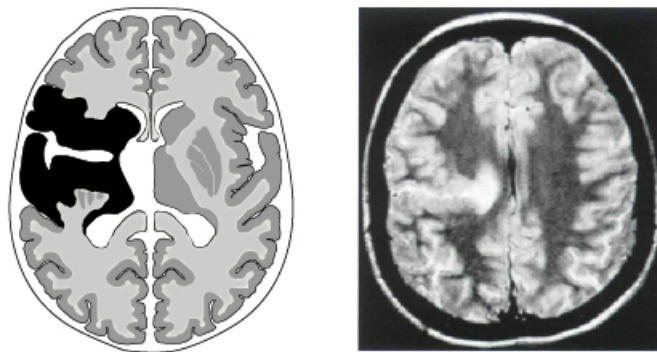


Common Brain Malformations and Disorders

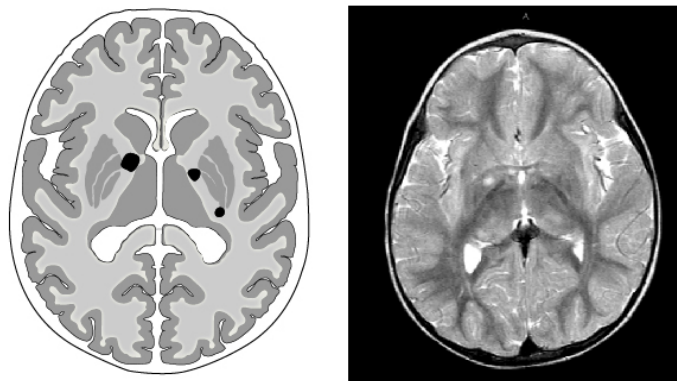
Schizencephaly

Developmental delay, cerebral palsy or seizure onset is the typical presentation. The defect can be unilateral or bilateral and involves clefts of the cortex associated with thickened cortex adjacent to the clefts (black regions on MRI diagram). Refractory seizures are often seen in the milder degrees of schizencephaly. EMX2 mutations occur in a minority of cases. Most cases appear to have occurred sporadically. Vascular disruptions during fetal brain development have been postulated as a causative factor in some cases.



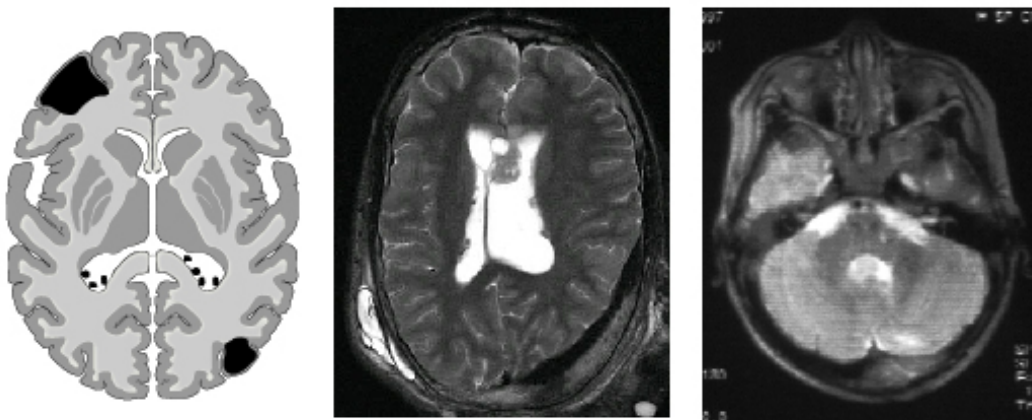
Neurofibromatosis, type 1 (NF1)

NF1 is usually diagnosed between 3-6 years of age due to appearance of multiple café-au-lait spots. Less than 10-15% of children present with problems attributable to the CNS such as optic nerve glioma or seizure disorder. However, 20-30% have absolute macrocephaly. The MRI in 50% of cases shows distinctive T2 signal changes (one is seen on this MRI and several are indicated by the black areas on the diagram). The changes are essentially benign and represent areas of minor glial cell dysplasia and increased fluid space. These T2 regions tend to improve and even disappear with age.



Tuberous Sclerosis (TS)

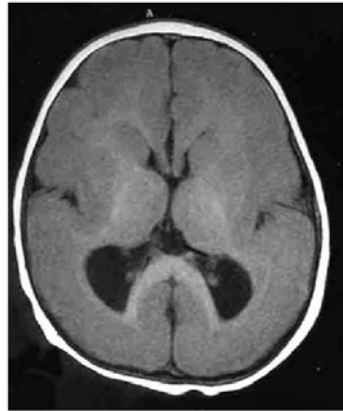
TS is commonly diagnosed in early childhood during the neurological evaluation for seizures or during a dermatological evaluation for hypopigmentation and/or angiofibroma-like facial or skin lesions. The MRI can reveal several changes, the most characteristic being subependymal nodules (with or without calcification) or focal regions of cortical dysgenesis (i.e., the cortical tuber). Black areas in the illustration indicate regions of brain involvement that are most pronounced. Cognitive function is normal in many but learning disability, autism and severe mental retardation may be seen.



Lissencephalies

This malformation includes a spectrum of cortex anomalies ranging from agyria to pachygyria to band heterotopias. Severity can be classified by grades 1-4, with type 1 representing the severe classic form of lissencephaly. Most cases show severe cognitive impairment and the diagnosis is often made in the neonate or young infant. X-linked forms show milder clinical manifestations in carrier females. The association of lissencephaly with muscular dystrophy is related to abnormal glycosylation of alpha-dystroglycan. Black areas in the illustration indicate regions of brain involvement that are most pronounced. These areas can help define the disorder's MRI phenotype.

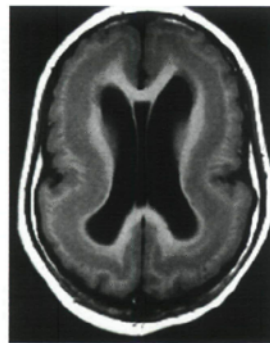
Lissencephaly, type 1



Cobblestone Lissencephaly (type II)

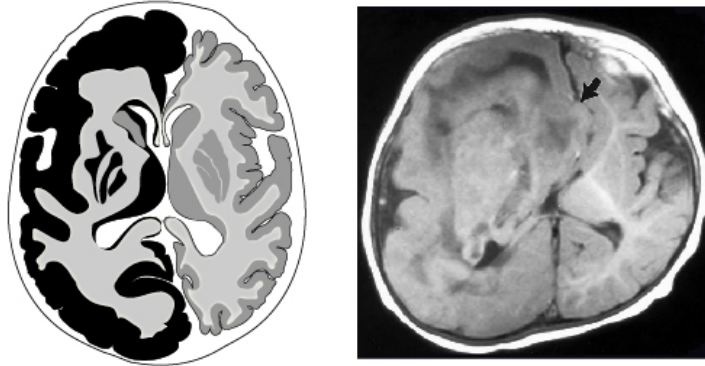


Lissencephaly, Double Cortex



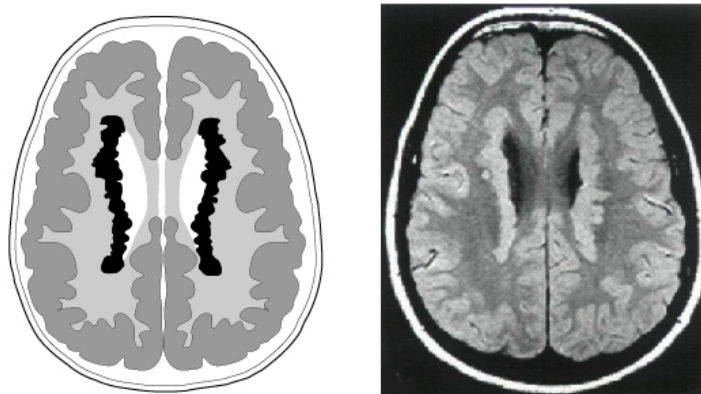
Hemimegalencephaly

This condition is usually a severe clinical disorder associated with refractory seizures and focal paresis. Sometimes it is associated with macrocephaly or cranial bone hemihypertrophy. Hemimegalencephaly has been observed in several genetic syndromes including TS, NF1, Proteus and Linear Sebaceous Nevus.



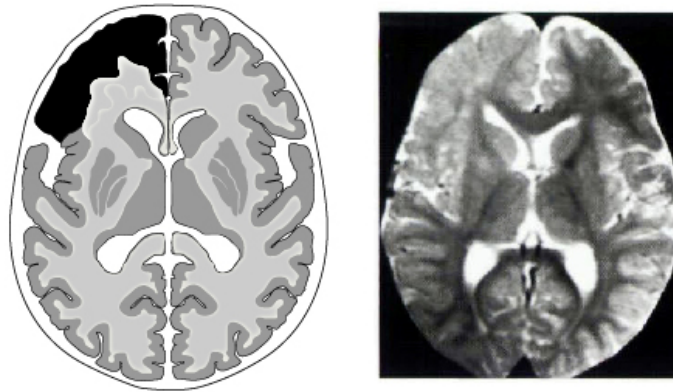
Periventricular Nodular Heterotopia

This malformation presents almost exclusively in females. Clinical manifestations include nonspecific developmental delay or seizure disorder. Evaluative MRI then detects the striking abnormalities of the ventricular heterotopia, as indicated in the black areas on the MRI diagram below. Many cases are due to heterozygous mutations in the Filamin A gene in females. Affected males are rare and early prenatal lethality is presumed.



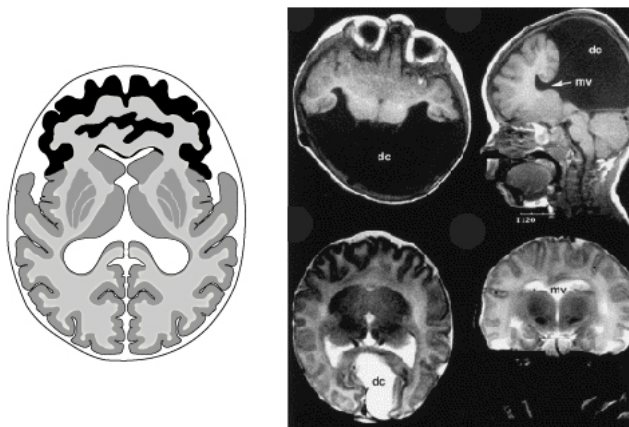
Focal Cortical Dysplasia

This entity is not yet associated with any single gene defect and familial occurrence is rarely observed. The clinical presentation is usually in the context of seizure onset. The focal areas show severe neuronal migrational defects with thickened cortex (black region in MRI diagram).

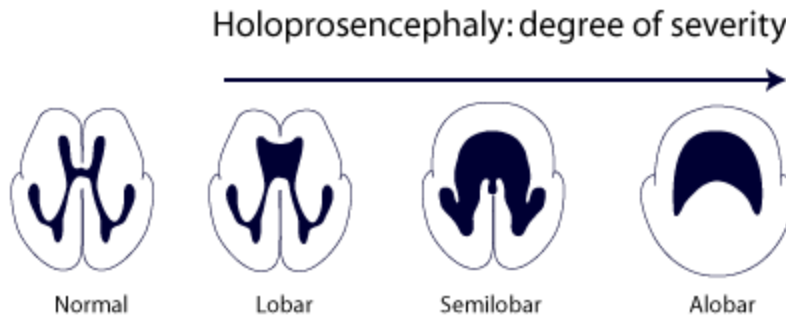


Holoprosencephaly

This malformation involves defects in midline septation of the brain. Various degrees of severity occur, ranging from alobar to lobar types as indicated in the diagram below. Holoprosencephaly is considered a developmental sequence and it can be the result of genetic and environmental factors. Affected children are usually diagnosed as neonates because of facial dysmorphism that includes close-set eyes, hypoplastic or absent nose, and microcephaly. Severe to profound mental impairment usually occurs.



from Kinsman, Plawner and Hahn,
Curr Opin Neurol, 2000



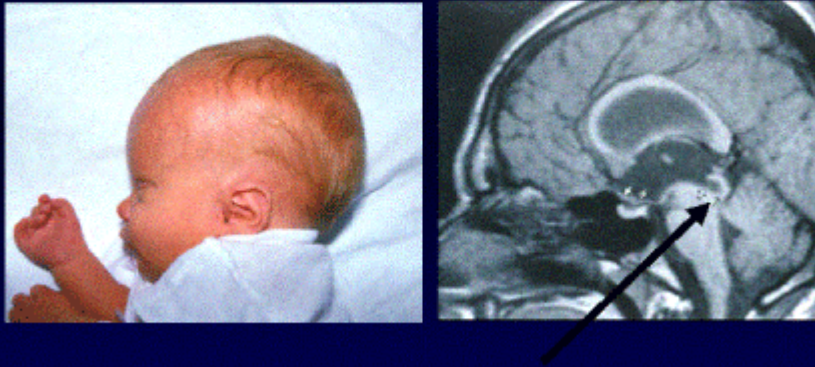
Holoprosencephaly

- 1/16,000 incidence
- Usually an "isolated" malformation
- Alobar, semi-lobar, lobar types
- Etiologic heterogeneity
 - Many genes: SHH, ZIC2, SIX3, TGIF, PTCH, TMEM1, ?HNF3B
 - Additional chromosome loci
 - Trisomies (e.g., 13)
 - Teratogens
 - Infections
- 6% recurrence risk

Hydrocephalus

Most occurrences of hydrocephalus are non-genetic and are due to the complications of prematurity, trauma or infection. Otherwise, congenital non-obstructive hydrocephalus is considered a multifactorial genetic disorder. Single genes are also implicated in some families with hydrocephalus associated with stenosis or obstruction of the Aqueduct of Sylvius.

Hydrocephalus



Aqueductal stenosis

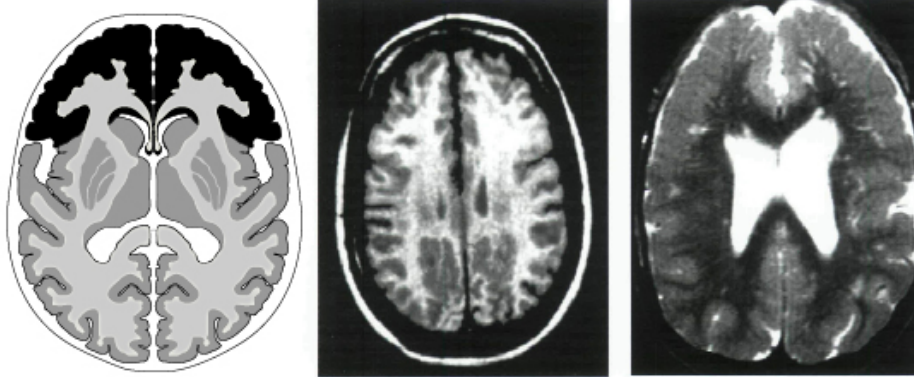
Congenital Hydrocephalus

- Incidence: 1/1000-2/1000
- Etiology
 - “Communicating” hydrocephalus
 - Meningomyelocele with Chiari II anomaly
 - Aqueductal stenosis
 - Dandy-Walker malformation
 - Other
- 15% have aqueductal stenosis
 - Sibling risk is 10% when male affected
- Sibling risk is 4% for uncomplicated types

Frontoparietal Polymicrogyria

The typical presentation involves seizures and developmental delay. MRI scanning shows bilateral fronto-parietal polymicrogyria (black areas on MRI diagram). Other regions of

polymicrogyria have been described and are usually bilateral (perisylvian, occipito-mesial). Several types have single gene causation.



Agenesis of the Corpus Callosum (ACC)

This malformation can occur as an isolated phenomenon without other structural brain defects, and these types tend to have higher cognitive function. More severe cognitive impairment is observed when ACC is associated with other CNS defects such as pachygyria or cerebellar hypoplasia. The MRI in many cases of ACC shows abnormal white matter bundles (Bundles of Probst, indicated by the arrows) that reflect presumed abnormal cellular tracking and migration. In the diagram, the normal corpus callosum is colored black. Over 100 single gene or chromosome defects have been associated with ACC but no single gene has been identified as a significant cause.



Agenesis of Corpus Callosum (ACC)

- **Presentation**
 - **Symptomatic: learning delay; seizures, etc.**
 - ACC + other brain anomalies
 - ACC is only brain defect
 - **Coincidental: prenatal U/S; adult MRI**
- **Extremely variable prognosis**
- **Sporadic occurrence (95%)**
- **Component of > 100 syndromes**
- **No major gene identified**

Familial Macrocephaly

The clinical presentation usually occurs between 6-12 months age when the occipital-frontal head circumference (OFC) measurements show values >98%, sometimes associated with acceleration of the growth rate that crosses percentiles. Cognitive function is usually normal and family history can show an apparent autosomal dominant pattern of inheritance. The MRI in infants is normal but often shows prominent subarachnoid spaces, especially in the frontal regions. The macrocephaly is most notable in infants and young children but by adolescence the craniofacial appearance is less distinctive and adults may appear normal except for having increased OFC measurement. Black areas in the illustration indicate regions of the subarachnoid space that are most pronounced. These areas can help define the disorder's MRI phenotype.



Glutaric Acidemia, Type 1

In early infancy, there is usually no evidence of metabolic acidosis or episodic illness but macrocephaly and developmental delay may be apparent. In rare situations, between 6-18 months of age, there can be rapid clinical deterioration due to acute injury to the basal ganglia area. At that time, the MRI scan can show distinctive bilateral striatal injury, apparently related to the excitatory effects of glutaric acid metabolites.



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