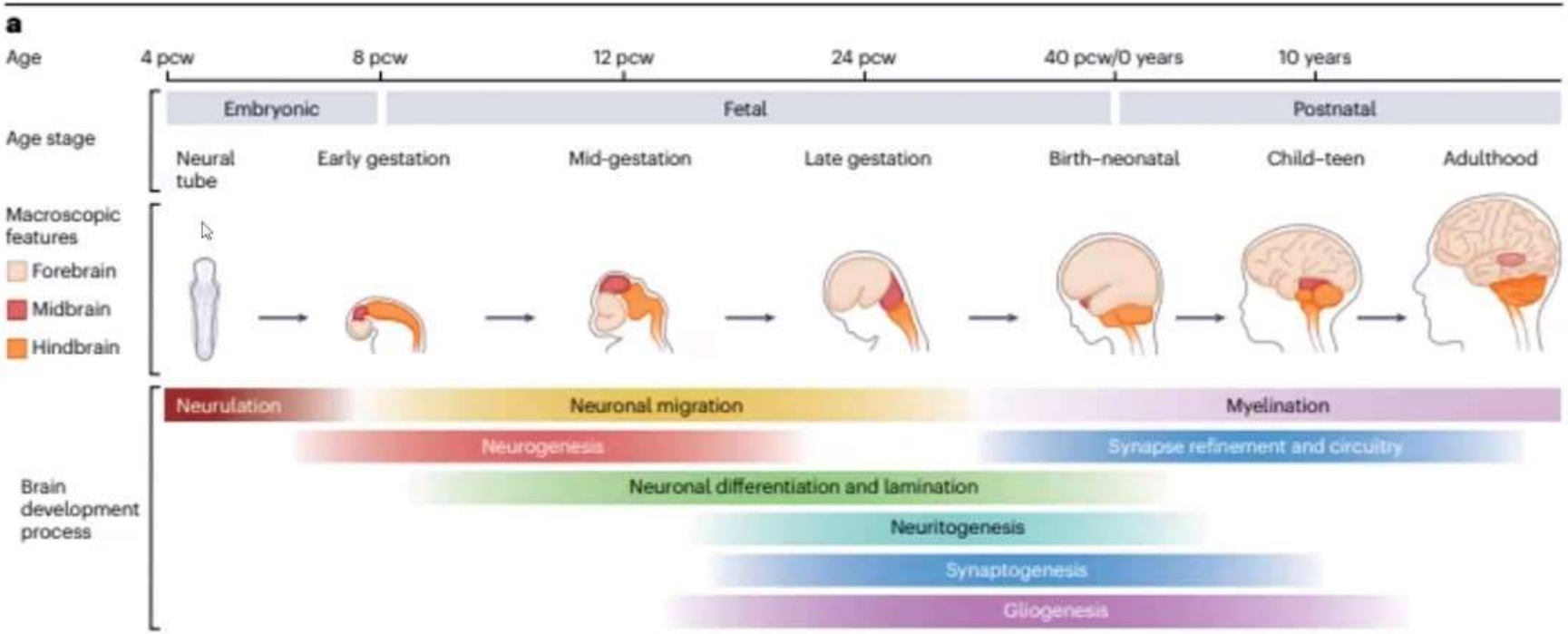
Nonjabulo Ndlovu

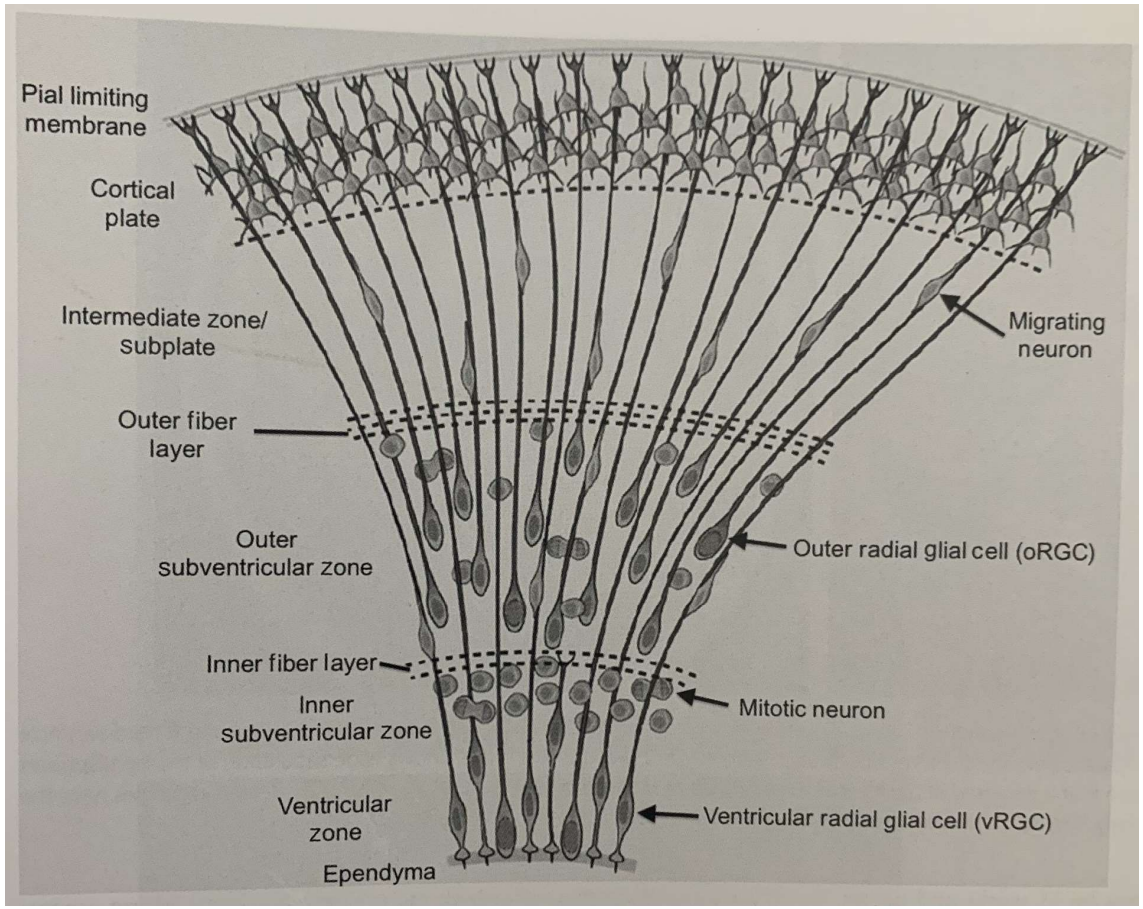
Layout

- Embryology of the brain
- Normal cortical and sulcal anatomy
- Causes of malformation
- Types

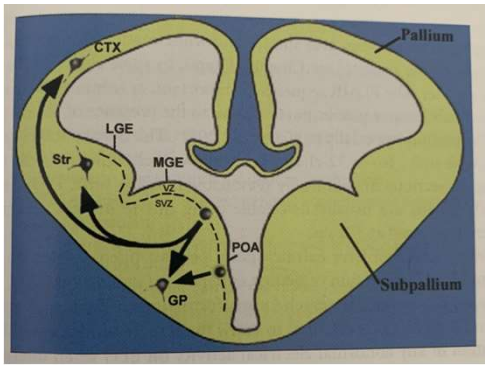
Embryology of the Brain

- An understanding of the normal development of the cerebral cortex is essential to understand malformations of cortical development.
- At the 7th week, there is proliferation of young neurons in the subependymal layer of the lateral ventricle walls.
- Migration then starts at the 8th week and a 6-layer cortex is formed by the 24th week.
- The movement of cells is initially easy but with increased distance to travel, radial glial cells are induced (these span the entire thickness of the hemisphere from the ventricular surface to the pia).


a
Age
4 pcw
8 pcw
12 pcw
24 pcw
40 pcw/0 years
10 years
Age stage
Embryonic
Fetal
Postnatal
Neural tube
Early gestation
Mid-gestation
Late gestation
Birth–neonatal
Child–teen
Adulthood
Macroscopic features
Forebrain
Midbrain
Hindbrain
Brain development process
Neurulation
Neuronal migration
Myelination
Neurogenesis
Synapse refinement and circuitry
Neuronal differentiation and lamination
Neuritogenesis
Synaptogenesis
Gliogenesis



1. Proliferation
2. Migration
3. Organization



- Ultimate goal is a 6 layer cortex

- RGC act as a guide but need
  - Recognition
  - Attachment
  - Calcium
  - Molecular ligands

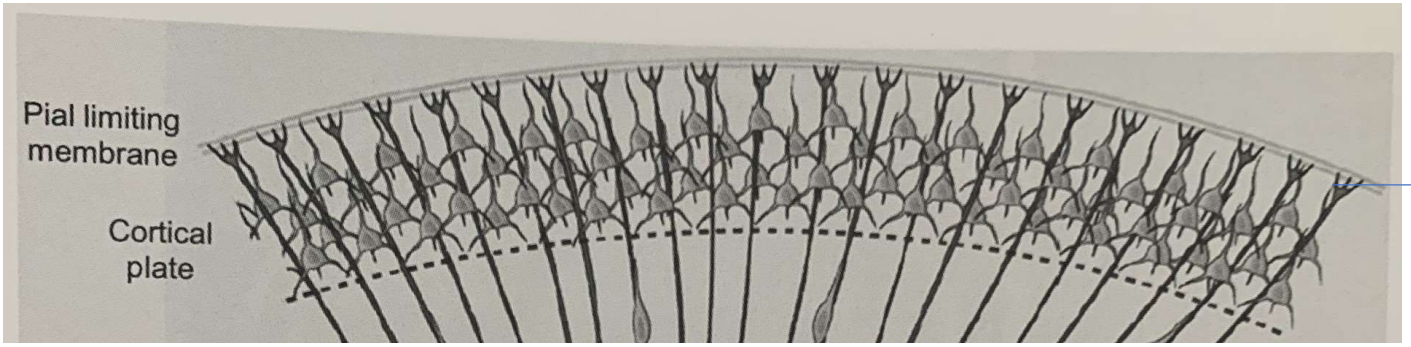
- Outer radial glial cells are very NB for proliferation from an evolutionary perspective

- Neurons migrate from an outside in sequence (6,5,4,3 and 2)

- There is an exception to the outside in rule in layer 1.

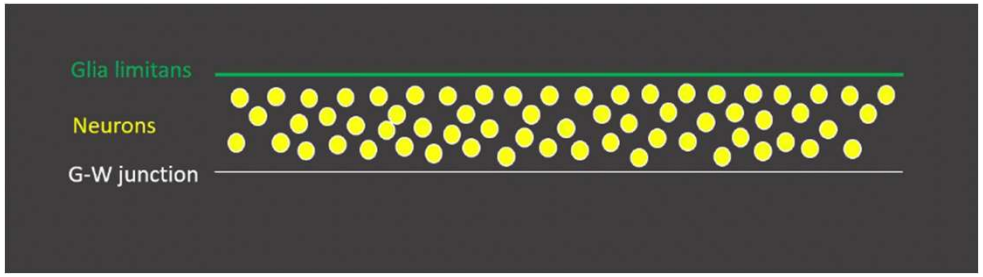
- Disengagement from RGC at a specific layer depends on protein and cell interaction.
- Reelin produced by Cajal Retzius cells induces migrating neurons to detach from radial glia.
- After disengagement they arrange in discrete lamina and establish synaptical connections = **Cortical organization**.
- Glial and retinal limiting membranes – Terminate neuronal migration and allow cortical organization.

Glia limitans



Astrocyte footplates forming GL

- Layer of surface-associated astrocytes beneath the pia mater
- Serves as a barrier between CSF space and CNS parenchyma
- <u>"Limits" the overmigration of neurons</u>

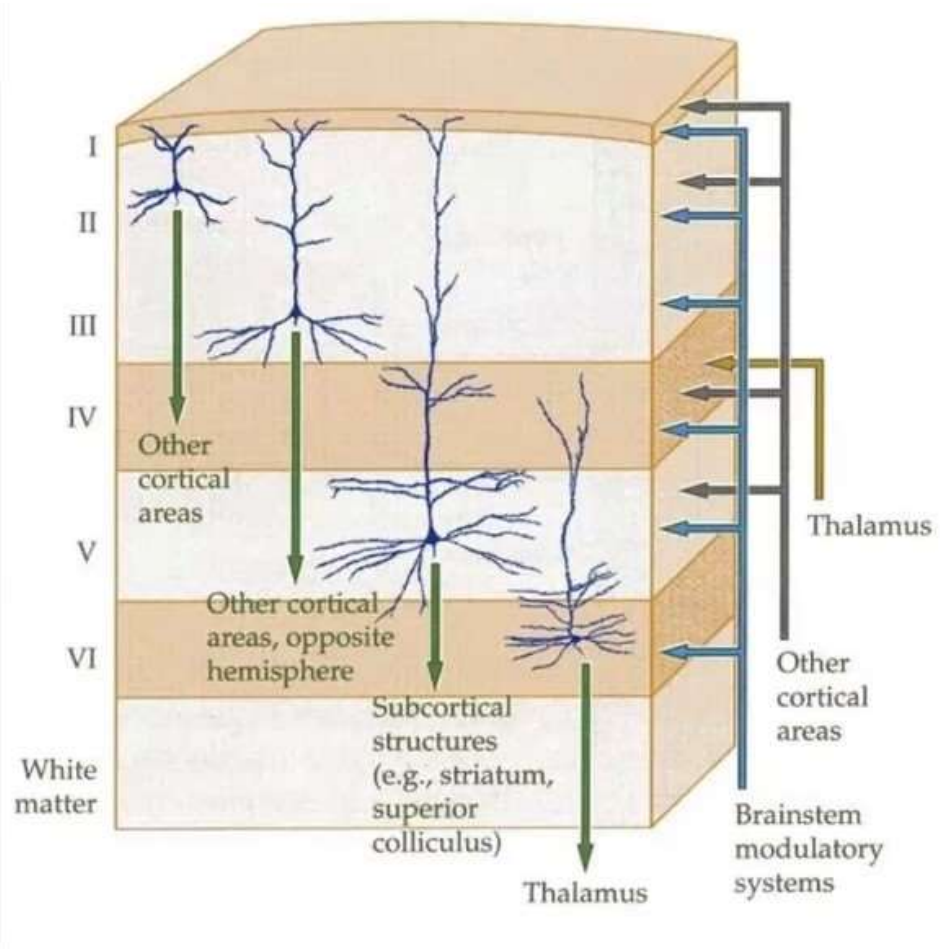


Post migrational development of the normal human cortex

- Arrangement of the cortex in layers
- Axonogenesis, dendritogenesis and synaptogenesis
- Primary, secondary and tertiary sulcation

Neocortex (90% of cortical surface) = 6 layers

Paleocortex (olfactory) and archicortex (hippocampus) = 3-4 layers

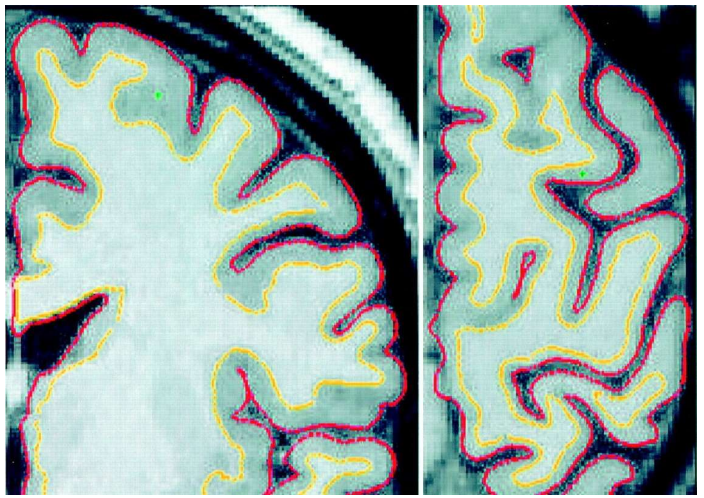


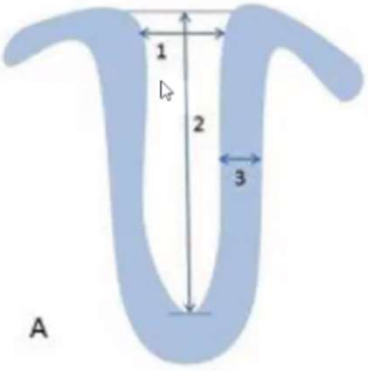
Normal cortical and sulcal anatomy

- Thickness of neocortex = 1- 4mm
- Thickest at crown of gyri

- Primary and secondary sulci may vary in shape slightly but are constant and symmetric in location
- Tertiary sulci appear mostly after birth and are variable

- Normal: Sulcal depth >> width

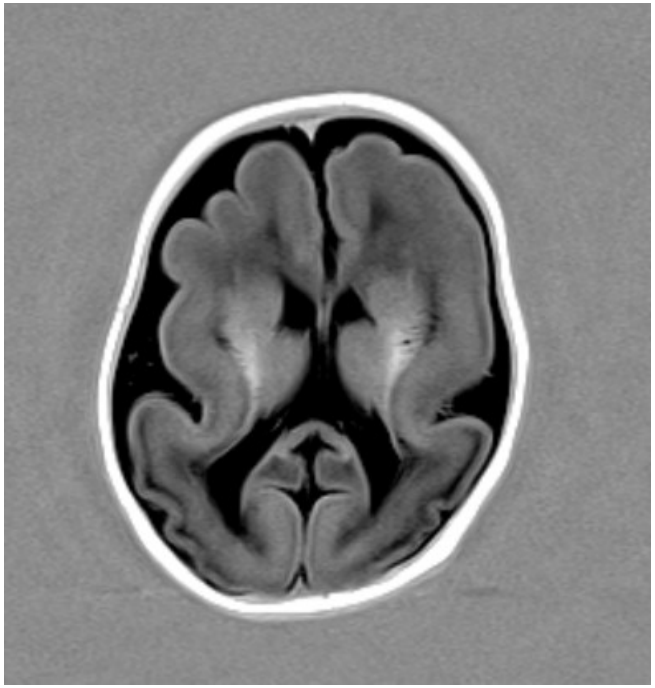




Causes of malformation

- Chromosomal
- Destructive
- Toxins

Chromosomal/Genetic



- Stem cell production
- Radial glial cell production
- Neuronal migration/organisation

eg. Miller-Dieker syndrome

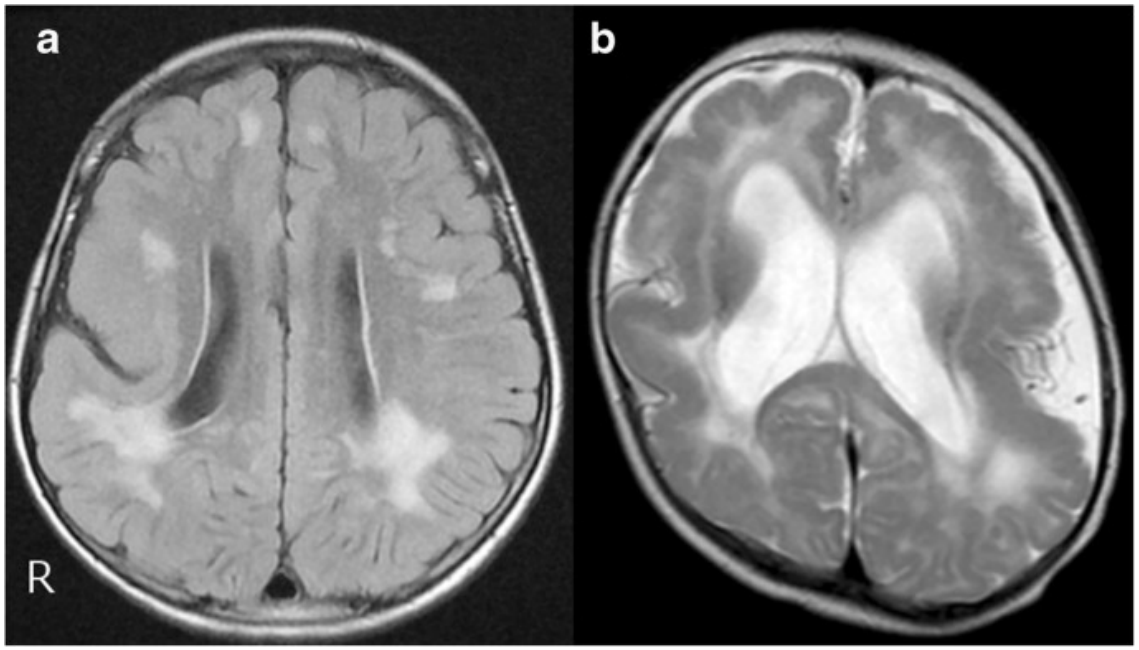
Results from a deletion in chromosome 17p13.3, which includes the PAFAH1B1 and YWHAE genes

It is thought to carry an autosomal dominant inheritance

Type 1 Lissencephaly

Destructive

- Radial glial cell
- Molecular layer
- Overlying pial-glial barrier

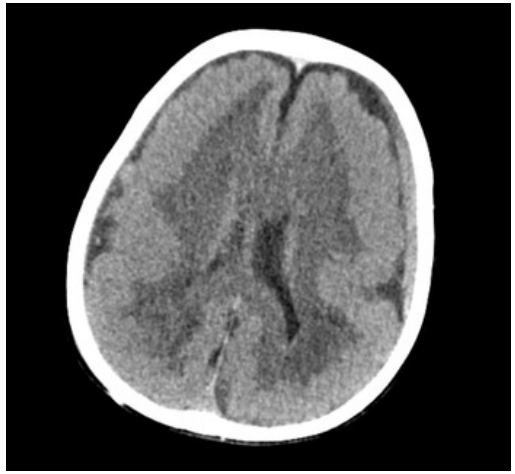


MRI of a patient with CMV showing cortical gyral abnormality - unilateral right fronto–parieto–temporal (**a**) and bilateral (**b**) polymicrogyria

Toxins

- Exogenous
- Endogenous (metabolic disorder)

  The prototypes of neurometabolic disorders associated with neuronal migration defects are peroxisomal disorders (peroxisome biogenesis disorders, peroxisomal ß-oxidation defects) and congenital disorders of O-glycosylation



Type 2 Lissencephaly – cobblestone 2ndry to O-glycosylation disorder

Malformations of cortical development may occur due to defects in:

1. Proliferation

2. Migration

3. Post migrational development

1. Malformations due to abnormal stem cell development and proliferation

1a. Decreased proliferation and/or increased apoptosis

Microcephaly (Microencephaly)

1b. Focal transmantle cortical dysplasia (FCD Type 2)

1c. Increased proliferation

Brain overgrowth spectrum

1a. Microcephaly

Reduction in the OFC below -2 SD (corresponding to the 3rd percentile) compared with age and gender matched controls

Primary (abnormal neurogenesis)

- Reduced progenitor cell size
- Reduced number of pool cycles
- Abnormal or increased apoptotic events

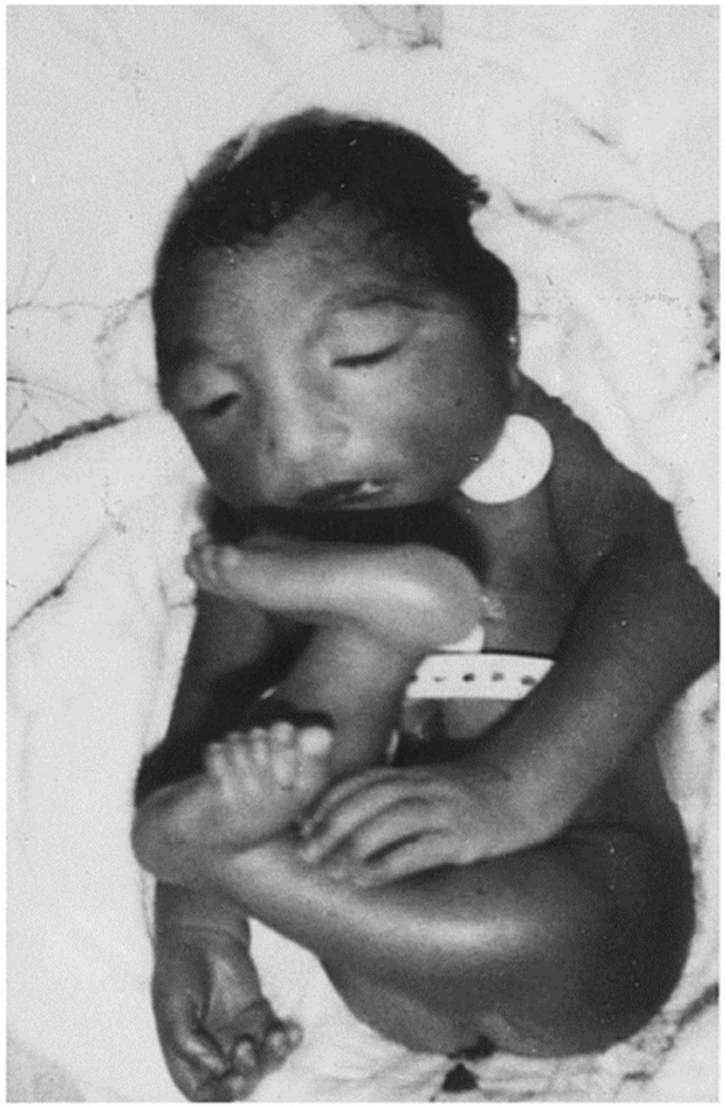
Secondary (disruption post neurogenesis)

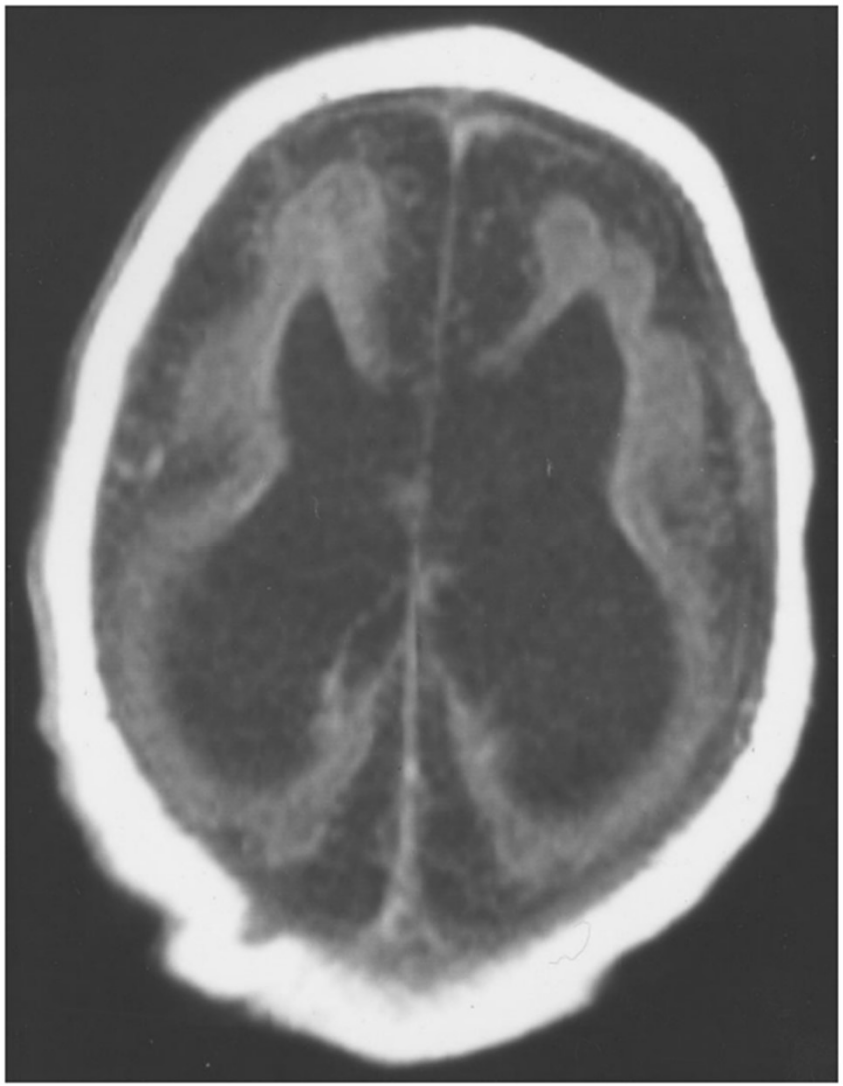
- Hypoxia
- Infection
- Toxic
- Deprivational
- Neurodegenerative conditions

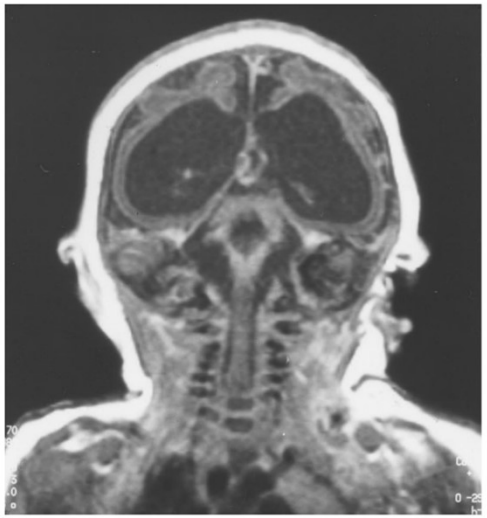
Acquired and genetic causes

Micro-lissencephaly

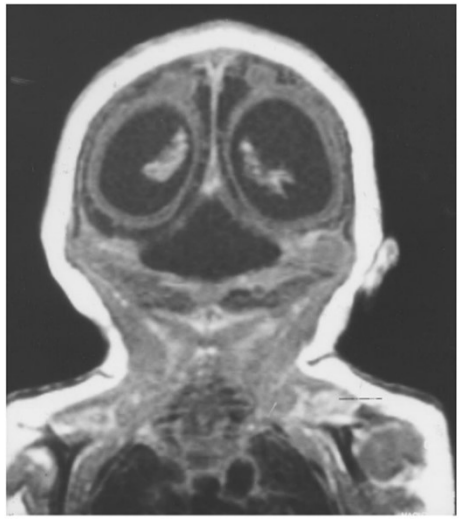
Microcephaly







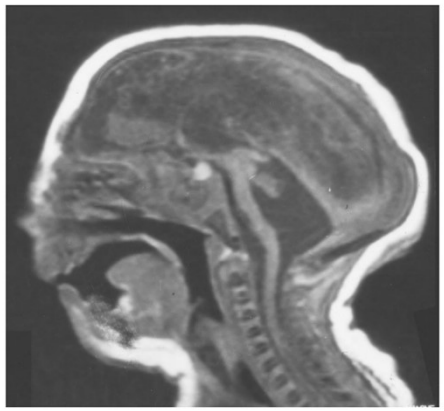
A



B

MRI:

- Few gyri and abnormal shallow sulci
- Reduced proliferation of neurons and glia in germinal zones



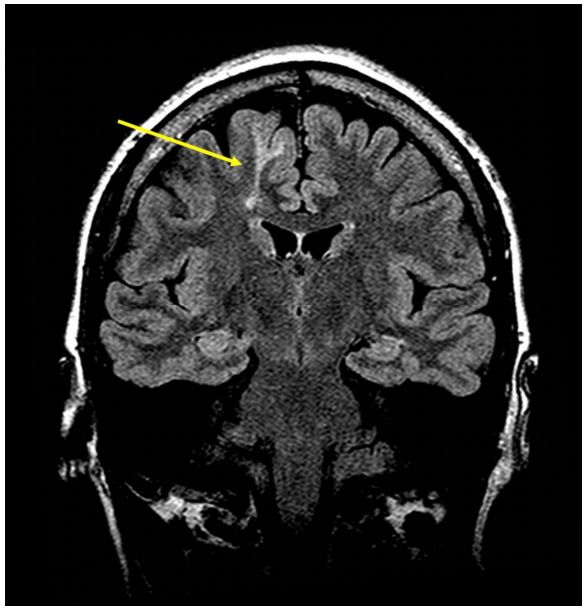
1b. Focal transmantle cortical dysplasia (FCD type 2)

Abnormal cells from wall of lateral ventricle to cortex

- Transmantle sign

Almost all have focal epilepsy

mTOR pathway – AKT3, TSC1, TSC2 and GATOR1 complex (incl. DEPDC5)

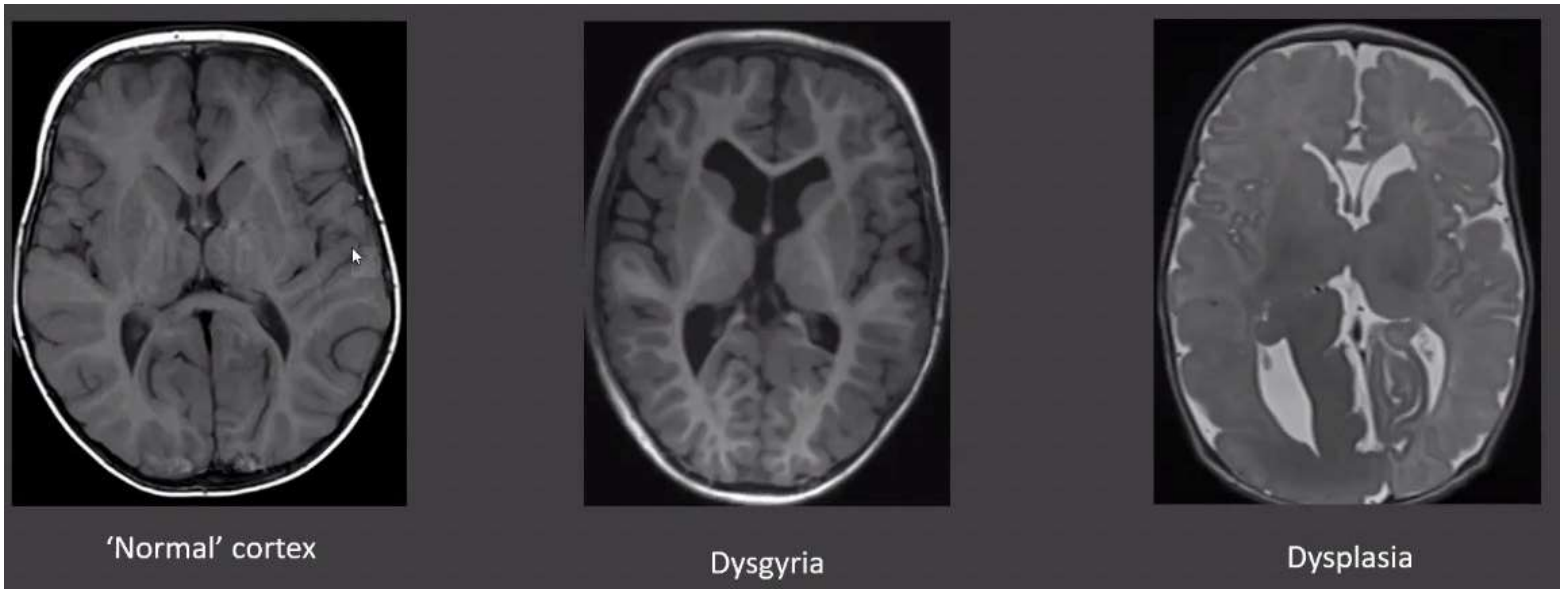


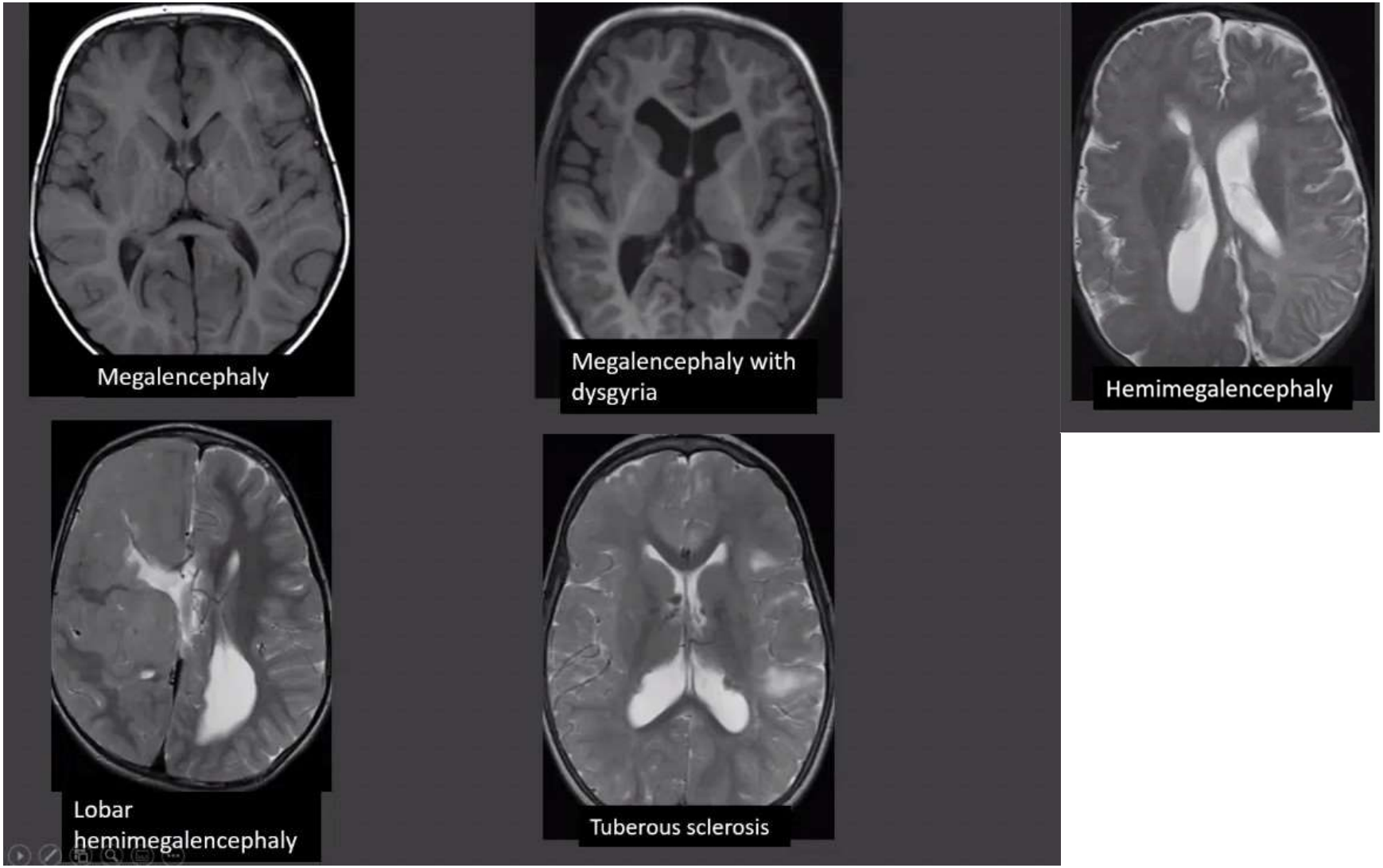
1c. Malformations due to increased proliferation

Brain overgrowth spectrum

Increase of brain parenchymal volume

Cortex may be normal, dysgyric or malformed




Megalencephaly
Megalencephaly with dysgyria
Hemimegalencephaly
Lobar hemimegalencephaly
Tuberous sclerosis

Hemimegalencephaly

- Harmatomatous overgrowth of all or part of cerebral hemisphere with defects in neuronal proliferation/ migration or organization.

- Clinically

  Macrocephaly, intractable seizures from early, hemiplegia and severe developmental delay

- Affected areas

  Pachygyria

  Polymicrogyria

  Heterotopia

Malformations of cortical development may occur due to defects in:

1. Proliferation

2. Migration

3. Post migrational development

2. Malformations due to abnormal neuronal migration

Due to arrested migration

2a. Lissencephalies – "smooth brain"

Spectrum which includes

- Agyria = absence of gyri
- Pachygyria = few broad flat gyri
- Subcortical band heterotopia

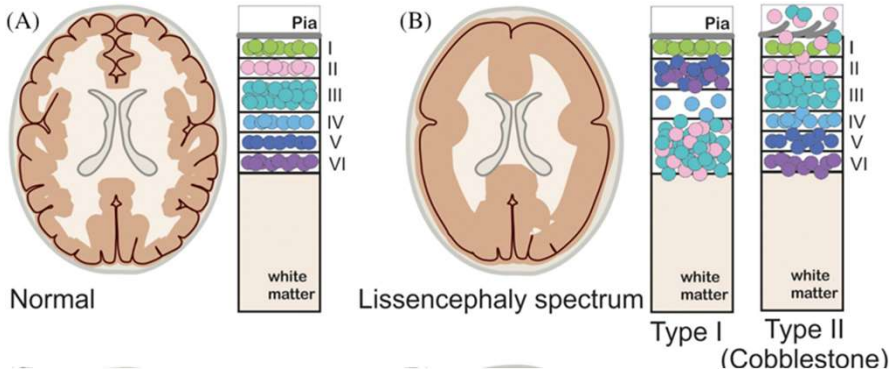
2b. Heterotopia

2c. Schizencephaly

2a. Lissencephaly

2 major types

- Type 1 - classical
- Type 2 – cobblestone



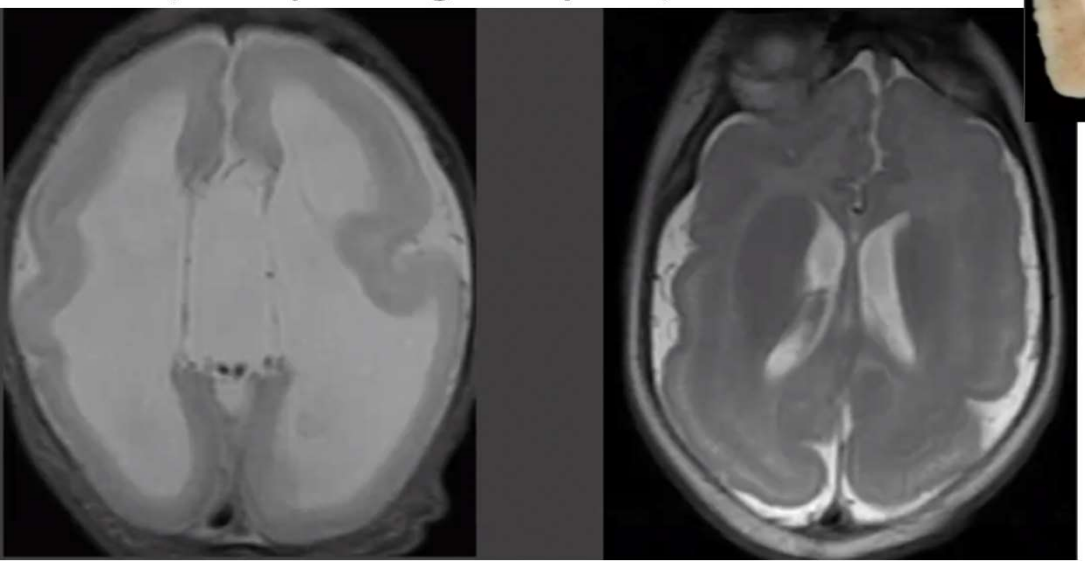
- Can have incomplete lissencephaly – areas of pachygyria and agyria

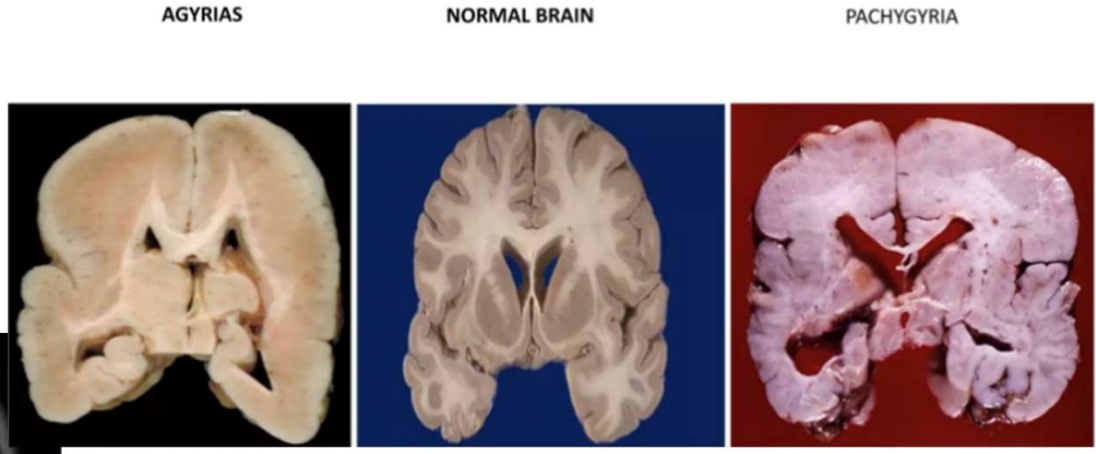
Agyria and pachygyria

Abnormal gyral pattern

Absent or broad gyri

Abnormally thick cortex (comprising 4 layers)





2a (i) Classical Lissencephaly

- GDD and seizures with severity depending on severity of malformation
- Chromosomal
  - Chromosome 17 (Miller-Dieker syndrome)
  - X-linked – Mothers have band heterotopias
- Clinically hypotonic at birth – appendicular and oropharyngeal spasticity with time
- Infantile spasms = common

- MRI:
  - Smooth brain surface
  - Reduced white matter
  - Shallow sylvian fissure
  - Often enlarged dysplastic ventricles

- Microscopically
  - Thin outer layer neurons
  - Cell-sparse zone
  - Thick inner layer

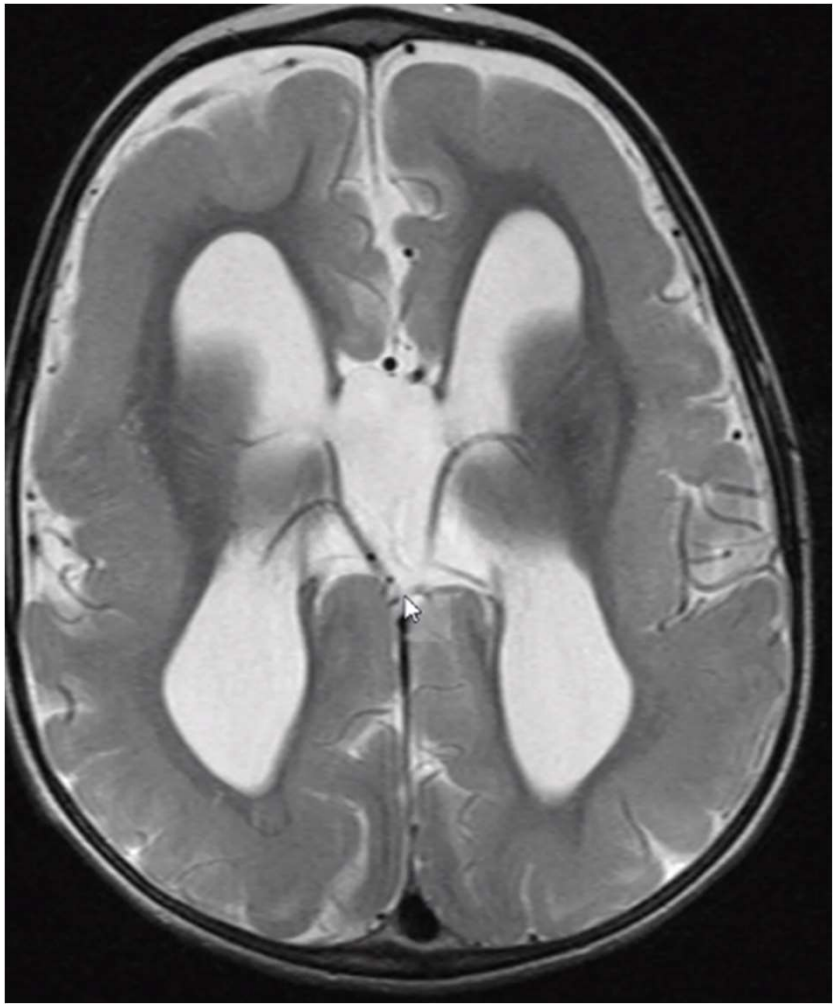


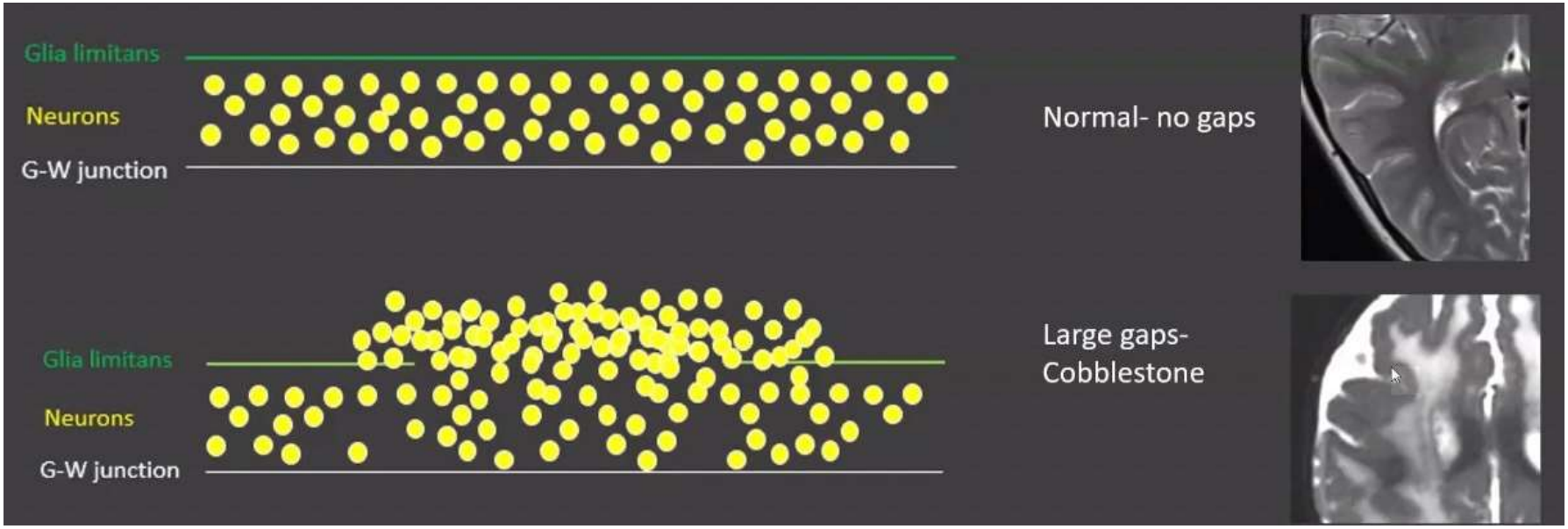
Table 5-6 Genes that Cause Classic Lissencephaly

Gene	Gene Location	Head Size	Gyrus Gradient	Corpus Callosum	Cerebellum
LIS1	17p13.3	Low normal	P>A	Vertical splenium	Mild anterior vermis hypoplasia
DCX	Xq23	Low normal	A>P	Normal	Normal
DYNC1H1	14q32.31	Low normal	P>A	Vertical splenium	Mild anterior vermis hypoplasia
KIF2A	5q12.1	Low normal	P>A	Thin	Normal
TUBA1A	12q13.12	Microcephaly	Variable	Absent or dysmorphic/thin	Small/very small
TUBG1	17q21.2	Severe microcephaly	P>A	Vertical splenium	Small/very small
ACTB	7p22.1	Severe microcephaly	A>P	Normal	Normal
ACTG1	17q25.3	Severe microcephaly	A>P	Normal	Normal
WDR62	19q13.12	Severe microcephaly	Variable	Variable	Normal

2a (ii) Cobblestone Lissencephaly

Due to over-migration

Disorders of migration due to disruption of the glia limitans



- Three Types
  - Walker-Warburg syndrome
  - Fukuyama congenital muscular dystrophy
  - Muscle-eye-brain disease

- The association of brain abnormality and congenital muscular dystrophy is due to deficiency of muscle proteins that are also thought to be important for CNS development

- eg. Merosin = substrate for migration of oligodendrocytes.
  - Other proteins are involved in the formation of glial and retinal limiting membranes
  - Therefore, overmigration of neurons into subarachnoid space

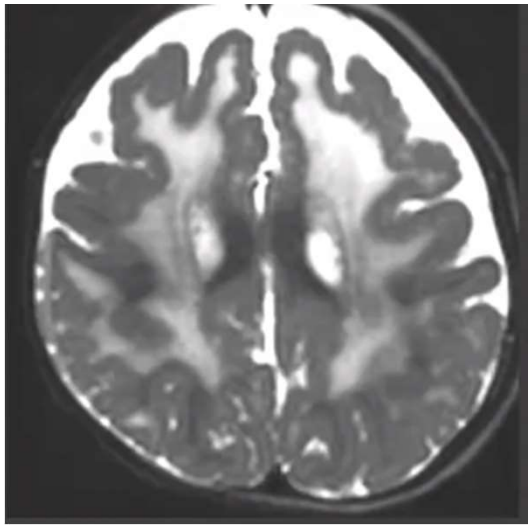
Irregular and ‘pebbled’ cerebral surface

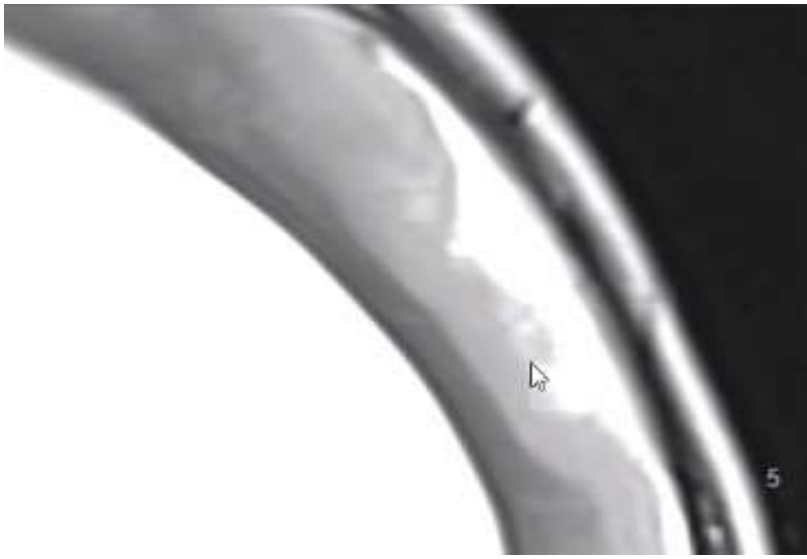
Moderately thick cortex

Jagged grey-white matter border

Frequent vertical (perpendicular to the cortex – WM border) striations

Majority due to Alpha-dystroglycanopathies

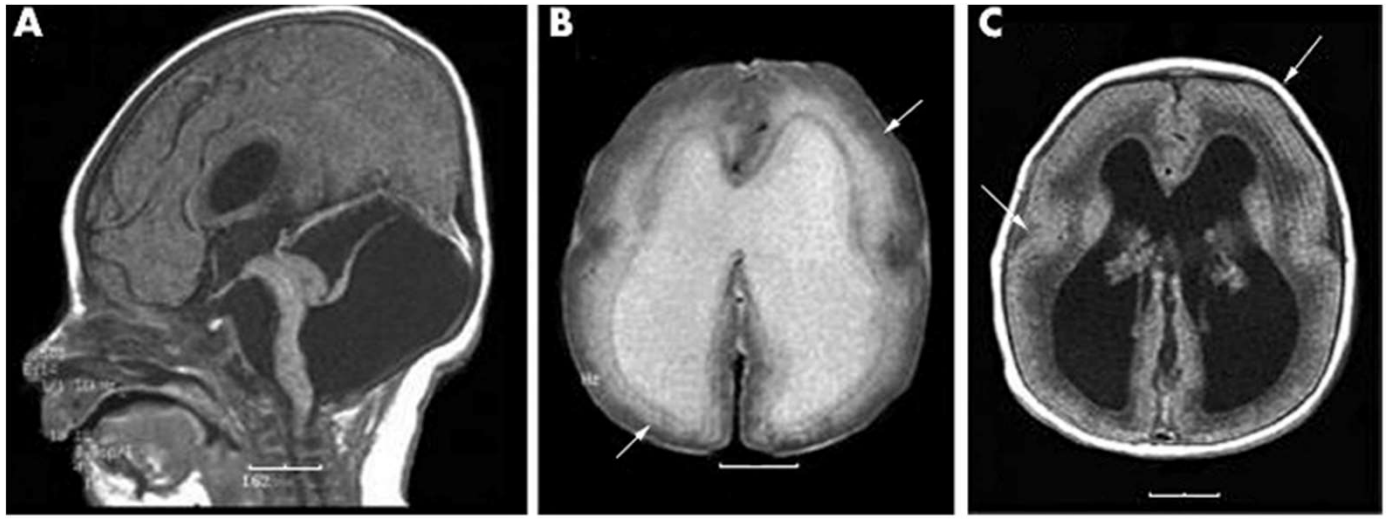




Walker-Warburg Syndrome

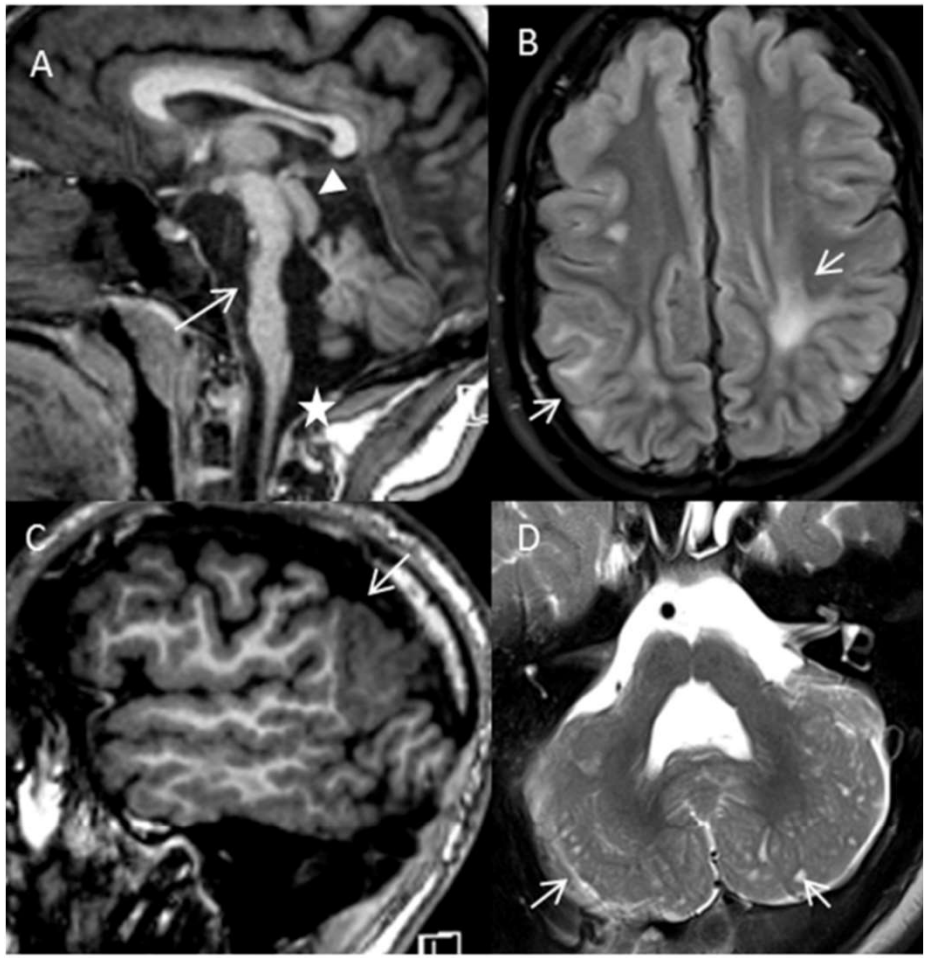
- Cobblestone lissencephaly, congenital hydrocephalus, hypotonia, eye malformation and progressive macrocephaly
- MRI:

  Thick cortex, shallow sulci, microphthalmia, hydrocephalus, corpus callosum agenesis, hypomyelination and irregular projection of cortex into white matter = cobblestoning



Fukuyama Congenital Muscular Dystrophy

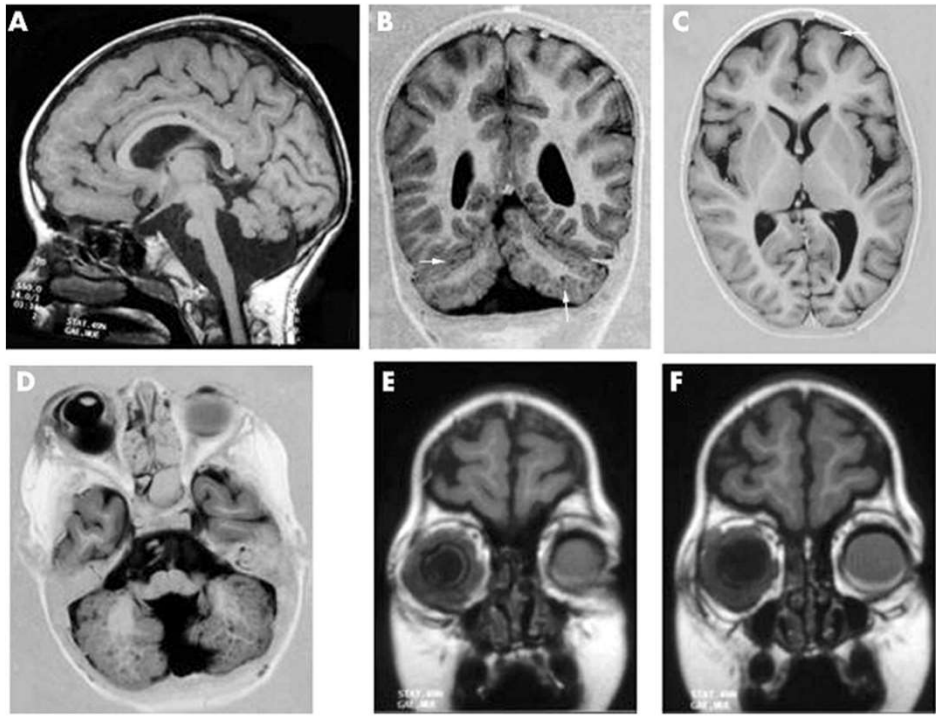
- Clinically
  - Hypotonia
  - Muscle weakness
  - Joint contracture
  - Normal eyes
- Autosomal recessive disorder
  - FKTN gene
- MRI:
  - Dysplastic cortex with subcortical cysts
  - Delayed myelination



Muscle-Eye-Brain disease

- Hypotonia with impaired vision, epilepsy and ID
- Mutations of POMGnT1 gene
- MRI:

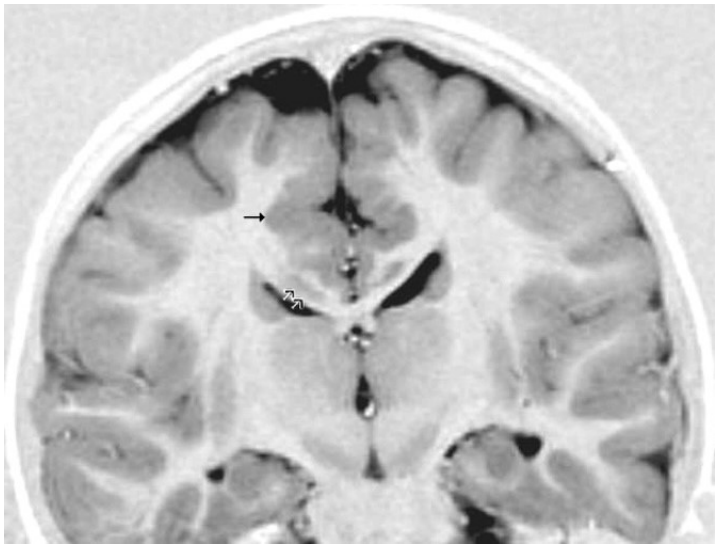
  Dysplastic cortex with cobblestones
  (thick with few sulci and gyri)
  Hypoplasia of the CC, pons and cerebellum
  Large sylvian fissures



2b. Heterotopia

- Collection of nerve cells in abnormal location secondary to an arrest of radial migration
- Present with seizure disorder

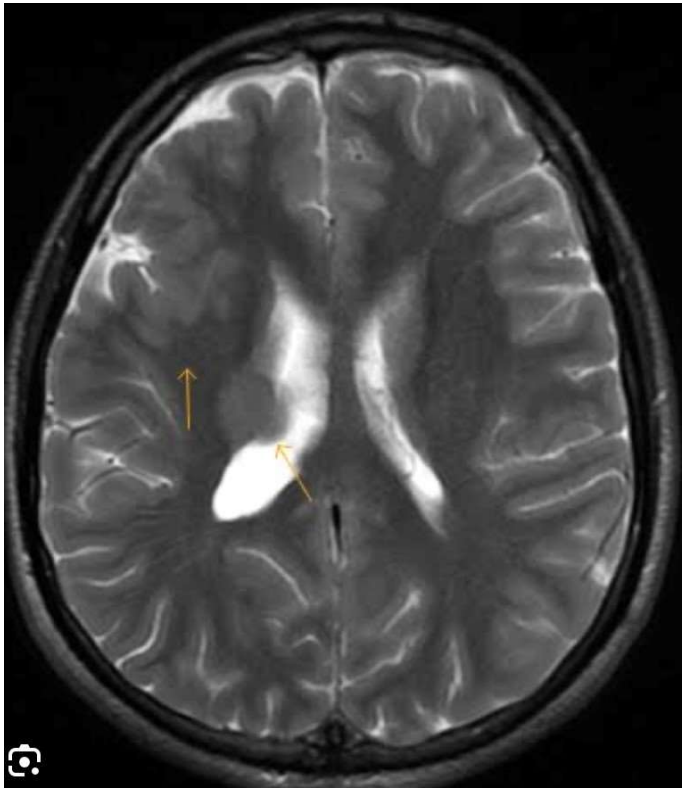
3 Groups:



1. Focal heterotopia

Ass. with other brain abnormalities (cc, basal ganglia)

Clinical presentation depends on size and location



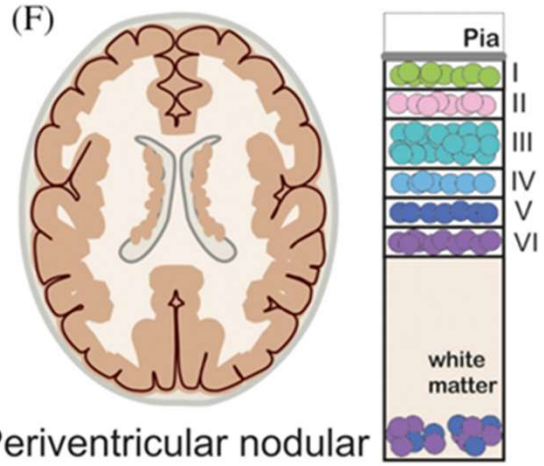
NB Distinguishing tumour from focal heterotopia
- Cortex overlying heterotopia is thin with shallow sulci
- Hemisphere with heterotopia is not enlarged
- No surrounding oedema

2. Subependymal heterotopia

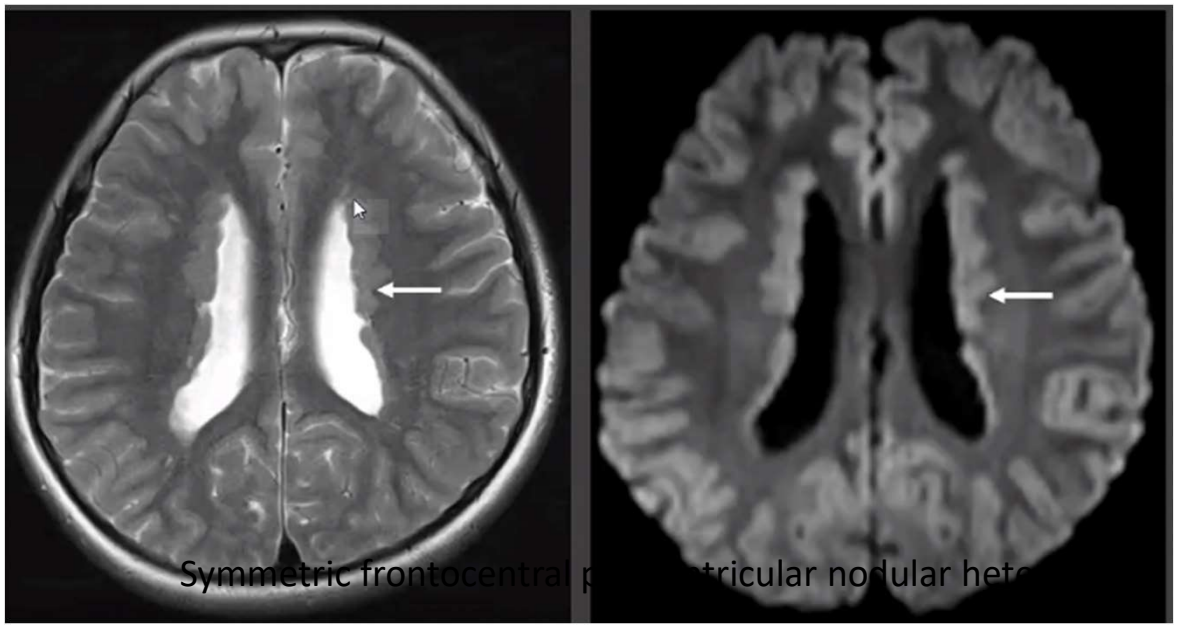
Asymmetrical and few (often ass. brain pathology)

Dense lining ventricle

X-linked recessive (often familial)



Periventricular nodular heterotopia



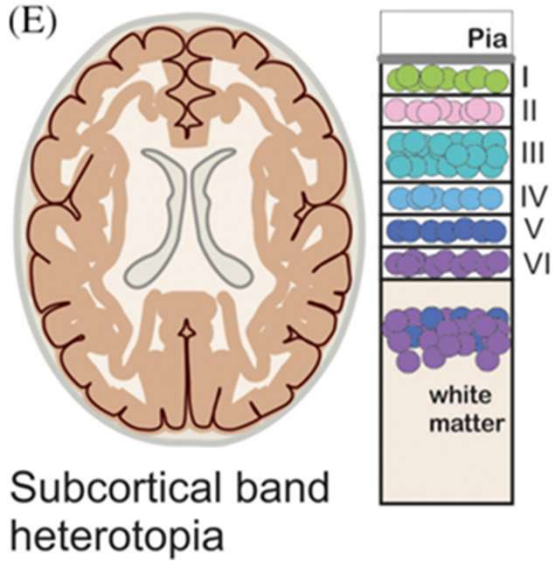
Symmetric frontocentral p tricular nodular hete

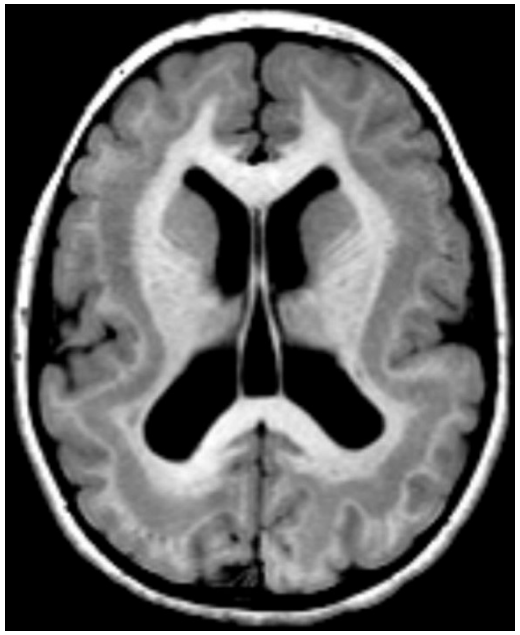
3. Band heterotopia

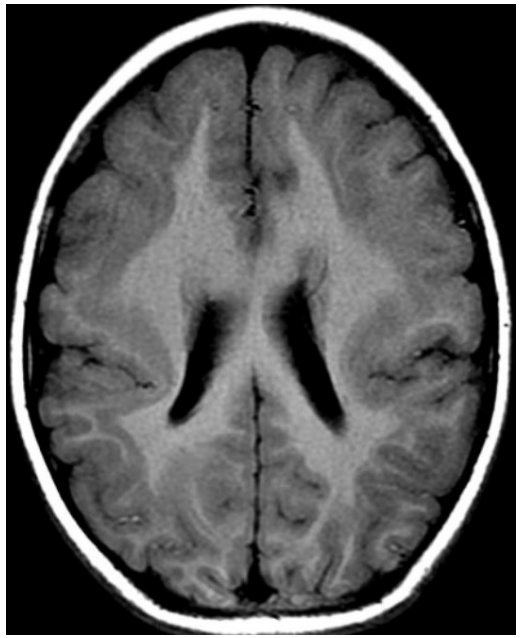
Band grey matter between lateral ventricle and cortex

“Double cortex”

Female predominance – Abnormality of DCX gene on Chromosome X







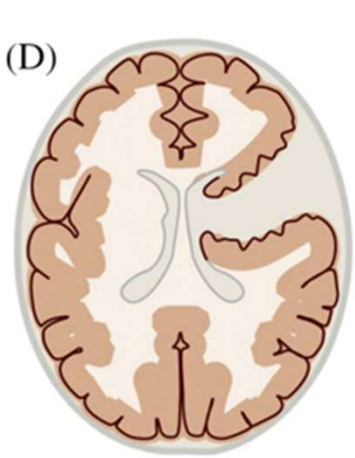
2c. Schizencephaly

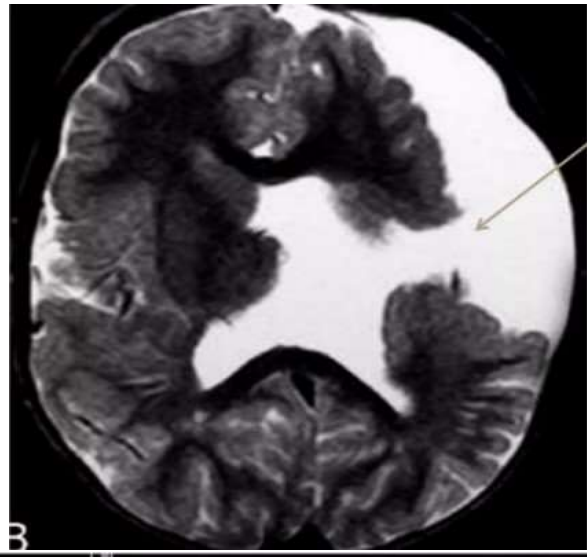
Grey matter lined clefts
- Ependymal lining to the pial covering
- Grey matter lining clefts is dysplastic

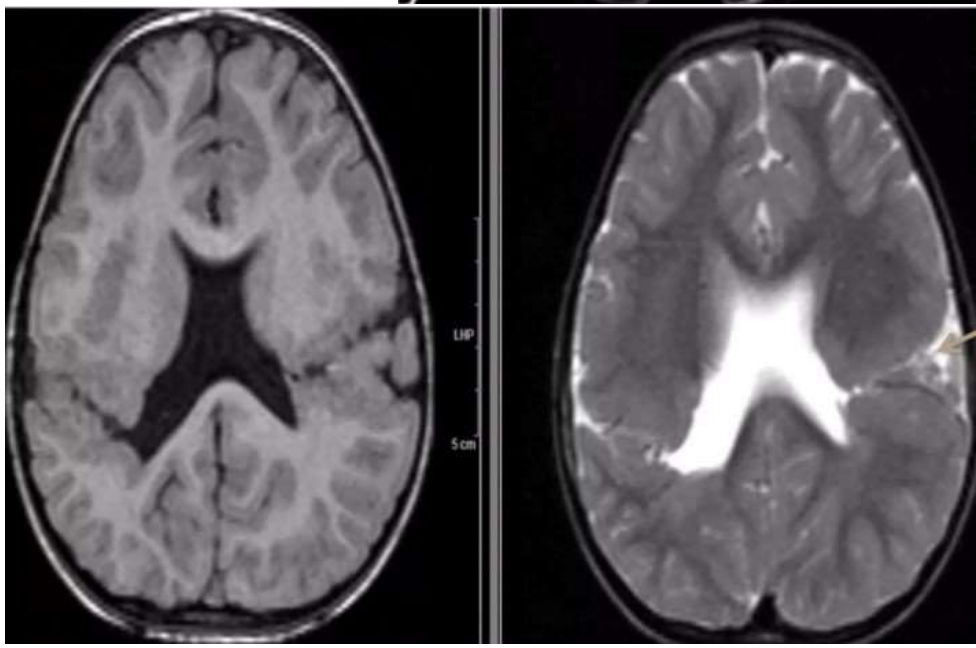
Genetic and acquired

Closed lip - wall appose directly obliterating CSF space

Open lip - CSF fills space from lateral ventricle to subarachnoid space







Unilateral cleft (60%)

Macrocephaly, hemiplegia, mild to moderate delay and >80% are epileptic

Bilateral cleft (40%)

Severe Intellectual Disability, early onset epilepsy and motor anomalies

80% of them will be symmetric

30% of cases = Optic nerve hypoplasia and therefore blindness

Malformations of cortical development may occur due to defects in:

1. Proliferation

2. Migration

3. Post migrational development

3a. Polymicrogyria

- Reach cortex BUT distribute abnormally
  - Multiple smooth gyri
- Clinically
  - Developmental delay, focal signs and epilepsy depending on portions involved
- Most common location is around the sylvian fissure
- Always important to consider:
  - Infection (TORCH-Z), CMV most common
  - Vasculodisruptive events
  - Metabolic (eg. peroxisomal disorders)

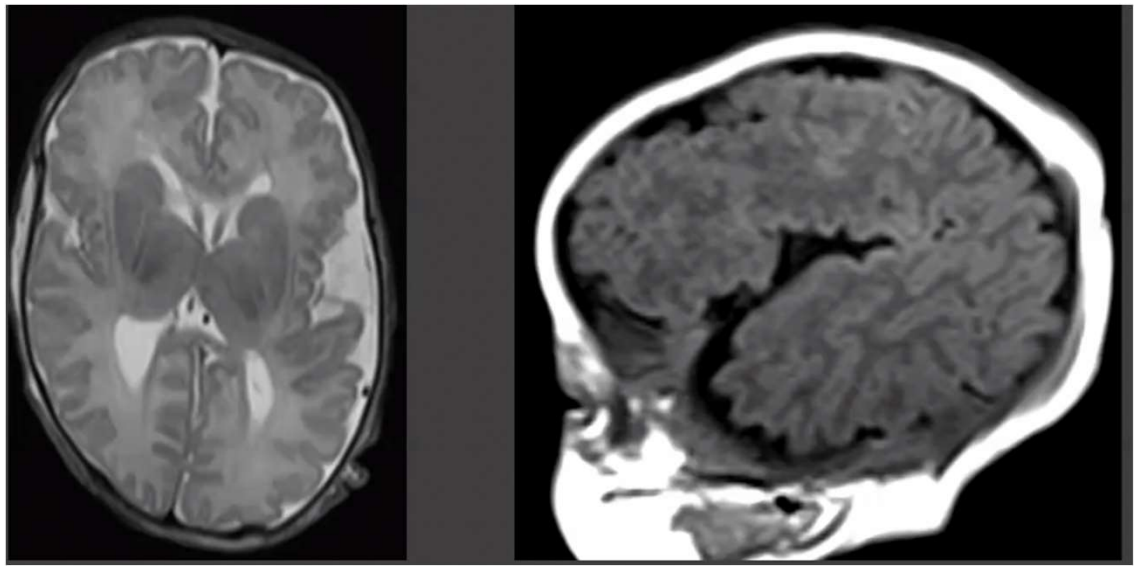
- Operculum syndrome (Congenital bilateral perisylvian syndrome) = Bilateral opercula polymicrogyria

  Pseudobulbar palsy, epilepsy, ID and arthrogryposis

  PIK3R2, Xq21.33-q23, 22q11.2 and Xq28 mutations

- MRI:

  Dysplastic cortex; therefore irregular, bumpy inner and outer cortical surface



<u>Neonate with seizures</u>
Radiological impression – Macrocephaly
- Bilateral frontal and perisylvian PMG

Conclusion

- The complexity in formation of the cortex can be affected by numerous events/factors (genetic, toxins or metabolic)

- When looking at an abnormal cortex ask yourself is it
  - Abnormal proliferation
  - Abnormal migration
  - Abnormal organization

References

- Paediatric neuroimaging – Barkovich 6th edition
- The developing human – Clinically oriented embryology
- Swaiman's Pediatric Neurology – Principles and practice 6th edition
- https://radiopaedia.org
- Subramanian L et al (2020) Cortical Malformations: Lessons in Human Brain Development. Front. Cell. Neurosci. 13:576.
- Schiller S et al (2020) Inborn errors of metabolism leading to neuronal migration defects. J Inherit Metab Dis 43:145-155.

Thank you!!!