

# Brain Anomalies

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|  |           |
|--|-----------|
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## Segmentation, Cleavage, and Midline Defects (s. Malformations of Ventral Induction)

- failure of prosencephalon to grow into two symmetrical hemispheres and defects in region of lamina terminalis.

### HOLOPROSENCEPHALY

- failure of embryonic prosencephalon to separate into two cerebral hemispheres (5–8 weeks of gestation)

→ *midline malformation* of ANTERIOR BRAIN-SKULL-FACE.

- INCIDENCE - 1 per 31,000 births.

### ETIOLOGY

- 1) **chromosomal** abnormalities (**trisomy 13**; rarely, trisomy 18).
- 2) **genetic** abnormalities (at least 2p21, 7q36\*, 18p11.3, and 21q22.3 may harbor genes responsible for holoprosencephaly).

3) **teratogenic** factors (incl. **maternal diabetes**).

\*gene for autosomal dominant familial holoprosencephaly (HPE3) as human Sonic hedgehog homolog (member of family of developmental signalling molecules).

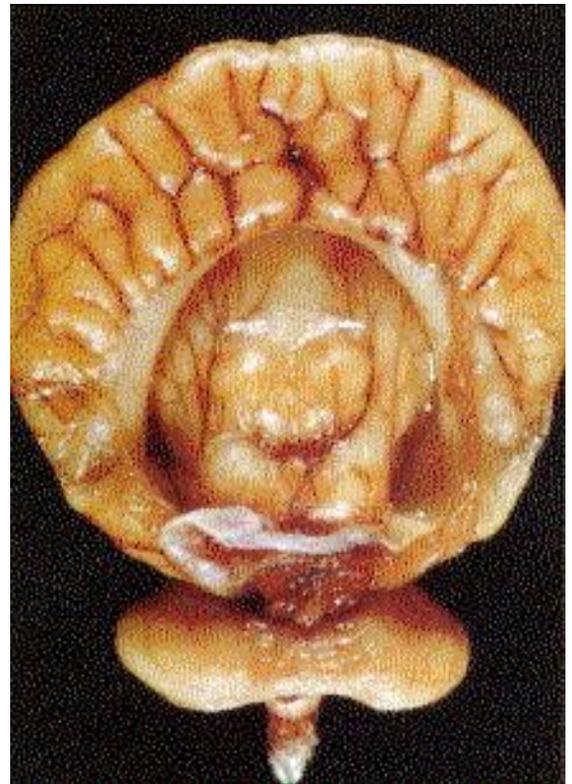
### CLINICAL FEATURES

- *posterior fossa contents* ≈ normal.
- absence of *corticospinal tracts* is common finding (consequence of severe malformation of cerebral cortex).
- spectrum of **DISTINCTIVE FACIAL DYSMORPHISMS** is part of *HOLOPROSENCEPHALIC MALFORMATION SEQUENCE* (affecting prechordal mesoderm - important in facial development) - in descending order of severity:
  - 1) **cyclopia** - eye and orbits fused or in various states of incomplete separation; nose is absent; *agnathia* may also be present.
  - 2) **ethmocephaly** - instead of nose, *proboscis* [cylindrical protuberance ≈ snout] is present and often located above incompletely separated, or severely hypoteloric, eyes.
  - 3) **cebocephaly** [monkey head] - nose now is between and below hypoteloric eyes, but there is only single blindly ending nostril.
  - 4) **premaxillary agenesis** or **aplasia of primary palate**, associated with hypotelorism and often midline *cleft lip* and *palate*.
  - 5) **milder facial dysmorphism** (hypotelorism, flat base of nose, milder midline or bilateral clefting).
  - 6) **minimal forms** (e.g. single central incisor).

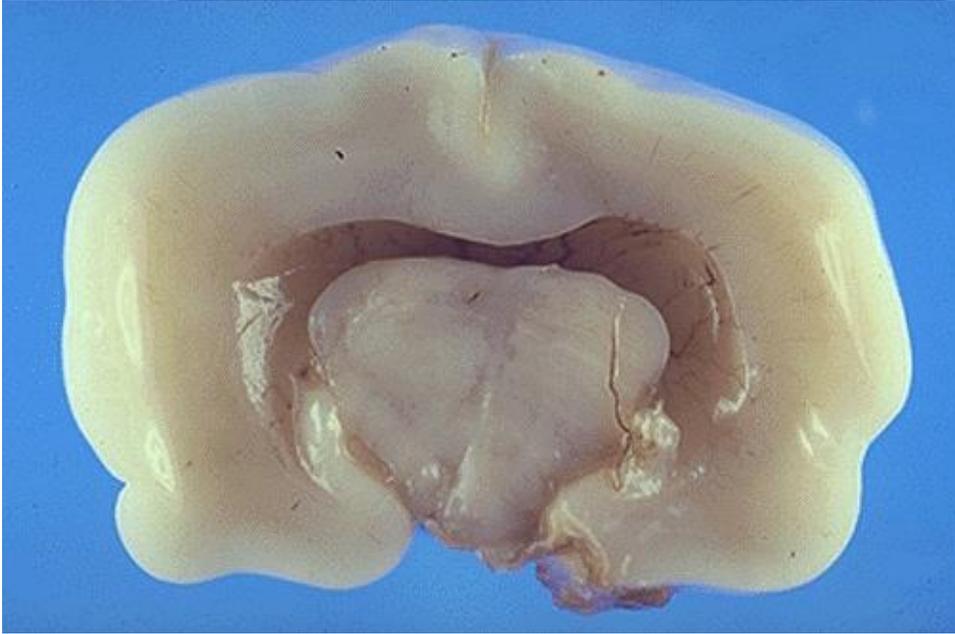
Face predicts **brain** in holoprosencephaly spectrum

**ALOBAR holoprosencephaly** (most severe form - often spontaneously aborted) – total arrest of evagination & invagination:

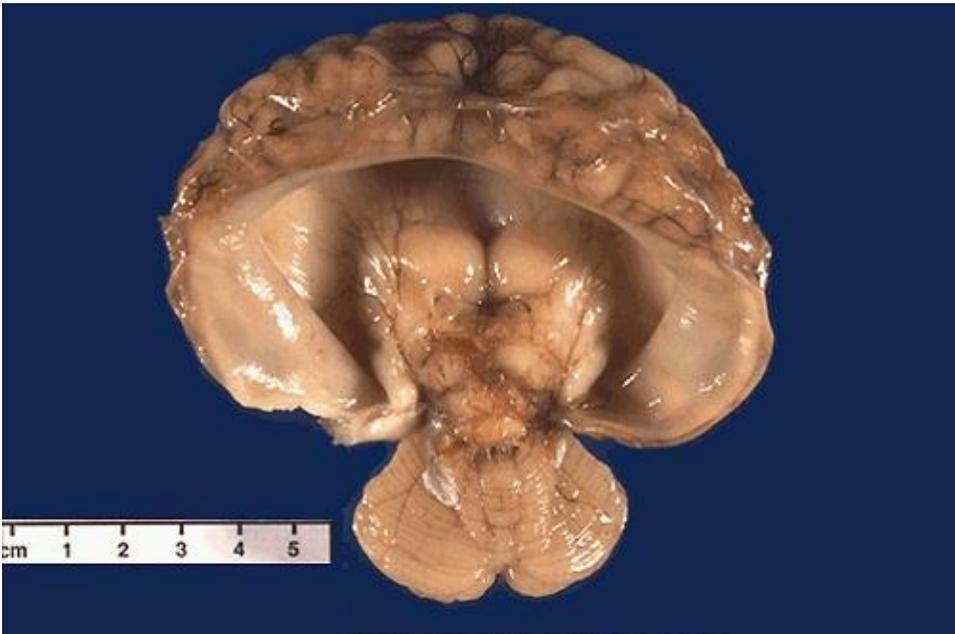
- 1) brain is small:
  - hemispheres are completely fused as one entity (holospheric prosencephalon – single hemisphere, single lobe).
  - CORTEX normally sulcated (normal histogenesis).
  - *basal ganglia* and *thalami* are also fused.
  - absent *corpus callosum*, *olfactory bulbs* and *tracts*.
  - **ventricular system** with single cavity (in continuity with large dorsal cyst).
  - *hydrocephalus* prevails (macrocrania in spite of microcephaly!).
- 2) severe mental retardation, seizures, severe motor impairments, poikilothermia, endocrine insufficiencies.
- 3) **severe facial malformations**: cyclopia, cyclopia with agnathia, ethmocephaly, cebocephaly, severe hypotelorism with agenesis of primary palate and median cleft lip and palate.



Normal sulci, no fissures – disorder of organogenesis!



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

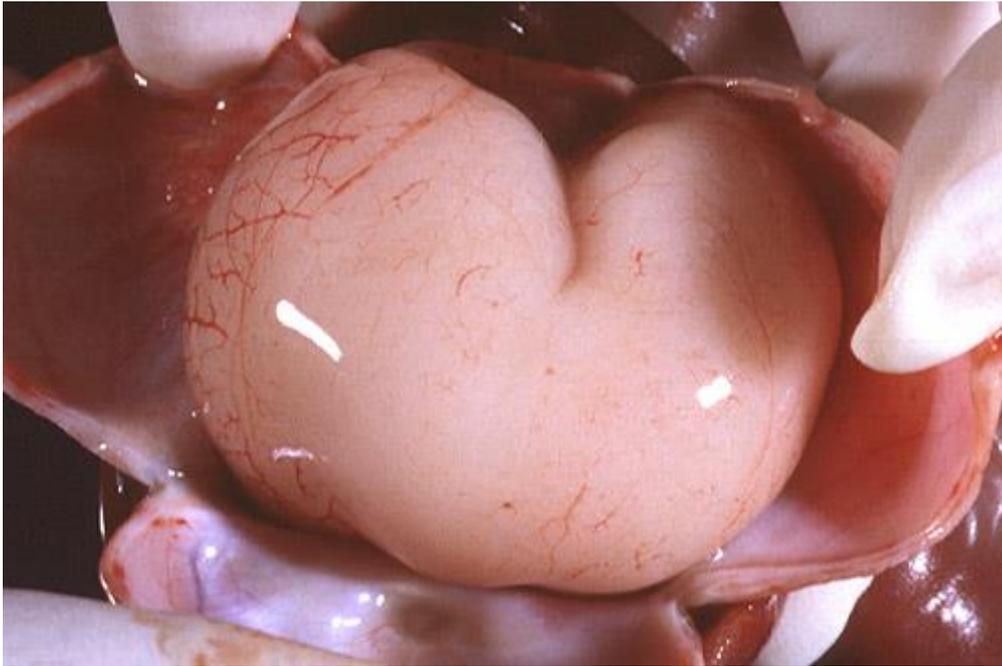


Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

**SEMILOBAR holoprosencephaly** (less severe - less reduction in brain volume):

- 1) interhemispheric fissure is partially formed occipitally;
  - *frontal lobes* are fused, but *thalami* are partially separated.
  - still single *ventricle* (but there is indication of third ventricle).
  - *corpus callosum* may be partially formed.
- 2) variable degrees of **mental retardation**.
- 3) **less sever facial malformations**: microphthalmia, coloboma, hypotelorism, nasal malformations.

Skull is opened to reveal "semilobar" holoprosencephaly (small cleft representing attempt to separate hemispheres); there is no lissencephaly (no gyral pattern) because fetus was < 20 weeks gestation:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

### LOBAR holoprosencephaly

- 1) brain has generally normal volume and almost complete separation into two hemispheres;
  - in depth of *frontal lobes* (medio-orbital region) there is continuous cerebral cortex between two lobes.
  - *falx* is often dysplastic anteriorly but otherwise normal.
  - *septum pellucidum* is absent.
  - *corpus callosum* is absent or dysmorphic, at least anteriorly.
  - *ventricular system* is well defined but may be dysmorphic.
- 2) normal intellect ÷ mild mental retardation.
- 3) mild (or absent) **facial malformations**.

### DIAGNOSIS

- INTRAUTERINE DIAGNOSIS of severe forms – **ultrasound** (lack of midline echo).
- high-resolution **karyotype analysis** (± fluorescent in situ hybridization [FISH] analysis) with special emphasis on chromosomes **2p21**, **3p**, **7q36**, **13q**, **18p11.3**, and **21q22.3** is recommended in all cases.
- coronal T1-weighted **MRI** - bridging of cerebral cortex across midline.

### MANAGEMENT

- focuses predominately on *seizure control*.
- *surgical correction* of craniofacial malformations.
- *hormone replacement* therapy.

## SEPTO-OPTIC DYSPLASIA

- absence of **septum pellucidum** + **optic nerve hypoplasia**.
- additional features:
  - 1) lateral geniculate, hypothalamic, posterior pituitary hypoplasia.
  - 2) cerebral and cerebellar dysplasia.

### ETIOLOGY

- a) locally destructive factors
  - b) mild end of holoprosencephaly spectrum.
- most cases are **sporadic**; however, there is existence of autosomal recessive form.

### CLINICAL FEATURES

- considerable heterogeneity:
  - 1) **visual impairment** (blindness ÷ normal vision).
  - 2) **endocrine abnormalities** (hypothalamic-pituitary insufficiency)
  - 3) **seizures**.
  - 4) **cognitive development** may be normal!

### DIAGNOSIS

- coronal T1-**MRI** - assess size of optic nerves and chiasm (diameter should be in same range as diameter of carotid arteries).

### MANAGEMENT

- **endocrine replacement** protocols.

## AGENESIS OF CORPUS CALLOSUM

- develops during gestation **weeks 11-20**.

### ETIOLOGY

- A. **Isolated malformation** – favorable prognosis!
- B. **In association with other malformations** (e.g. holoprosencephaly):

| Syndrome            | Characteristics  |
|---------------------|--|
| APERT               | see p. Dev9 >>   |
| AICARDI             | see p. E9 >>   |
| Oral-facial-digital | Mental retardation, midline oral and facial defects, hand and finger abnormalities, renal microcysts, cerebral migration defects   |
| MILLER-DIEKER       | <i>see below &gt;&gt;</i>  |
| NEU-LAXOVA          | Autosomal recessive; death in weeks; ocular abnormalities, everted lips, short neck, ichthyosis, edema, limb deformities, lissencephaly and cerebral, cerebellar, brain stem atrophy |

| Syndrome  | Characteristics   |
|---|---|
| FANCONI anemia  | Autosomal recessive, pancytopenia, skeletal anomalies (incl. radial aplasia)  |
| Sensorimotor neuropathy and agenesis of corpus callosum | Autosomal recessive; sensorimotor agenesis of corpus callosum, neuropathy, dysmorphism  |
| SHAPIRO   | Genitourinary and cardiac defects, mental retardation, hydrocephalus, holoprosencephaly, episodic hyperhidrosis, hypothermia / hyperthermia |
| Osteochondrodysplasia                                   | Nonlethal rhizomelic osteochondrodysplasia, hypertension, thrombocytopenia, hydrocephalus.  |

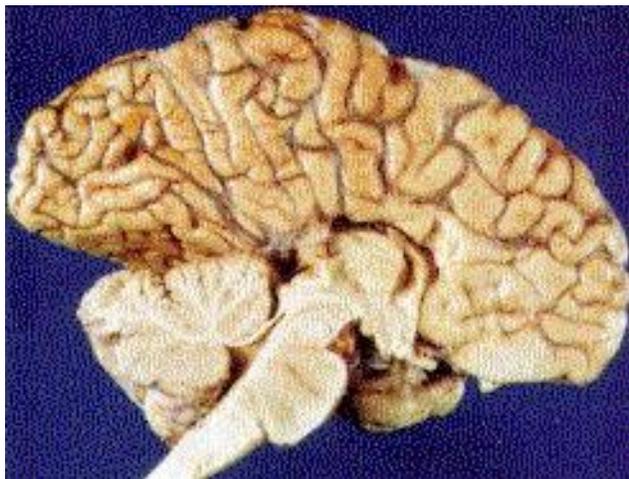
- may be associated with specific chromosomal disorders (esp. 8-trisomy and 18-trisomy).
- growing number of *inborn errors of metabolism* also include agenesis\* of corpus callosum (e.g. nonketotic hyperglycinemia, infantile lactic acidosis associated with pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, adenyly succinate deficiency, Smith-Lemli-Opitz syndrome, Zellweger's syndrome, Menkes syndrome).

\*corpus callosum shrinkage may be postnatal in origin.

## PATHOLOGY

### A. Complete agenesis

- absent *cingulate gyrus* (formation of cingulate gyrus is linked to callosal development) - sulci radiate down medial aspect of brain from dorsal surface to high-riding roof of third ventricle.
  - normal cingulum is replaced by abnormal white matter **bundle of Probst** (running anteroposterior just above lateral ventricle, where fibers of corpus callosum would normally collect into commissure) - this causes characteristic straightening (on axial images) and bull's horn appearance (on coronal images) of frontal horns of lateral ventricles.
- widely separated and angular *lateral ventricles* in coronal sections; medial ventricular wall is convex, and cavity is small ("**bat-wing**" contour).
- *anterior commissure* (also derived from lamina terminalis) may be absent.



**B. Partial agenesis** - absence (to variable degrees) of **posterior corpus callosum** (lipoma sometimes occupies defect), with sparing of rostrum and genu.

- *cingulate gyrus* is present only to extent that corpus callosum exists.

- *anterior commissure* is usually spared.

## CLINICAL FEATURES

– **largely silent** – patient has alternative pathways of information transfer, probably via intercollicular connections and posterior commissure (*disconnection syndrome* only rarely\* may be discovered, and only on careful neuropsychological assessment).

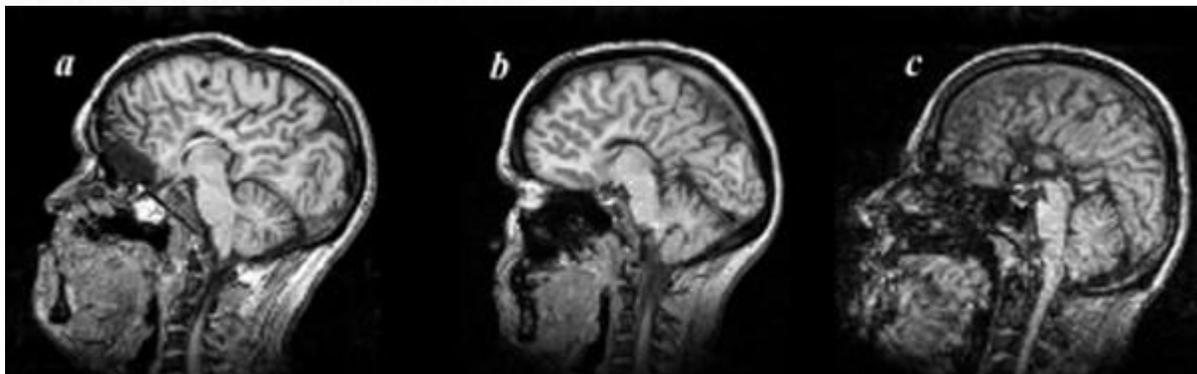
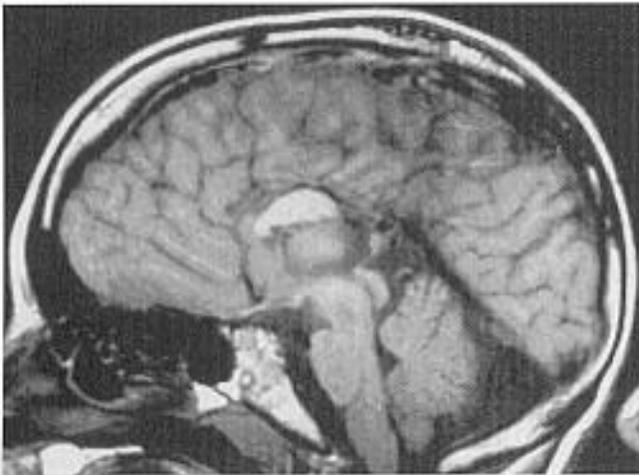
\*vs. surgical callosotomy in adults → clinical evidence of hemispheric disconnection.

- patients have higher incidence of *seizures* and *mental retardation* - reflects slightly higher incidence of neuronal migrational abnormalities (but patients with mental retardation or seizures are also more likely to undergo CNS imaging).

## IMAGING

- 1) **high riding third ventricle** (i.e. upward extension of 3rd ventricle roof).
  - 2) marked separation and parallel configuration of lateral ventricles (“**batwings**”).
  - 3) radial arrangement of **medial cerebral sulci**.
  - 4) **colpocephaly** (enlarged atria and occipital horns of ventricles - because of lack of splenium and white matter connecting occipital lobes).
- **MRI** is far superior to **CT** in diagnosing associated abnormalities.
  - PRENATAL detection with **ultrasound**.

**Incomplete genesis of corpus callosum** (T1-MRI): truncated genu and bulbous anterior body of corpus callosum; posterior body, splenium, and rostrum are absent; cingulate sulcus is absent; medial hemispheric sulci radiate all way down to 3<sup>rd</sup> ventricle posteriorly, where corpus callosum has not formed:



## ARRHINENCEPHALY

- absence of **olfactory bulbs and tracts**.

- A. **Isolated malformation** - result from number of independent mechanisms (e.g. may be mild manifestation of holoprosencephaly spectrum).
- B. **In association with other malformations** (e.g. holoprosencephaly, Kallmann's syndrome).

Clinically - **anosmia**.

**KALLMANN'S syndrome** - most common in **men** (female cases are rare):

- 1) **arrhinencephaly** (→ **anosmia**)
- 2) **gonadotropin-releasing hormone deficiency** (→ **hypogonadotropic hypogonadism**)
  - *GnRH neurosecretory neurons* develop in olfactory placode and migrate up olfactory nerves into hypothalamus. also see p. 2581 >>, p. 2738 >>
- 3) associated with **midline facial defects** (incl. color blindness, **cleft lip or palate**), unilateral kidney agenesis.
  - etiology - X-linked recessive *KALIG-1* (*Kallmann's syndrome interval gene 1*) defect.
    - KALIG-1 regulates adhesion proteins facilitating neuronal migration.
  - treatment - pulsatile GnRH (or hCG).

## COLPOCEPHALY

- disproportionate **enlargement of occipital horns** of lateral ventricles; abnormally thick gray matter with **diminished thickness of white matter** (thin poorly myelinated white matter - result of absence of corpus callosum).

- associated with: partial or complete **agenesis of corpus callosum**, Chiari malformation, lissencephaly, microcephaly.
- has been associated with chromosomal abnormalities such as **trisomy 8 mosaic** and **trisomy 9 mosaic**.
- few reports of **genetically** transmitted colpocephaly.

Clinically - **seizures** (early after birth), various degrees of **motor disabilities**, cerebral palsy, spasticity, **visual defects** (crossing of eyes, missing visual fields, and optic nerve hypoplasia), moderate to severe **mental retardation**.

- significant number of children suffer only from minor disabilities.
- not associated with increased ICP.

Imaging: ventricular system has unique appearance of crown of king (“**CROWN**” SIGN).



No specific treatment exists.

# Neuronal Migration and Cortical Formation disorders

- disorders of HISTOGENETIC period.

- one of most important mechanisms in control of neuronal migration is *radial glial fiber system* (guides neurons to their proper site – from periventricular germinal matrix to cortex).

## ETIOLOGY

- variety of **inheritance** patterns (incl. various metabolic disorders - Zellweger's syndrome, etc).  
> 25 human genetic syndromes are associated with malformations of cortical development!
- sporadic** (in utero retinoic acid, methylmercury, radiation, viral infections)

## CLINICAL FEATURES

- **seizures** and **mental retardation** (or lesser diminution of IQ) - related to degree of cortical disorganization (very severe in LISSENCEPHALY ÷ very mild or absent in small amounts of NODULAR HETEROTOPIA).

## DIAGNOSIS

- **MRI**.

## LISSENCEPHALY (s. AGYRIA), PACHYGYRIA (s. MACROGYRIA)

– severe failure of neurons to migrate completely through developing white matter → **markedly thickened disordered cerebral cortex** and **smooth agyric surface**;

(LISSENCEPHALY and PACHYGYRIA represent spectrum of same disorder: LISSENCEPHALY - diffuse bilateral; PACHYGYRIA - focal or multifocal)

Normal fissures, no sulci – disorder of histogenesis!

- appear early in cortical neurogenesis (beginning at 10-12 weeks of gestation).
- blurred *junction* between gray and white matter.
- *nodules of gray matter heterotopia* are common in white matter.
- *sylvian fissure* is primitive in appearance: broad groove with absent or poorly formed opercula (“figure 8” sign).
- remainder of brain is relatively spared.

## TYPES

- Type I lissencephaly (“classic”)** - extremely thick cortex (at expense of white matter) organized into four abnormal layers.
  - classically associated with *Miller-Dieker syndrome*, although autosomal recessive and X- linked (Xq22) forms have been identified.

**MILLER-DIEKER syndrome** (mapped to 17p13 - *LISI gene* with unknown function).

- **classic facial features**: bitemporal hollowing, short nose with broad bridge and upturned nares, prominent (long and thin) upper lip, small chin (micrognathia), mildly low-set and posteriorly rotated ears.
- marked **hypotonia** in neonatal period → later, **spastic quadriparesis** dominates.
- **seizures!!!** (neonatal seizures, infantile spasms, Lennox-Gastaut syndrome); EEG - fast  $\alpha$ - and  $\beta$ -activity admixed with high-amplitude slow activity.

- **profound psychomotor retardation** → death in first decade.
- cardiac anomalies (20-25%), males genital anomalies (70%).
- eyes and muscles unaffected (vs. type II lissencephaly).

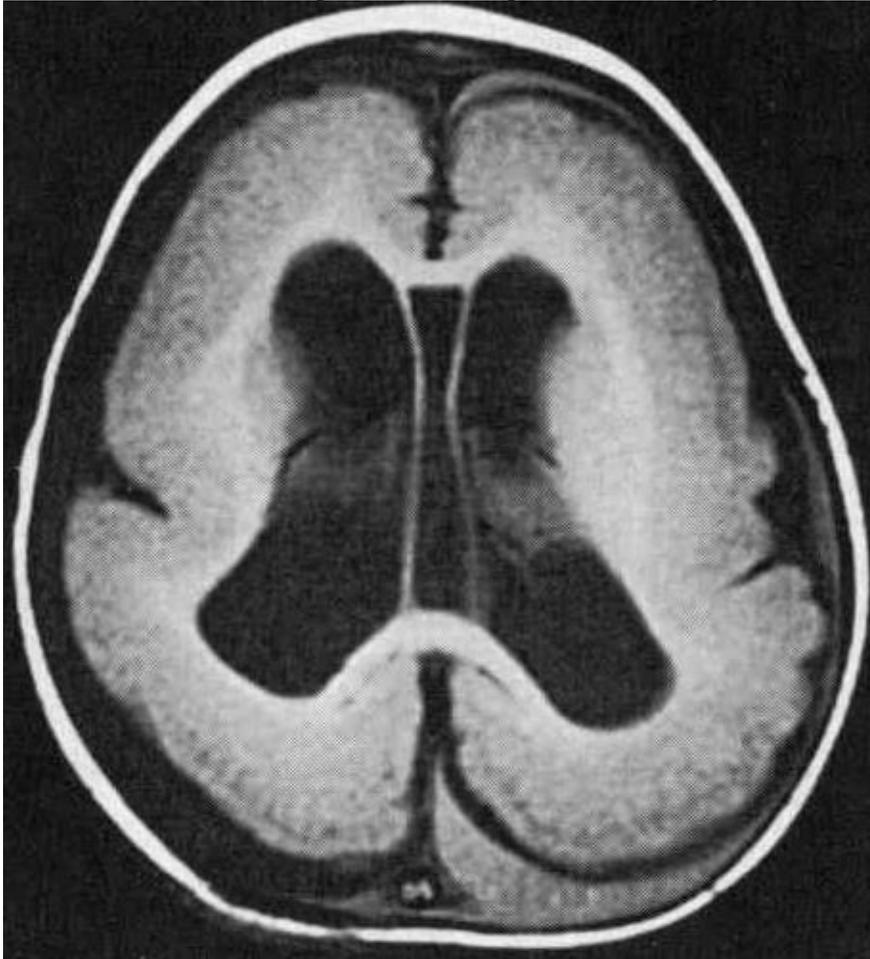
**Isolated lissencephaly sequence** (17p13.3 microdeletions in significant number of cases)

- lack of distinctive facial features.

2. **Type II lissencephaly (“cobblestone”)** - cerebral hemisphere in cross sections  $\approx$  one half gray matter and one half white matter (i.e. gray to white matter ratio of 1:1).
  - occurs in **congenital muscular dystrophies with eye involvement**: see p. Mus5 >>
    - 1) *muscle-eye-brain disease of Santavuori*
    - 2) *Fukuyama congenital muscular dystrophy*
    - 3) *Walker-Warburg syndrome (s. cerebral-ocular dysplasia)* - most severe (high proportion of neonatal lethality).

**Lissencephaly** (MRI) - note absence of sulci and maldeveloped sylvian fissures associated with enlarged ventricles (appearance of 3-4 month fetal brain\*):

*\*fetal brain is smooth* with few if any developed sulci - migrational malformations (as agyria) are impossible to detect prior to 18 weeks' gestation.



– failure of neurons to migrate normally → cerebral *cortex* with **small numerous irregular gyri that appear fused** (rather featureless grossly) with shallow intervening sulci.

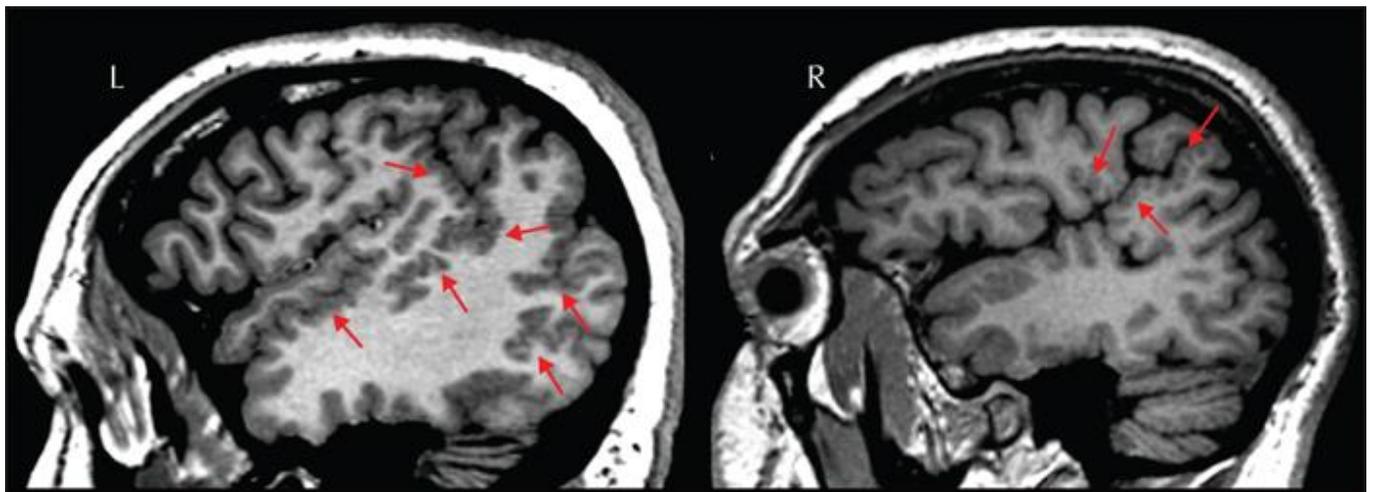
- time of appearance is later (than lissencephaly) – **17-26 weeks** of gestation.
- nonspecific nature - multiple PATHOGENESES & ETIOLOGIES - may be as malformation or as disruption (esp. CMV infection)
- recognized as *fine stubbing on brain surface* (similar to Moroccan leather).
- border between polymicrogyria and normal cortex is distinct.
- gray matter is composed of four layers (or fewer), with entrapment of apparent meningeal tissue at points of fusion of what would otherwise be cortical surface.
- can be unilateral, bilateral symmetric or asymmetric, mostly seen in the perisylvian region.

### CLINICAL FEATURES

- 50% present with focal **seizures**.

### DIAGNOSIS

- small surface features are too small to be routinely seen radiologically - difficult to differentiate from pachygyria (H: very thin **MRI** slices).



### TREATMENT

- **resective surgery** - for medically refractory seizures well localized to region of polymicrogyria.

## NEURONAL HETEROTOPIA

- groups of neurons fail to migrate fully to their cortical destination → **groups of neurons** (as collections of disorganized gray matter) **remain in inappropriate places**:

- a) **(SUBEPENDYMAL / PERIVENTRICULAR) NODULAR heterotopia** - group of neurons fails to migrate *at all* from germinal matrix area → neurons remain **periventricular** (multiple bilateral gray matter nodules in walls of lateral ventricles).
- b) **BAND heterotopia** - *late wave* of neuronal migration is halted after cortex is fairly well populated (reasonably normal gyri and sulci) → **subcortical** stripe of neurons.
  - “**double cortex**” - islands of subcortical laminar heterotopia separated from malformed cortex by band of white matter.

- may be strikingly *symmetrical*.
- cortex is generally well formed grossly (occasionally, overlying cortical malformation) but functionally abnormal (has EEG spikes).
- “heterotopia plus” – heterotopia along with other developmental abnormalities.
- **glial heterotopia** is often found in leptomeninges overlying cortical anomaly (plaque over brain surface).

### ETIOLOGY

- a) **sporadic**
- b) **familial** (mapping to different regions on X chromosome; e.g. Xq22 in band heterotopia, Xq28 in nodular heterotopia).
  - affected males show more severe brain malformations (incl. lissencephaly).
- c) **part of** more complex syndrome (e.g. Aicardi syndrome, Smith-Lemli-Opitz syndrome).

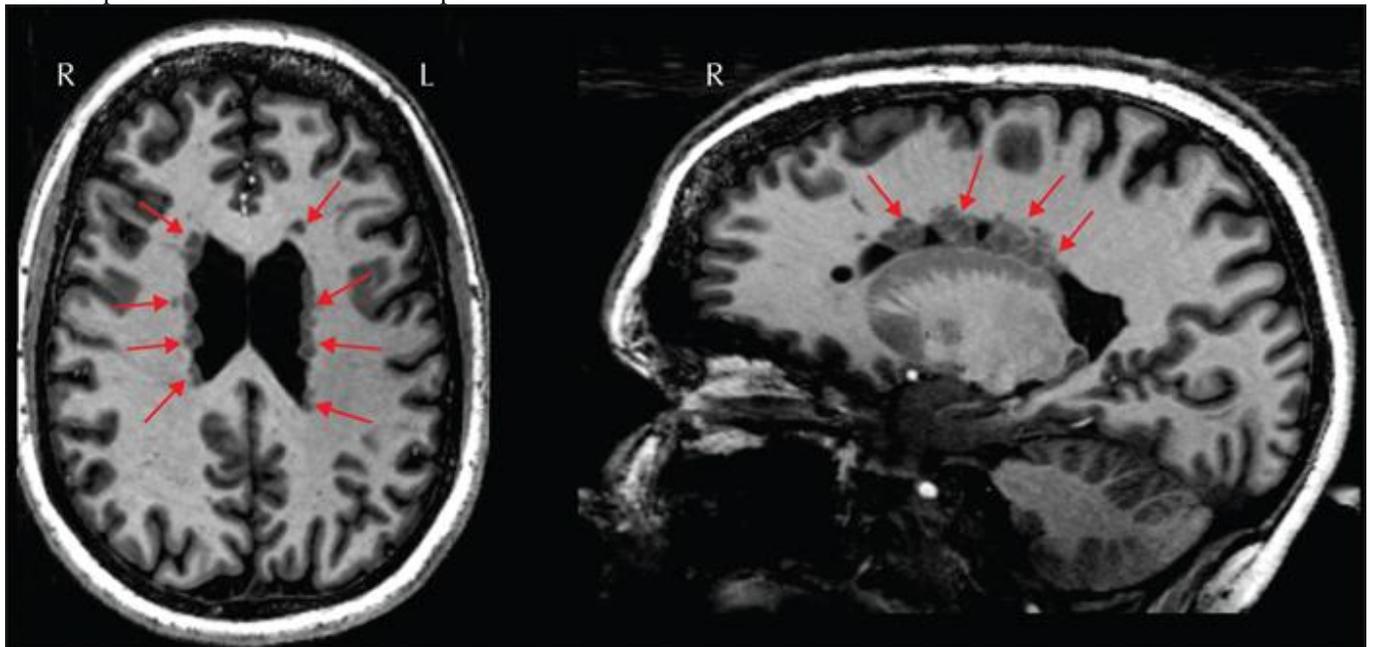
### CLINICAL FEATURES

- main presenting feature is **seizures** of various kinds.
  - onset can be from childhood (most commonly) to adulthood.
- **motor impairments** and **mental retardation** may coexist (esp. in band heterotopias - band thickness correlates with ultimate neurologic outcome).
- small heterotopias may be **asymptomatic**.

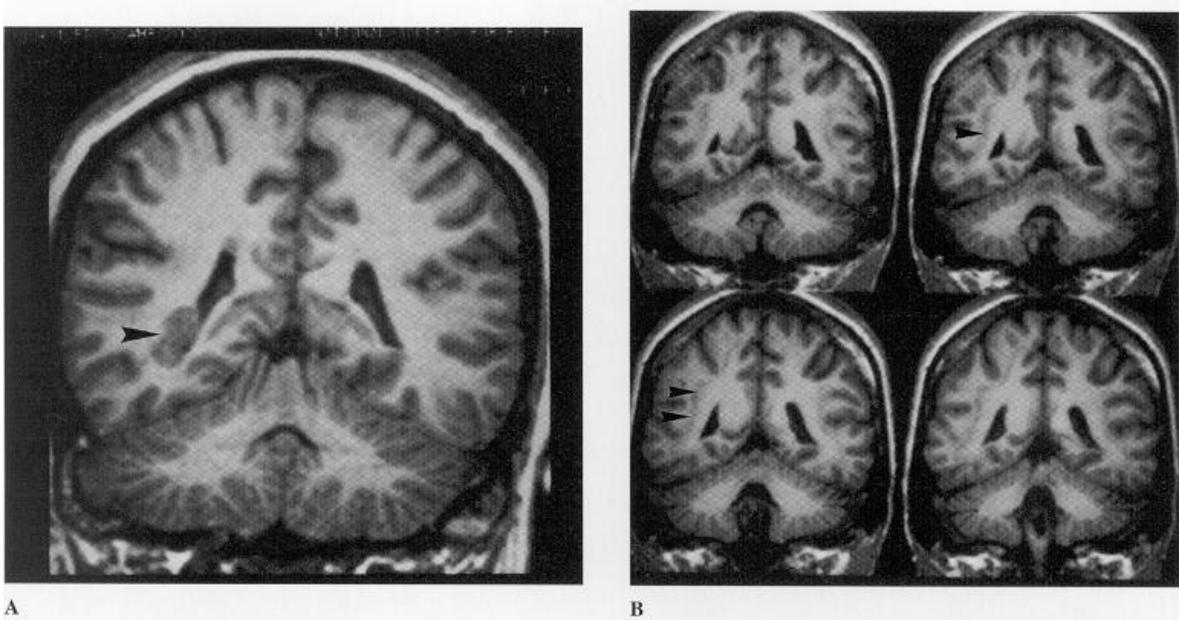
### DIAGNOSIS

- extremely **high-resolution MRI** (7T MRI can show many more heterotopias)
- for proper counseling, mother of child with BAND HETEROTOPIA should undergo MRI even if asymptomatic.
- **PET** – heterotopia may be iso- or hypo- metabolic.
- Italian school (“Claudio Molinari epilepsy center”) – **DTI** is a must – shows connection to the cortex

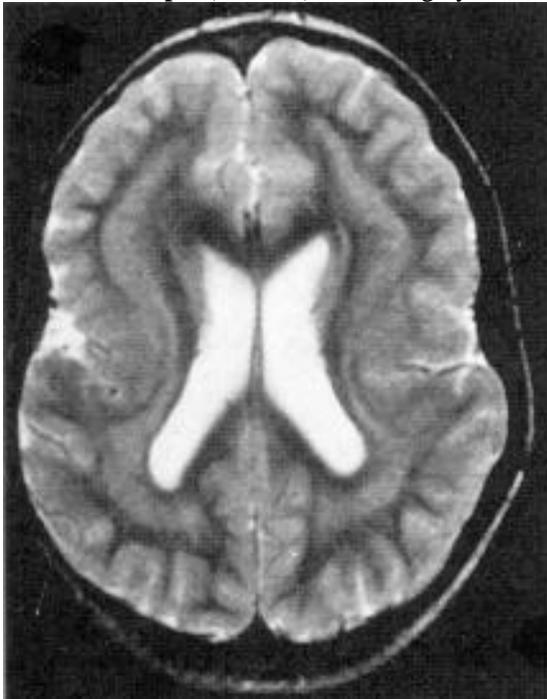
Bilateral periventricular nodular heterotopia:



T1-MRI: (A) **nodular heterotopia** (*arrowhead*), (B) **band heterotopia** (*arrowheads*):



**Band heterotopia** (T2-MRI) - band of gray matter beneath nearly normal cortex:



## TREATMENT

For epileptogenic heterotopias → **surgery** (defining the extent of the EZ with SEEG\* appears critical, as more extensive ablations or resections may be needed):

- a) isolated heterotopias → **surgical excision / thermoablation** (i.e. if patient has solitary nodule, behavior of it is unpredictable – OK to do LITT without icEEG but prepare patient for potential more than one surgery)
- b) diffuse bilateral band heterotopias (→ drop attacks) → **callosotomy**.

\*heterotopias connect to:

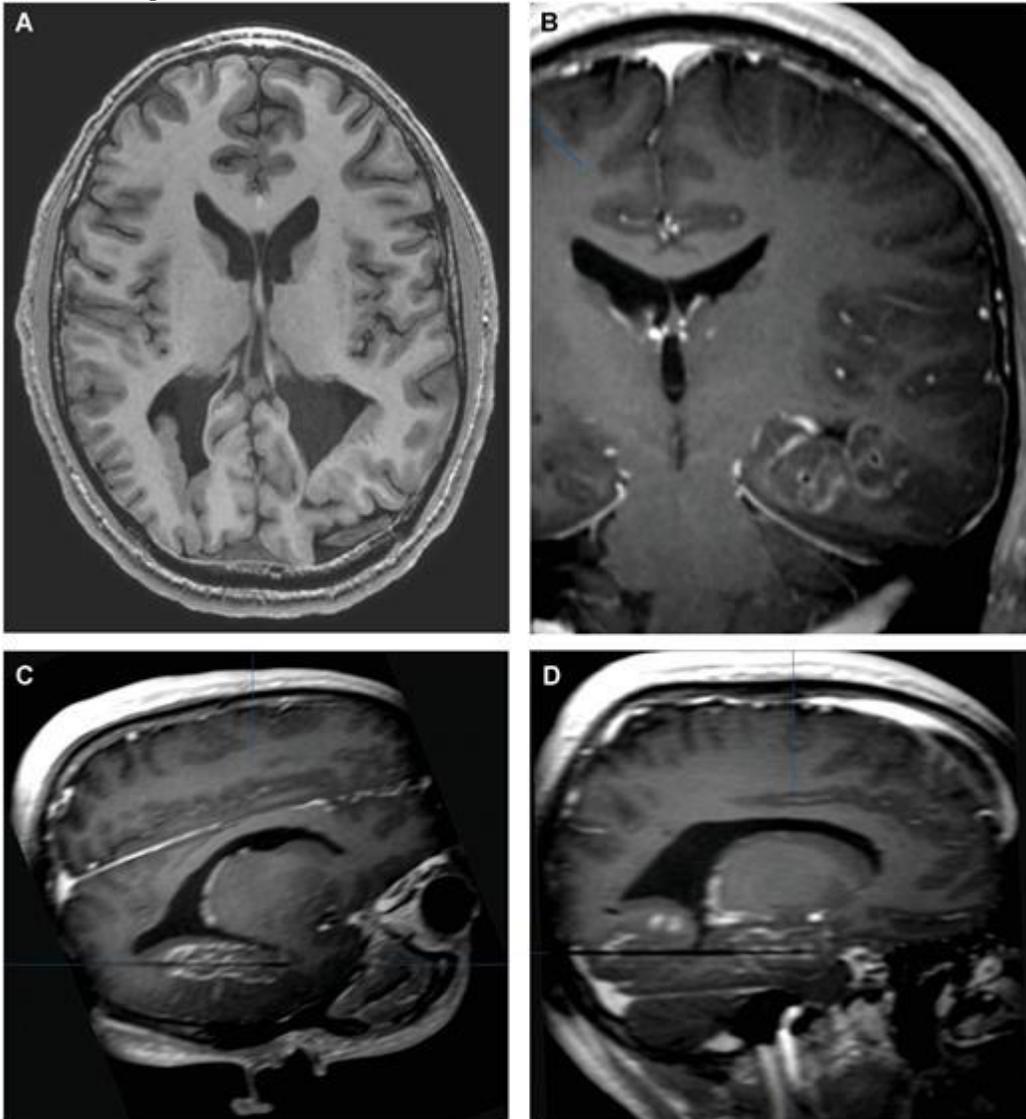
- a) associated cortex (ictal discharges originate in heterotopia or/and associated abnormal cortex)
- b) mesial temporal structures (implant it!) – especially posterior nodular heterotopias.

N.B. PVNH is frequently **part of a larger epileptogenic network!**

- if heterotopia is easily accessible surgically, remove it.

N.B. patients can have other heterotopias - most likely going to need to stay on AEDs in the long run.

**A**, Preoperative T1 MRI demonstrating bilateral temporo-occipital PVNH. **B**, Postoperative T1 gadolinium enhanced MRI demonstrating laser ablation of mesial temporal lobe and adjacent PVNH with 2 fiber trajectories. **C**, Ablation of PVNH. **D**, Ablation of mesial temporal lobe.



## FOCAL CORTICAL DYSPLASIA (FCD)

- lies at the milder end of the spectrum of neuronal migration disorders.
- some evidence supports a genetic basis for FCD or at least a genetic contribution to its pathogenesis; some studies show postzygotic mutations are involved.

**PATHOLOGY**

- disruption in lamination and columnar organization patterns (architectural abnormalities) → **maloriented neurons in inappropriate layers** (including layer 1 and white matter).

More severe forms of FCD are characterized by the presence of abnormal neuronal elements:

- 1) **immature neurons** - round homogeneous cells with large nuclei.
- 2) **dysmorphic neurons** - accumulation of neurofilaments within the cytoplasm → distorted cell body, axon, and dendrite morphology.
- 3) **giant cells** - increased in size but are normal in shape and do not show an accumulation of neurofilaments.
- 4) **balloon cells** (**hallmark of FCD**, although they are not present in all patients) - eosinophilic cytoplasm and eccentric nucleus, both neuronal and glial characteristics; exact role of balloon cells in production of an epilepsy phenotype is unknown.

|  | Abnormal radial cortical lamination | Abnormal tangential cortical lamination | Dysmorphic neurons   | Balloon cells | Associated with other pathology                   |
|--|-------------------------------------|---|--|---------------|---|
| Ia   | ✓                                   |   |  |               |   |
| Ib   |                                     | ✓                                       |  |               |   |
| Ic   | ✓                                   | ✓                                       |  |               |   |
| Abnormal cortical architecture/lamination    |                                     |   |  |               |   |
| IIa  | ✓                                   |   | ✓  |               |   |
| IIb  | ✓                                   |   | ✓  | ✓             |   |
| IIIa   | ✓                                   |   | Heterotopic or hypertrophic neurons in different patterns across IIIa variants |               | Hippocampal sclerosis                             |
| IIIb   | ✓                                   |   | Hypertrophic neurons   |               | Glial or glioneuronal tumor                       |
| IIIc   | ✓                                   |   | Hypertrophic neurons   |               | Vascular malformation                             |
| IIId   | ✓                                   |   | Hypertrophic neurons   |               | Pathology acquired during early life <sup>5</sup> |
| ILAE, International League Against Epilepsy. |                                     |   |  |               |   |

Type I - **no abnormal cells** are present (i.e. no dysmorphic neurons or balloon cells).

Type IA - isolated architectural abnormalities, usually **laminar or columnar disorganization**.

Type IB - also characterized by architectural abnormalities, but giant cells or immature neurons are also seen.

Type II - **abnormal neurons** are found.

Type IIA - there are **dysmorphic** cells but no balloon cells.

Type IIB - both **dysmorphic** cells and **balloon** cells are found.

Type III – **associated pathology** is present.

## CLINICAL FEATURES

- various types of **seizures** in childhood (but can be delayed into adulthood and can be as early as infancy\*).

\*e.g. onset during first few days of life as Early Infantile Epileptic Encephalopathy (EIEE)

- most frequent (50%) anomaly found in *medically intractable seizures* (EEG - **focal very high amplitude\* rhythmical activity**).

\*other EEG patterns (such as focal abnormal fast activity) have no predictive value for focal dysplasia.

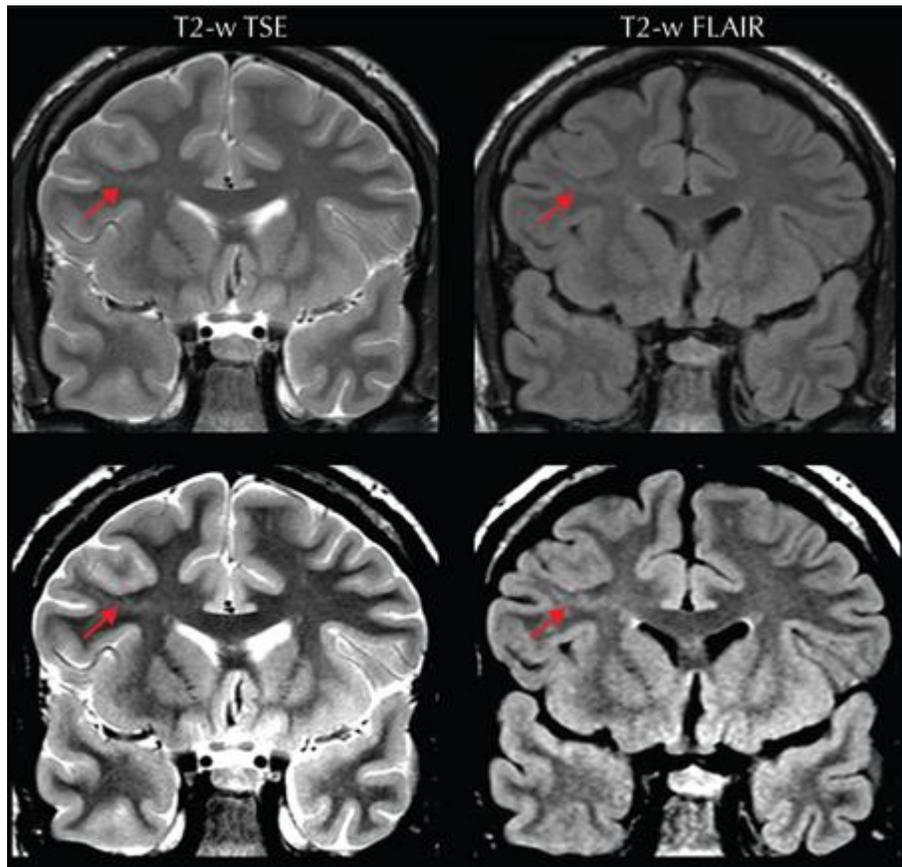
Type I FCD can be clinically silent (found in 1.7% of healthy brains) or have **cognitive impairment** instead of epilepsy.

## DIAGNOSIS

**MRI** (sensitivity 60-90%, i.e. brain MRI looks normal in 1/3 of patients):

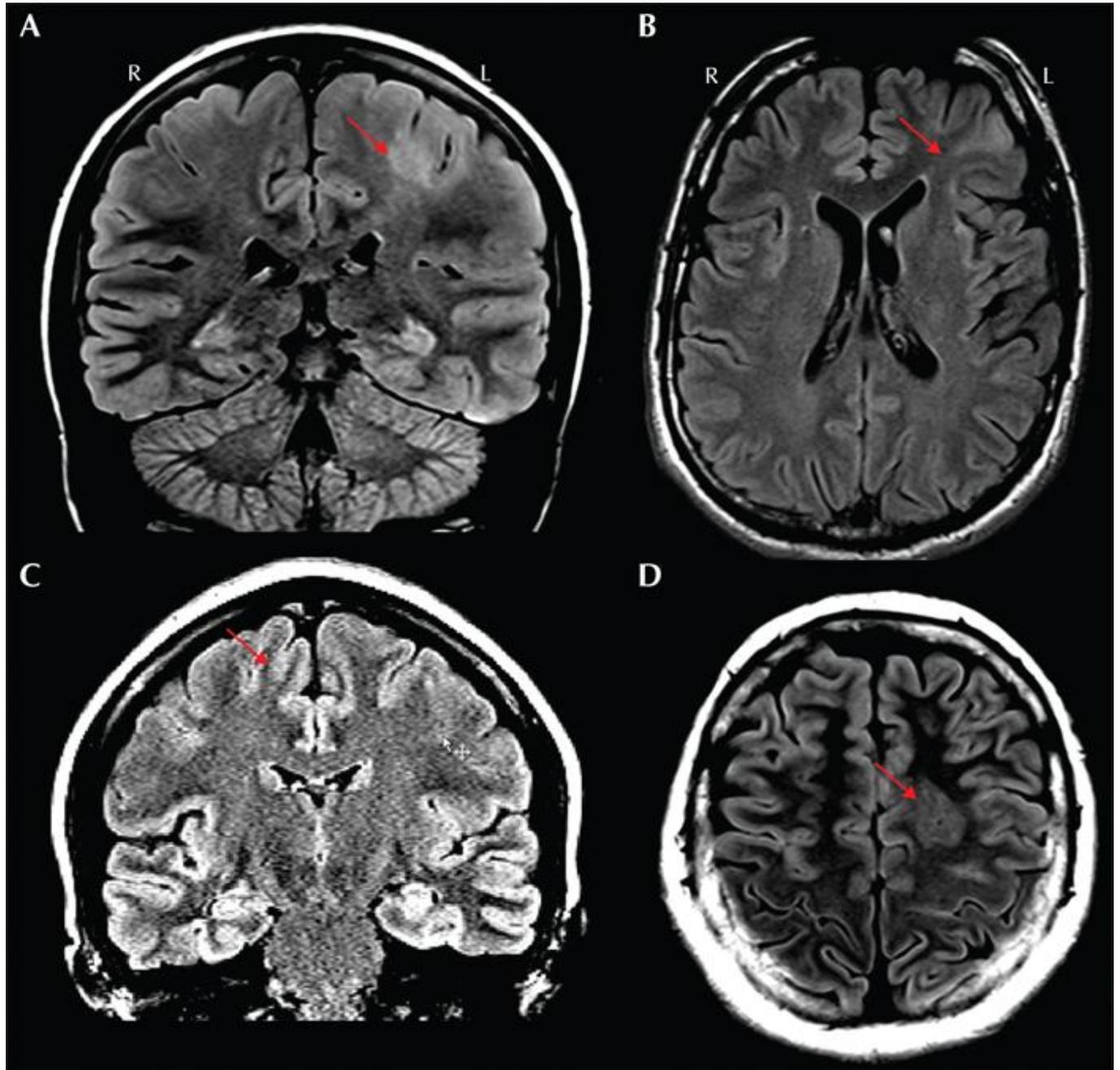
- 1) focal abnormal **gyral thickening**
    - small FCDs are preferentially located at the bottom of deep sulci - review of sulci anatomy is crucial.
    - there is software (e.g. FreeSurfer) for automated cortical thickness analysis – esp. useful for FCD detection.
  - 2) **blurring of cortical-white matter junction** (reduced demarcation)
  - 3) **transmantle sign** – funnel-shaped signal extending across the white matter, from the lateral ventricle to the cortex harboring the lesion (evident on T2 and FLAIR after contrast adjustment) – generally associated with type IIb.
  - 4) **signal changes** (T2 hyperdensity of gray and subcortical white matter, T1 hypodensity of subcortical white matter)
  - 5) atrophy of the white matter core
- **T1 sequence** should include **3D volume using thin (1–1.5 mm) partition size** with imaging in coronal plane → volume is reformatted → *each gyrus is analyzed in planes parallel and perpendicular to its axis* - complete cortex should be assessed (thickness, demarcation from subcortical white matter) - very time consuming, but should be undertaken in every case of suspected cortical dysplasia.
  - **FLAIR and DTI** show subtle subjacent white matter changes.

Transmantle sign:



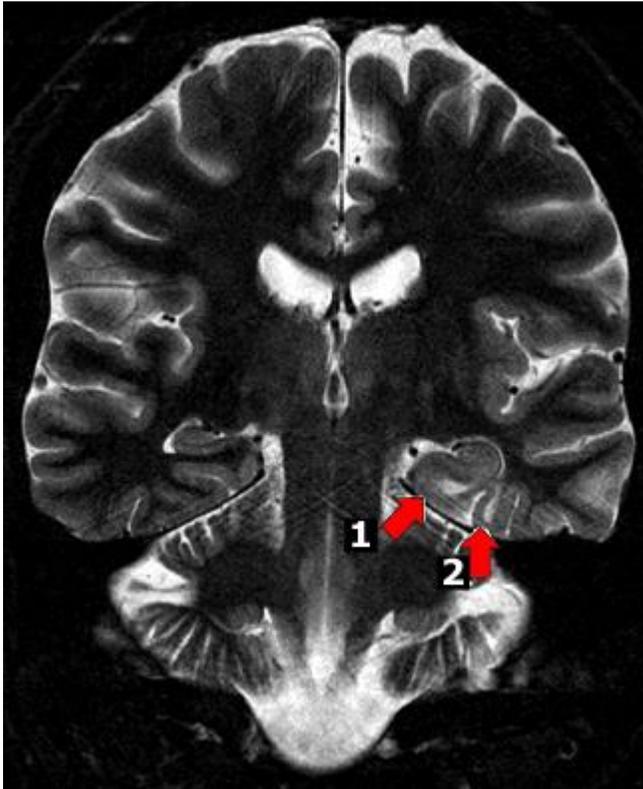
Wang et al. 2020

A-C. Three examples of FCD type IIb with varying degrees of the transmante sign.  
D. FCD type IIa with thickened cortex and hyperintensity on T2-weighted FLAIR.

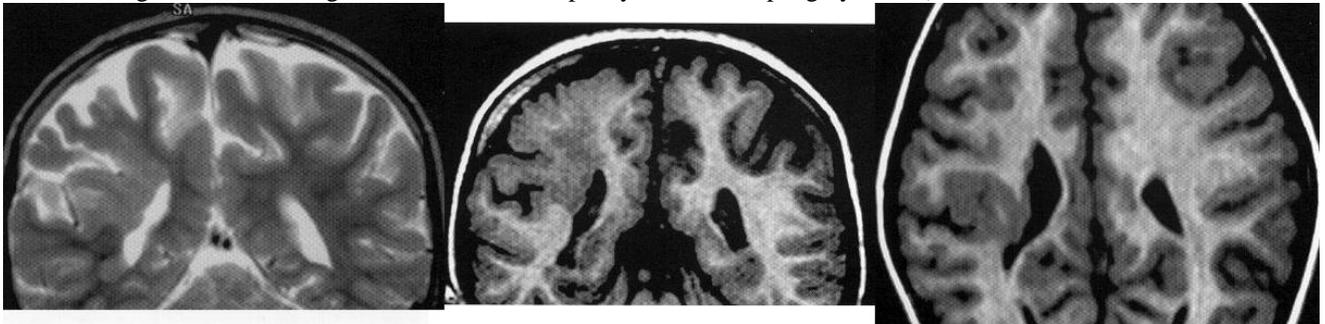


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**Focal cortical dysplasia** in the left parahippocampal gyrus (arrow 1) and occipitotemporal gyrus (arrow 2). Cortical thickening, increased signal in the subcortical white matter, and blurring of the gray-white margin are appreciable in these two regions:



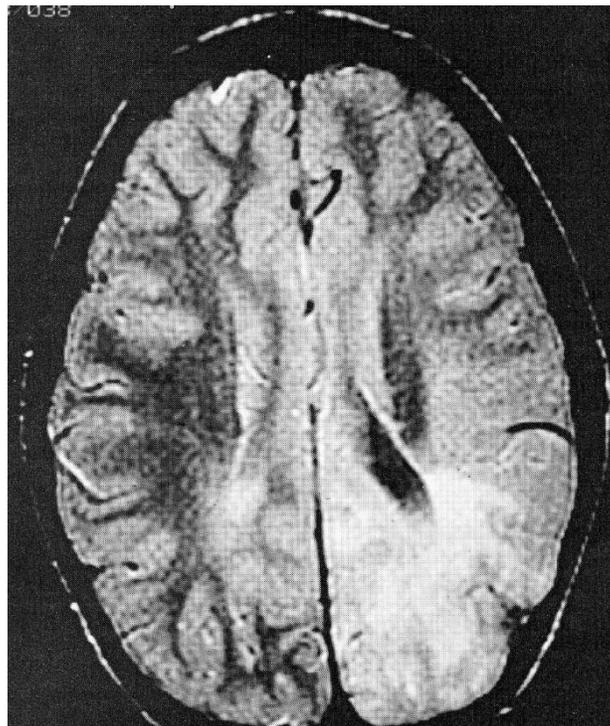
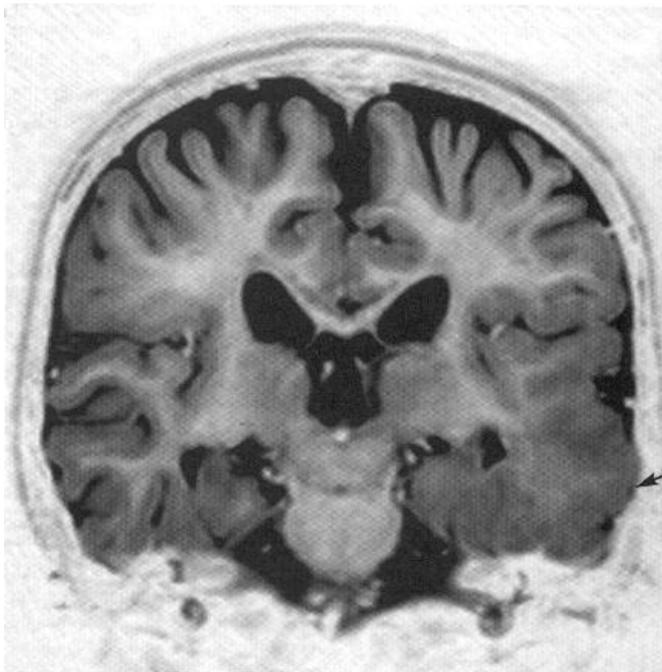
**Cortical dysplasia and heterotopia:** A. Coronal T2; B. Coronal T1; C. Axial reformatted from coronal 3D volume acquisition. - right-sided temporoparietal abnormality with dysmorphic grey matter extending from ventricle to brain surface (abnormality extends along lateral wall of right ventricle with subependymal heterotopic grey matter):



Source of picture: Ronald G. Grainger, David J. Allison "Grainger & Allison's Diagnostic Radiology: A Textbook of Medical Imaging", 4<sup>th</sup> ed. (2001); Churchill Livingstone, Inc.; ISBN-13: 978-0443064326 >>

Heavily T1-weighted (IR) coronal scan - left temporal lobe with very thick cortex (*arrow*), without sulci and poor demarcation of white matter:

Areas of dysplasia (white areas) most prominent in left posterior hemisphere:



Source of picture: Ronald G. Grainger, David J. Allison "Grainger & Allison's Diagnostic Radiology: A Textbook of Medical Imaging", 4<sup>th</sup> ed. (2001); Churchill Livingstone, Inc.; ISBN-13: 978-0443064326 >>

## TREATMENT

- **surgical extirpation** of epileptogenic lesion.

- **earlier surgical intervention** may improve overall developmental prognosis.
- **multifocality** is not contraindication - major focus extirpation may result in overall improvement of seizure control; H: SEEG ± RF ablation
- complete lesion resection is the most important factor for complete seizure control.
  - N.B. it is important to recognize that regions of **histological FCD may extend beyond the abnormal areas identified on MR images** – it is paramount to have **intracranial grids to determine the extent of resection!**
  - When the results from published surgical series were combined, 60% of patients with FCD experienced good seizure control after resection of the lesion!
- if possible, resect all accessible FCD (even if not involved on SEEG or grid recordings) – they tend to activate later after resection of other EZs (e.g. resecting epileptogenic cavernoma).
- **multiple subpial resections** may offer additional benefit, especially for patients in whom the abnormal tissue cannot be resected due to functional considerations; alternative – **thermococoagulation** (SEEG-guided RF or LITT) or **RNS**.
- **role of SEEG** (add stimulation to induce seizures to increase certainty):
  - normal appearing MRI (1/3 of patients with FCD).
  - sampling from the difficult to access areas ideally suited for LITT (if patient has solitary FCD, behavior of it is unpredictable – OK to do LITT without icEEG but prepare patient for potential more than one surgery)

## Outcomes

- **resection** achieves 50-70% seizure freedom.
- **LITT** (in surgically inaccessible areas) achieves  $\leq 50\%$  seizure freedom.
- **SRS** achieves 33% seizure freedom.

- **RF-TC** performed via existing SEEG electrodes - seizure freedom is low (approximately 18%).

## HYPOTHALAMIC HAMARTOMA (HH)

- rare congenital non-neoplastic lesions of the ventral hypothalamus composed of phenotypically normal clusters of neurons with abnormal cytological architecture.

### CLINICAL FEATURES

- **gelastic seizures** - burst of mechanical laughter with retained consciousness.
- how HHs cause seizures – by proximity to mammillary bodies.  
N.B. there are case reports when HH was not involved in seizures.
- development of **secondary seizure types** due to kindling (38% patients).
- progressive cognitive and behavioral difficulties and widespread **encephalopathy**.

### TREATMENT

- difficult to control with pharmaceutical therapy alone.
- do not need to remove / ablate the whole HH; enough to disconnect it from the network!

### RESECTIVE SURGERY

- **20-54% seizure freedom**
- significant operative morbidity: transient hemiparesis (2-30%), hormonal disturbances (8-57%), weight gain (11-59%), long-term memory impairment (8-43%), optic tract injury (3-10%), stroke (15-31%), and death (0-20%).

### RNS

- reports of RNS implantation into thalamus.

### LITT

- some experts think it is a treatment of choice

- complete ablation of the lesion is not necessary; focus should be on disconnection of the epileptogenic network.
- staged approach with multiple ablations (esp. larger hamartomas) allows adequate disconnection of the hamartoma while mitigating risk to surrounding structures.
  - bilaterally attached HHs often do not require a bilateral approach for adequate functional disconnection.
  - resting-state functional MRI (rs-fMRI) shows promise in elucidating the functional connectivity of HHs and providing targets for disconnection.
- critical nearby structures: hypothalamus, fornices, mammillary bodies, mamillothalamic tract, cerebral peduncles.
- transient neurologic deficits – 39-50%

## Dr. Curry case series

Curry DJ, Raskin J, Ali I, Wilfong AA. MR-guided laser ablation for the treatment of hypothalamic hamartomas. *Epilepsy Res.* 2018;142:131-134.

- 71 patients (25% of these patients had failed other surgical or radiosurgical intervention).
- 93% 1-yr gelastic seizure freedom.

## LITT outcome study in pediatric population

Nisha Gadgil et al. Staged Magnetic Resonance-Guided Laser Interstitial Thermal Therapy for Hypothalamic Hamartoma: Analysis of Ablation Volumes and Morphological Considerations. *Neurosurgery*, Volume 86, Issue 6, June 2020, Pages 808–816,

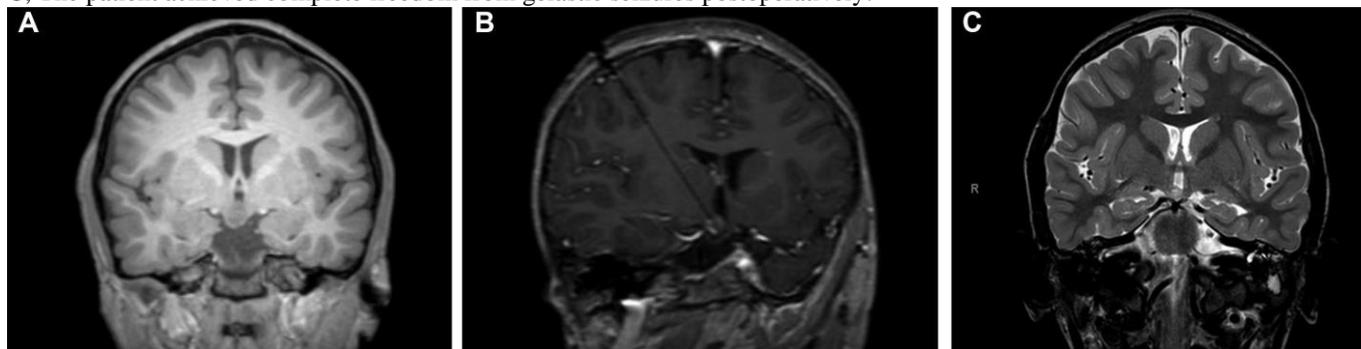
- all patients had improvement in their seizure burden; no patients were unchanged or worsened
- 81% of patients were completely free of gelastic seizures at last follow-up.
- only outcome predictors:
  - 1) age (at time of LITT): older children faring better in seizure control.
  - 2) smaller percentage residual hamartoma volume (ideally, < 50%).
- overall Engel outcome scores (gelastic and nongelastic seizures): 69.0% Engel class 1, 12.1% Engel class II, and 19.0% Engel class III.
- 50.0% were off all AEDs at last follow-up.

Preoperative T1 coronal MRI of a 3-yr-old male with frequent daily gelastic seizures - predominantly right-sided hypothalamic hamartoma:

A, Intraoperative oblique T1-weighted MRI with contrast depicts sequential right-sided laser ablation trajectory.

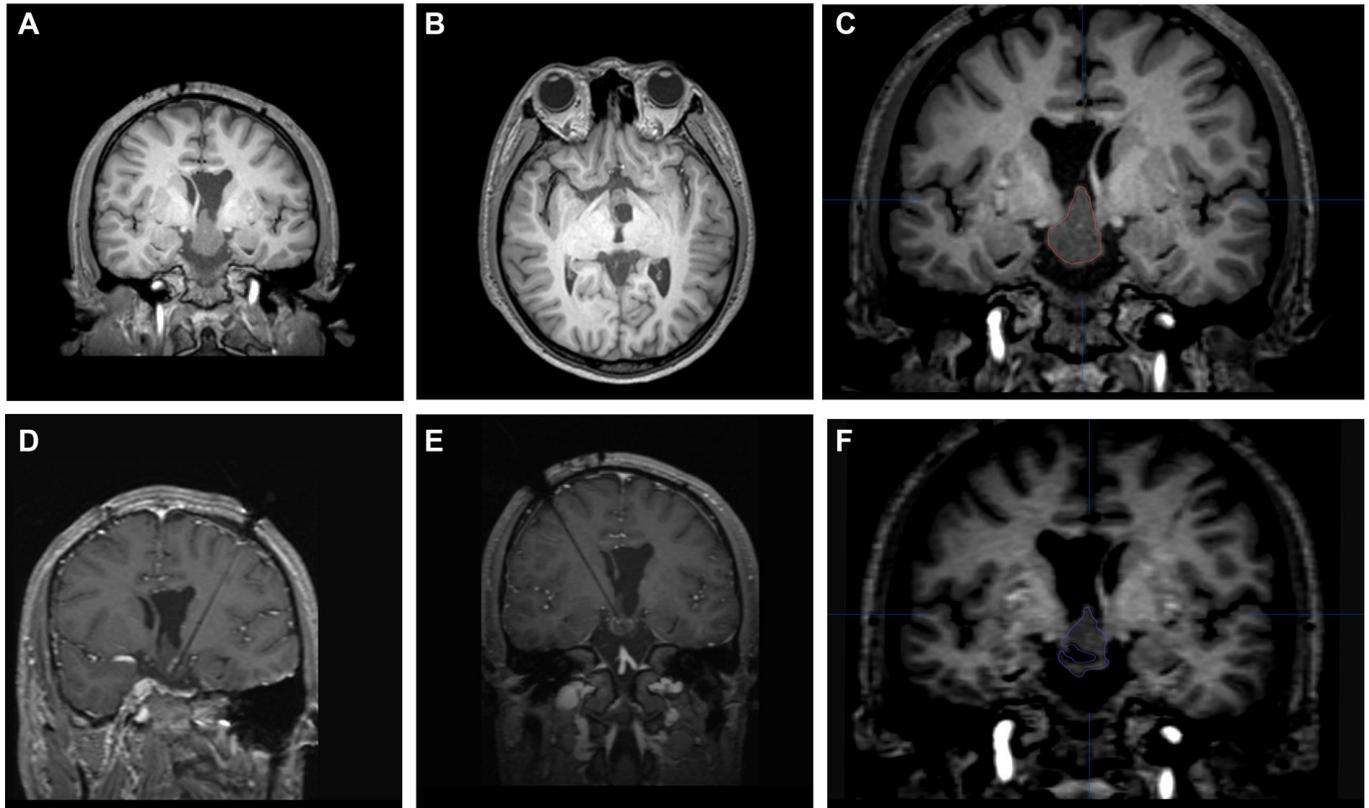
B, region of contrast enhancement indicates the extent of tissue ablation. Postoperative T2-weighted coronal MRI demonstrates decreased size of hamartoma with visible ablation cavity.

C, The patient achieved complete freedom from gelastic seizures postoperatively.



Preoperative T1 coronal, A, and axial, B, MRI of a 14-yr-old male with intractable gelastic epilepsy who had undergone prior transcallosal partial resection of large hypothalamic hamartoma. A previous central resection cavity necessitated sequential bilateral ablations because of introduction of central heat sink. Hamartoma contour was outlined slice-by-slice, C, and imaging software used to create a 3-D volumetric reconstruction of the hamartoma.

Intraoperative coronal T1-weighted MRI with contrast depicts sequential left-sided, D, and right-sided, E, laser ablation trajectories that were performed during separate operations. Region of contrast enhancement indicates the extent of tissue ablation. Volumetric measurement of postoperative hamartoma residual is depicted, F, approximately 50% of the hamartoma remained. The patient achieved complete freedom from gelastic seizures postoperatively.



### SRS

- seizure freedom ranges 37-60%.
- treatment effect is delayed by several months.

### TREATMENT COMPLICATIONS

diabetes insipidus  
 short-term memory dysfunction (rarely, permanent)  
 hypothalamic obesity  
 endocrine dysfunction

### Youmans ch. 68

HHs are rare congenital heterotopic lesions that are intrinsically epileptogenic when closely connected to the mammillary bodies.<sup>185,189</sup> Patients classically experience gelastic seizures during the first years of life.<sup>190</sup> In more severe forms of the disease, an epileptic encephalopathy characterized by drug resistance, various types of seizures with generalization (including drop attacks),<sup>190</sup> cognitive decline,<sup>191-193</sup> and severe psychiatric comorbidity develops in affected patients during the following years.<sup>194</sup> Usually, the seizures begin early in life and are often particularly drug resistant from the onset. Commonly, the seizure semiology suggests the involvement of temporal or frontal lobe regions and a phenomenon of secondary epileptogenesis. HHs may also be asymptomatic or be associated with precocious puberty, neurological disorders (including epilepsy, behavior disturbances, and cognitive impairment), or both. In 1969, Paillas and coworkers first showed that the epilepsy associated with HH can be alleviated by surgical resection of the HH lesion itself.<sup>189</sup> Direct proof of the role of HH in generating seizure activity was provided by Munari and associates,<sup>195</sup> who relied on data obtained from stereo encephalographic recordings from

implanted depth electrodes.<sup>196,197</sup> This evidence was reinforced by ictal single-photon emission computed tomographic studies<sup>198-200</sup> and by other studies using depth electrodes.

The natural history is unfavorable in the majority of patients because of behavioral symptoms (particularly aggressive behavior) and mental decline, which occur as a direct effect of the seizures.<sup>203</sup> Interestingly, in our experience, reversal of these behavioral symptoms after radiosurgery seems to begin even before complete cessation of the seizures and appears to be correlated to the improvement in background electroencephalographic (EEG) activity. It is the authors' speculation that these continuous discharges lead to the disorganization of several systems, including the limbic system, and that their disappearance accounts for the improvement seen in attention, memory, cognitive performance, and impulsive behavior. In these cases, radiosurgery's role in reversal of the behavioral symptoms may be as or more important than its effect on decreasing seizure occurrence. Consequently, we consider it essential to operate on these young patients as early as possible, whatever the surgical approach being considered (resection or radiosurgery).

### **SURGICAL APPROACH**

Even though the first successful and safe removal of an HH was reported by Paillas and coauthors in 1969,<sup>189</sup> interest in surgical cure of this specific group of patients developed only in the 1990s. According to Valdueza and colleagues, epilepsy-related HH is observed only with medium/large sessile HHs broadly attached to tuber cinereum or mammillary body.<sup>204</sup> Microsurgical resection in this critical area is associated with a significant risk for oculomotor palsy, hemiparesis, and visual field deficits.<sup>205,206</sup> The first clinical series evaluating microsurgical resection via pterional and midline frontal approaches did not emphasize complications.<sup>204,207-210</sup> However, in 2002, Palmi and coworkers observed severe complications after microsurgical resection in 7 of 13 patients by analyzing patients treated in several of the best centers for epilepsy surgery around the world.<sup>211</sup> These complications included thalamocapsular infarcts with contralateral hemiplegia in 4 patients (with subtotal recovery), a transient third nerve paresis in 4 patients, central diabetes insipidus, and nonreversible hyperphagia. <sup>211</sup> Nonetheless, they confirmed the efficacy of surgery for this kind of pathologic condition. More specifically, 3 patients showed complete seizure cessation and the remaining 10 patients had a greater than 90% reduction in the frequency of their seizures. The rationale for surgical disconnection treatment of HH is that the lesion is not a neoplasm and removal of it is therefore not mandatory. A further factor favoring a disconnection technique is the possibility of avoiding the complications that may occur during dissection in the cisterns, a maneuver necessary for microsurgical resection. Delalande and associates actually stressed this point as favoring the simple disconnection of an HH versus complete excision of it because of the occurrence of severe complications in their first patient.<sup>205</sup> When the clinical result is not satisfactory and the upper part of the lesion is mainly in the third ventricle, Delalande and colleagues proposed a second step via an endoscopic approach to the third ventricle. In 2003, Delalande and Fohlen published a series of 17 patients with a follow-up of between 1 month and 5.4 years.<sup>205a</sup> A second intervention (usually endoscopic) was necessary in 8 patients. In this excellent series, 47% of the patients (8 of 17) were seizure free, including 3 patients operated on twice. The authors reported some permanent severe complications, namely, 1 patient with hemiplegia, 1 with hemiparesis, 2 with hyperphagia, 1 with panhypopituitarism, 1 with hypothyroidism, and 1 with growth hormone deficiency. Transient morbidity included one case of meningitis and two cases of diabetes insipidus. In addition, the authors reported a postoperative frontal lobe ischemic complication that was apparently asymptomatic. In conclusion, only 6 patients (35%) were seizure free with no permanent toxicity. In contrast to reports of the use of a transcallosal approach, Delalande and Fohlen did not observe any memory deficit. Finally, the authors found a correlation between the completeness of exclusion and control of the seizures.

### **TRANSCALLOSAL INTERFORNICEAL APPROACH**

The transcallosal interforniceal route was initially proposed by the Melbourne team to approach HH via the third ventricle.<sup>212,213</sup> In January 2001 this team published a series of 5 patients operated on with this approach. Two of the patients were seizure free, 2 others were very much improved, and 1 failed to improve. No permanent complications were reported except an increased appetite in 2 subjects (obesity developing in 1 of them). Some months later, they reported a series of 25 patients operated on by the same route, including 21 with sufficient follow-up for evaluation (follow-up of 3 to 52 months). The results were not as favorable with regard to complications in this larger group but more favorable in terms of seizure cessation rate (67% instead of 40%). Resection was nearly complete (95% to 100%) in 13 of the 21 (62%) patients. Some transient side effects were reported: hypernatremia (>150 mEq/L) in 12 patients (57%), somnolence in 7 (33%), body temperature instability in 5 (24%), and third nerve palsy in 1 patient. Permanent complications were also reported: thalamic infarct in 2 patients (capsulothalamic in 1), appetite stimulation in 10 patients (48%) with permanence in 5 (24%); low thyroxin level in 6 (29%), permanent in 4 (19%); anxiety and depression in 4 (19%), permanent in 3 (14%); and short-term memory deficit in 8 patients (38%), permanent in 3 (14%). In this group of 21 patients, a total of 38 transient complications and 18 permanent complications occurred. The more important concern, according to the authors, was the short-term memory deficits. Thus, transcallosal interforniceal resection is a very attractive approach for stage I, II, and III HH.<sup>185</sup> Both the Barrow<sup>214</sup> and Melbourne<sup>215</sup> series report very good results, with 54% and 52% of patients, respectively, seizure free postoperatively. The major problem with these approaches is the frequent injury to the fornices. In fact, a clear short-term memory deficit was observed in 58% and 48% of the children, respectively. The long-term neuropsychological outcomes were not known precisely because the majority of the children lived in places distant from the hospital and could not be monitored adequately with appropriate neuropsychological testing, especially in the Kerrigan team report.<sup>216</sup> With this limitation, it is noteworthy that a persistent major short-term memory deficit was described in 8% and 14% of the children. In the Barrow series, major weight gain was reported in 19% of the patients on short-term postoperative observation, but no reduction in the long-term observation. Diabetes insipidus was reported in 15% of the children in short-term and in 4% in long-term follow-up. Permanent hemianopia was observed in 4%. According to family perception, behavioral function was better in 88.5% of the patients operated on and worse in 3.8%. Kerrigan and coworkers found age, duration of the epilepsy, lesion size, and extent of resection to be predictors of complete seizure cessation after transcallosal resection of HH.<sup>216</sup> The mean percent resection in seizure-free patients was 90% versus 76% in non-seizure-free patients. The interhemispheric transchoroidal approach may be an interesting alternative to the transcallosal interforniceal one in reducing the risk for postoperative permanent memory deficit.

## **RADIOFREQUENCY THERMOCOAGULATION**

Stereotactic radiofrequency thermocoagulation was proposed by some authors for lesioning of HH instead of the direct microsurgical approach.<sup>199,217,218</sup> Because of the irregular conformation and close proximity to the normal hypothalamus, mammillary bodies, and visual pathways, direct lesioning with a stereotactic probe carries a certain risk. The interface between HH and the normal hypothalamus may also be unclear, so damage to perforating vessels “en passage” (e.g., thalamoperforating vessels) may be possible. Guthrie (personal communication, Montreal, 2001) reported on 12 patients who underwent thermocoagulation (mainly for small lesions). Of these 12 patients, only 3 were seizure free (25%) after thermocoagulation, thus demonstrating that this procedure is less successful than microsurgery or radiosurgery. Additionally, the author reported some transient complications in 2 patients (1 with transient third nerve palsy and 1 with a transient amnesic deficit) and a very severe complication in 1 (brainstem infarction). Finally, according to the author, the main disadvantages of this technique are blind passage of the probe, difficulty accessing the hamartoma, absence of control over the extent of the physical effect, and the theoretical requirement for multiple passes of the probe (implying greater increments of risk)

because of the complexity of shape and relationship to critical structures in the majority of cases. In addition, we know from the literature that a 1% to 2% risk for hemorrhage is associated with all insertions of a stereotactic probe into the brain.

### STIMULATION OF THE HYPOTHALAMIC HAMARTOMA

Other authors, such as the Grenoble team, proposed stimulation of the HH. The condition of the patient reported by this team was significantly improved after stimulation, but the severity of the side effects (weight gain) led them to renounce this therapy.<sup>219</sup> Sadikot and Dubeau reported a patient treated by implantation in both the anterior thalamus and the HH, with an unsatisfactory clinical result (Dubeau, personal communication, Montreal, 2001).

### VAGUS NERVE STIMULATION

Finally, left vagus nerve stimulation was reported by Murphy and colleagues in six children with HH and epilepsy.<sup>220</sup> In this small group, none of the patients were seizure free after stimulation; three were improved, but no significant improvement was seen in three. Brandberg and coauthors reported the Swedish experience, including five patients treated with this technique. In the five patients with implants, none demonstrated any kind of improvement.<sup>221</sup> This experience clearly indicates that vagus nerve stimulation is a palliative and poorly effective therapy in comparison to radiosurgery or microsurgery, in which almost all patients have their conditions improved and more than 50% become seizure free. This limitation in efficacy, cost, the requirement for changing the battery every 4 to 5 years, and the 3% risk for infection related to pacemaker implantation, in our opinion, must lead one to consider vagus nerve stimulation as only a second or third choice when radiosurgery, microsurgery, or both have failed or are contraindicated. However, in such circumstances there are several arguments in favor of vagus nerve stimulation instead of callosotomy. The efficacy of callosotomy is actually very limited,<sup>222</sup> surgical risk is high, and the effect on behavior and psychiatric symptoms is very poor. Conversely, in Murphy and coworkers' report of four patients with severe autistic behavior, all four were dramatically improved by intermittent stimulation.<sup>220</sup>

### INTERSTITIAL RADIOSURGERY

Interstitial radiosurgery has recently been proposed as an additional possible treatment of HH.<sup>223</sup> The Freiburg neurosurgical team has a large experience with the use of brachytherapy for a variety of neurosurgical conditions. This team has recently reported a series of seven patients with a relatively short follow-up. The efficacy of the treatment was quite poor, with a seizure cessation rate of just 28.6% (two of seven).<sup>223</sup> The authors have not reported any "major" permanent deficits up to the present in this series. The principle of interstitial radiosurgery is insertion of a seed of radioactive material (in this case <sup>125</sup>I) into the lesion. The advantage of this technique is the very reliable falloff of the radioisotopic dose. Its major limitation is the absence of any possibility of shaping of the field of irradiation. Because of the close vicinity of the mammillary body and fornix, this limitation forces the operator to undercover the part of the lesion surrounding these structures. This technical failure perhaps explains the very low rate of cessation of seizures and makes the method poorly adapted to the treatment of HH. On the contrary, GKRS allows the shaping of complex, very conformal irradiation fields and specific dose planning, thus making it more adapted to HH.

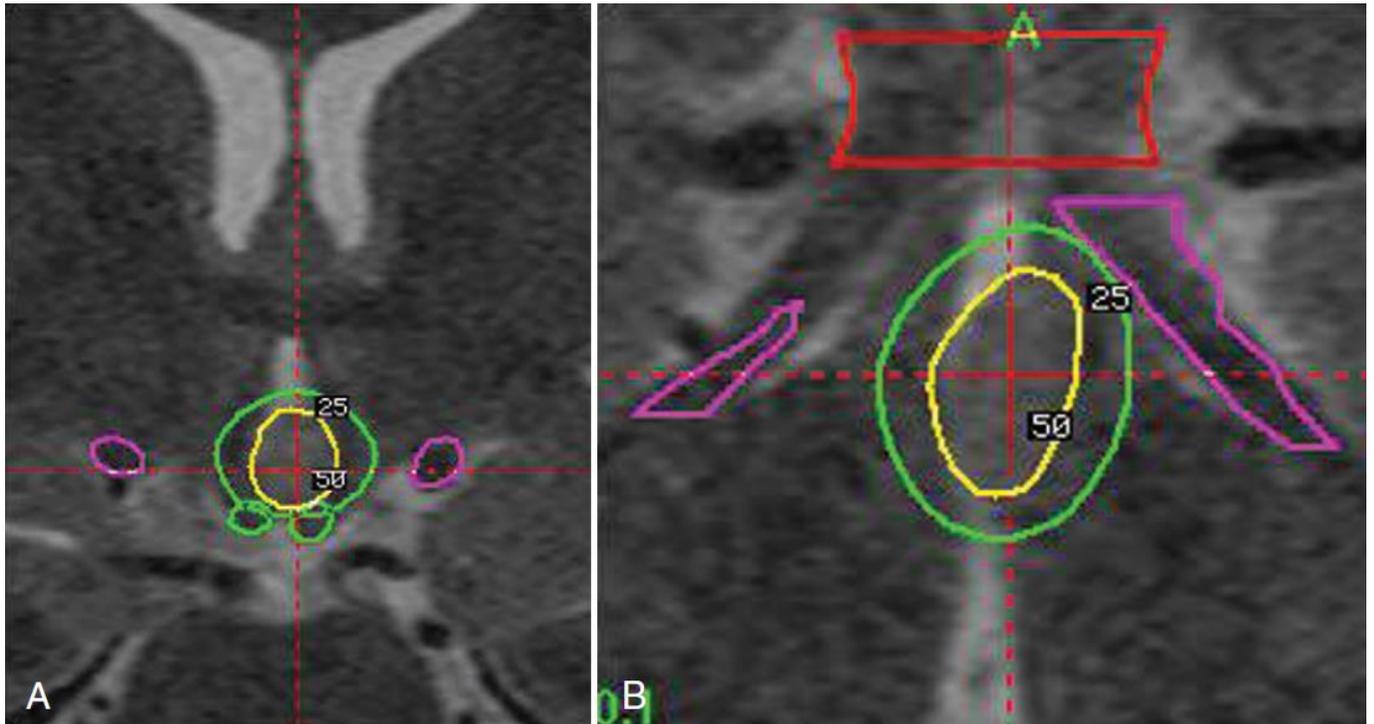
## RADIOSURGERY

- 4 cases of hypothalamic hamartoma epilepsy; 16-20 Gy at margins; no complications; 3 improved at 22 months, 2 reached Engel class II.

*2006 Mathieu et al. Stereotactic and functional neurosurgery, 2006, vol. 84, pp. 82-87*

We retrospectively analyzed the results of radiosurgery in a series of 10 patients from centers around the world.<sup>148</sup> The excellent safety-to-efficacy ratio (all improved, 50% cured, and no adverse effects except 1 patient with poikilothermia) led us to organize a prospective multicenter trial. Our series of 55 prospectively evaluated patients is unique in number and has been published in a preliminary report.<sup>185</sup> Satisfactory follow-up was available for 27 patients. The preoperative cognitive deficits, behavioral disturbances, and relationship of seizure severity and anatomic type to cognitive abilities were characterized.<sup>191</sup> The goal of the preoperative work-up was to adequately select candidates for inclusion and evaluate the patients' baseline neurological and endocrinologic function. All radiosurgical procedures were carried out with the Leksell 201-source Cobalt 60 Gamma Knife (Elekta Instrument, Stockholm). We consistently used multi-isocentric complex dose planning of high conformity and selectivity (Fig. 68-3). We used low peripheral doses to take into account the close relationship with the optic pathways and the hypothalamus (median, 17 Gy; range, 13 to 26 Gy). The lesions treated were generally small (median, 9.5 mm; range, 5 to 26 mm). We paid special attention to the dose delivered to the mamillary body and to the fornix, and we always tried to tailor the dose plan for each patient based on the use of a single run of shots with the 4-mm collimator. Patients were evaluated with respect to seizures, cognition, behavior, and endocrine status 6, 12, 18, 24, and 36 months after radiosurgery and then every year thereafter. Among these patients, 10 are seizure free (37%) and 6 are very much improved (22.2%) with a huge reduction in seizures (usually only rare residual gelastic seizures) associated with a dramatic improvement in behavior and cognition. Overall, an excellent result was obtained in 60% of the patients. According to our policy, the patient and family are offered a second radiosurgery in the event of a partial benefit when the lesion is anatomically small and well defined. Five patients (18.5%) with small hamartomas were only modestly improved and are being considered for a second session of radiosurgery. Two have reported no significant improvement up to the present. A microsurgical approach was performed in 4 patients (14.8%) with quite large HHs and poor efficacy of radiosurgery. Of these patients, 2 have been cured and 2 failed to respond. The radiosurgical treatment was carried out twice in 9 patients.

FIGURE 68-3 Typical good indication for radiosurgery for type II hypothalamic hamartoma according to our original classification. The marginal isodose (17 Gy) is displayed in yellow. The green line corresponds to the 25% isodose line and is illustrating the very good falloff in the dose gradient. The average number of seizures before radiosurgery was 300 per month. Five months after radiosurgery, the seizures have disappeared completely without any changes in magnetic resonance imaging.



## TOPOLOGIC CLASSIFICATION AND TREATMENT STRATEGY

- key feature in the decision-making process.

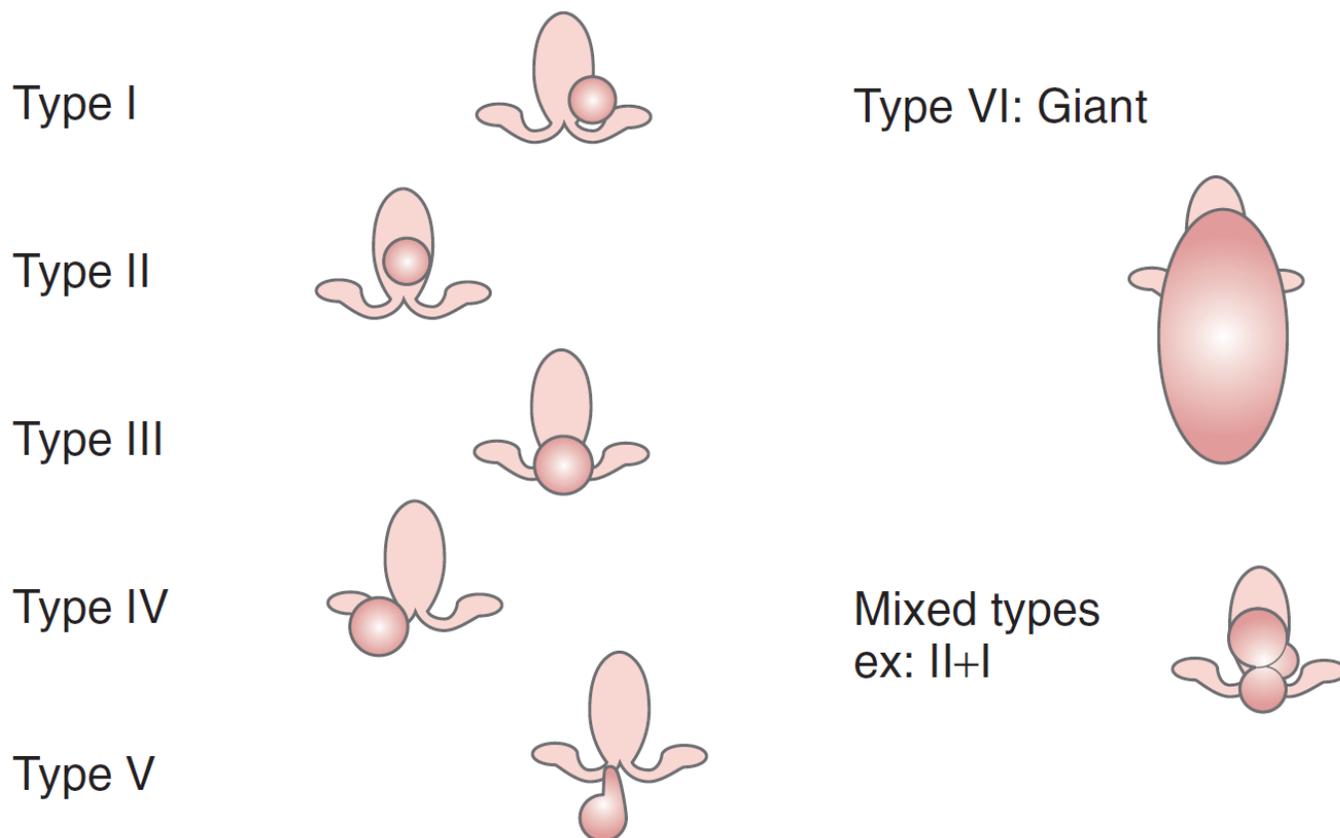
Delalande system

*Delalande O, Fohlen M. Disconnecting surgical treatment of hypothalamic hamartoma in children and adults with refractory epilepsy and proposal of a new classification. Neurol Med Chir. 2003;43(2):61-68.*

Regis system

*Régis J, Scavarda D, Tamura M et al. . Gamma knife surgery for epilepsy related to hypothalamic hamartomas. Semin Pediatr Neurol. 2007;14(2):73-79.*

Classification of hypothalamic hamartomas (clear correlation between symptoms and the subsequent clinical course - pertinent for clinical management):



*Régis J, Hayashi M, Eupierre LP, et al. Gamma knife surgery for epilepsy related to hypothalamic hamartomas. Acta Neurochir Suppl. 2004;91:33-50*

Previous classifications have been based on anatomic<sup>51,224,225</sup> or surgical<sup>51</sup> considerations. These classifications do not describe the large diversity of these lesions and their therapeutic consequences. As underlined by Palmieri and coworkers, the exact location of the lesion in relation to the interpeduncular fossa and the walls of the third ventricle correlates with the extent of excision, seizure control, and complication rate.<sup>211</sup> Accordingly, we classify HHs according to their topology based on our original classification.<sup>226</sup> In our experience, this classification correlates with clinical semiology and severity and is especially critical for selection of the surgical strategy. Type I lesions (small HHs located inside the hypothalamus and extending more or less into the third ventricle) are certainly the best candidates for GKRS. In this population the morbidity of microsurgical removal is likely to be potentially high. In type II lesions (when the lesion is small and mainly in the third ventricle), radiosurgery is certainly a safer alternative. Even though the endoscopic and transcallosal interforaminal approaches have been well described, the risks of short-term deterioration in memory, endocrinologic disturbance (hyperphagia with obesity, low thyroxin, disturbance in sodium metabolism), and thalamic or thalamocapsular infarcts have been reported even in the hands of highly skilled and experienced neurosurgeons. In exceptional cases of very severe recurrent status epilepticus, we recommend open surgery through either a transcallosal interforaminal approach or an endoscopic approach (depending on the width of the third ventricle). If the lesion is small and the third ventricle large, an endoscopic approach is chosen (see Fig. 68-3). In type III lesions (lesion located essentially in the floor), we prefer GKRS given the extremely close relationship between the mammillary body, the fornix, and the lesion. We speculate that sessile HHs always have more or less of an “extension” into the hypothalamus close to the mammillary body. Thus, when a lesion is classified as type II, it means that the lesion appears on MRI as though it is located in the third ventricle but is likely to have a “root” in the hypothalamus. The same assumption is made for type III lesions. In type IV lesions (the lesion is sessile in the cistern), disconnection can be discussed (pterional approach with or without orbitozygomatic osteotomy). However, if the lesion is small, GKRS can be recommended because of its safety and ability to simultaneously treat the small associated part of the lesion in the

hypothalamus itself, which is frequently visible on high resolution MRI. In Delalande and Fohlen's experience, just 2 of 14 patients were seizure free after a single disconnection through a pterional approach.<sup>51</sup> Consequently, we recommend this approach only for lesions too large for GKRS as a first step in a staged approach. In most circumstances, the patient is improved but not seizure free after the first surgical step, and GKRS is initiated at 3 months as a second step in the treatment. Type V lesions (pediculate) are rarely epileptic and can easily be cured by radiosurgery or disconnection through a pterional approach. In cases of severe epilepsy, the latter therapeutic modality will certainly allow faster cessation of seizures. However, distant extension of the HH into the hypothalamus close to the mammillary bodies must be carefully searched for on highresolution MRI, and discovery of such extension will eventually lead us to recommend GKRS so that both parts of the lesion can be treated, especially in cases in which the cisternal component is small. Type VI lesions (giant) are not good candidates for initial radiosurgery, and in nearly all patients a combination of several therapeutic modalities should be used. Even if GKRS does not seem to be suitable when the lesion is large, "radiosurgical" disconnection can be envisaged. Radiosurgically targeting only the superior part in the hypothalamus or the third ventricle (or both) with the lesion left lower than the untreated floor has been uniformly disappointing. In our opinion this strategy may result in loss of precious developmental time in which the child could be treated effectively. Consequently, we do not advocate such a strategy. When microsurgical resection has left a small remnant in the third ventricle and the patient is not seizure free, we recommend GKRS.

### **EFFECT OF GAMMA KNIFE RADIOSURGERY ON BEHAVIOR AND COGNITIVE FUNCTIONS**

The improvement was dramatic in nine of these patients. All the patients with paroxysmal aggressivity improved substantially. Increased alertness, elevated mood, and greater speech production were observed in some patients with excessive behavioral inhibition. A positive effect on sleep was frequently reported by the parents, especially in younger patients. Finally, dramatic developmental acceleration was observed in three young patients. Because of the very critical location of these lesions, we always try to tailor the dose plan for each patient based on the use of a single run of shots with the 4-mm collimator. We pay special attention to the dose delivered to the mammillary body and to the fornix.

### **LIMITS AND STRENGTHS OF RADIOSURGERY FOR HYPOTHALAMIC HAMARTOMA**

Two major questions remain. First, we know that complete treatment or resection of the lesion is not always necessary for control,<sup>213,227,228</sup> but we do not know how to predict in an individual patient the amount (and mapping) of the HH that must be treated to obtain a complete antiepileptic effect. Second, we know that these patients frequently have an electroclinical semiology that suggests involvement of the temporal or frontal lobe and that it can mimic a secondary epileptogenesis phenomenon.<sup>195,229</sup> In our experience, some of these patients can be cured completely by isolated treatment of the HH, whereas in others, a partial result is obtained, with residual seizures despite significant overall psychiatric and cognitive improvement. In this second group, it is tempting to propose that a secondary epileptogenic area is accounting for the partial failure. Our initial results indicate that GKRS is as effective as microsurgical resection with reduced morbidity. GKRS also avoids the vascular risk related to radiofrequency lesioning or stimulation. The disadvantage of radiosurgery is its delayed action. Longer follow-up is mandatory for proper evaluation of the role of GKRS. Results are obtained more quickly and are more complete in patients with smaller lesions inside the third ventricle (type II). The early effect on subclinical EEG discharges appears to play a major role in the dramatic benefit in sleep quality, behavior, and cognitive-developmental improvement. GKRS can safely lead to reversal of the epileptic encephalopathy. Because

of the poor clinical prognosis of the majority of patients with HH and the invasiveness of microsurgical resection, GKRS can now be considered a first-line intervention for small to middle-sized HHs associated with epilepsy because it can lead to dramatic improvements in these unfortunate young patients. The role of secondary epileptogenesis or widespread cortical dysgenesis in these patients needs to be further evaluated and understood to optimize patient selection and define the best treatment strategy.

#### Addendum from Youmans

**RADIOSURGICAL TREATMENT OF EPILEPSY ASSOCIATED WITH HYPOTHALAMIC HAMARTOMAS AND CAVERNOMAS** Once it is established that resection of a small, deeply seated lesion is associated with a significant risk for surgical complications or functional worsening (or both), GKRS must be discussed as an alternative. For these indications, GKRS frequently compares favorably with microsurgical removal in terms of safety, efficacy, and cost-effectiveness. The first radiosurgical treatments in epilepsy surgery were performed by Talairach in the 1950s.<sup>167</sup> Unlike Leksell, he already had expertise in epilepsy surgery and led one of the first large comprehensive programs for epilepsy surgery. As early as 1974, Talairach reported on the use of radioactive yttrium implants in patients with MTLE without space-occupying lesions and showed a high rate of seizure control in patients with epilepsies confined to the mesial structures of the temporal lobe.<sup>167</sup> In 1980, Elomaa<sup>165</sup> promoted the idea of the use of focal irradiation for the treatment of temporal lobe epilepsy based on the preliminary reports of Tracy, Von Wieser, and Baudouin.<sup>168,169</sup> Furthermore, clinical experience with the use of GKRS and LINAC-based radiosurgery for arteriovenous malformations and cortical-subcortical tumors (mostly metastases and low-grade glial tumors) revealed an anticonvulsive effect of radiosurgery in the absence of tissue necrosis.<sup>138,170,171</sup> A series of experimental studies in small animals confirmed this effect<sup>134,172</sup> and emphasized a relationship to the dose delivered.<sup>153,154</sup> Barcia Salorio and colleagues and later Lindquist and coauthors reported on a small and heterogeneous group of patients treated by radiosurgery for the purpose of alleviating seizures. However, their data were poor<sup>173-175</sup> and unfortunately were never published in peer-reviewed papers, so precise data are unavailable. The Department of Functional Surgery in Marseille is a major referral center for epilepsy surgery and radiosurgery and has reported the first comprehensively evaluated series of MTLE successfully treated by GKRS. The first use of GKRS for MTLE took place in 1993 and was reported in 1995 by this group.<sup>145</sup> Several prospective trials by this group have demonstrated (1) the safety and efficacy of this approach,<sup>121,146</sup> (2) a very specific timetable for the clinical and radiologic events,<sup>146,176</sup> (3) the importance of the anterior parahippocampal cortex for seizure cessation,<sup>177,178</sup> (4) the importance of the marginal dose (24 Gy) for efficacy,<sup>178</sup> (5) sparing of verbal memory in dominant-side epilepsy,<sup>121</sup> and (6) the nonlesional mechanism of action of radiosurgery.<sup>179</sup> Recently, all these findings have been confirmed by a prospective trial in the United States.<sup>180</sup> Since 1993, among a total of 8590 GKRS procedures, the Marseille group performed GKRS for epilepsy in 155 patients. The majority of these patients had MTLE (56 patients) or hypothalamic hamartoma (HH, 55 patients). The rest of the patients suffered from severe epilepsy associated with small benign lesions such as cavernous malformations (CMs), for which the epileptic zone was considered to be confined to the surrounding cortex.<sup>181</sup> Cessation of seizures may be generated by a specific neuromodulatory effect of radiosurgery, without induction of a significant amount of histologic necrosis.<sup>145,176,179,182,183</sup> Selection of the appropriate technical parameters (e.g., dose, volume target) that allow us to accurately achieve the desired functional effect without histologic damage remains an important challenge. A review of these cases, as well as other clinical and experimental data, suggests that the use of radiosurgery is beneficial only in patients in whom a strict preoperative definition of the extent of the epileptogenic network has been achieved<sup>184</sup> and in whom strict rules of dose planning have been followed.<sup>178</sup> The strategy is to identify patients in whom the safety-to-efficacy ratio makes radiosurgery advantageous or at least comparable to craniotomy and cortectomy. In patients with HH, GKRS offers very low morbidity with efficacy similar to that of microsurgical alternatives.<sup>148,185</sup> This has led us to systematically consider radiosurgery as the first-line

treatment in patients with limited type I, II, and III and possibly type IV HH. 185 Patients with CMs and a longer duration of epilepsy are thought to have a more widespread epileptogenic zone involving distant cortical structures. 186-188 In patients with seizures arising from eloquent cortex surrounding the lesion, GKRS appears to be a suitable alternative. It is essential that electroclinical correlation be established for this strategy to work. Microsurgical excision remains the preferred approach for cortical-subcortical epileptogenic CMs that are not located in functional cortex.

“Intrahypothalamic” hypothalamic hamartomas (HH) may be associated with intractable partial, gelastic, and generalized seizures, 251 as well as retardation and behavioral disorders, whereas precocious puberty predominates in the “parahypothalamic” subset. 252 Although several reports have documented successful surgical removal of these lesions and relief of seizures with transcallosal or modified subfrontal approaches, 253 such intrahypothalamic surgery raises concern regarding complications of the approach, as opposed to direct intrahypothalamic resection of these lesions. A recent study reported the results of transcallosal surgical resection of HH in 26 patients with refractory epilepsy in a prospective outcome study. 254 Fourteen (54%) patients were completely seizure free, and 9 (35%) had at least a 90% improvement in total seizure frequency. They also reported postoperative improvement in behavior and cognition. The likelihood of a seizure-free outcome seemed to correlate with younger age, shorter lifetime duration of epilepsy, smaller preoperative HH volume, and 100% HH resection. Another recent study looked at 37 patients with HH and symptomatic epilepsy who underwent transcortical transventricular endoscopic resection. 255 Eighteen patients (48.6%) were seizure free. Seizures were reduced more than 90% in 26 patients (70.3%) and by 50% to 90% in 8 patients (21.6%). Additionally, the mean postoperative hospital stay may be shorter in endoscopic patients than in patients who undergo transcallosal resection.

## ULEGYRIA

- **fusion of layer 1 at depths of sulci** (with relative sparing of crests of gyri\*) → narrow distorted gyri.
  - \*gyrus in cross section - *mushroom appearance* (scarring at depth of sulcus and sparing at brain surface).
- associated with **neuronal loss, obliteration of cortical lamination** and **gliosis** in cortex.
- very well-defined borders and discrete islands of preserved neurons within lesion.
- frequently located in arterial zone - ulegyria arises **late in gestation or in early neonatal life** as **vascular injury** to immature cortex (e.g. *hypoperfusion*).
- clinically:
  - a) silent
  - b) seizures.

## SCHIZENCEPHALY

- **cleft within cerebral hemisphere** lined with **gray matter** (vs. *PORENCEPHALY* – lined with white matter).
  - etiology - **focal destructive lesion** (entire cerebral mantle is affected) early in brain development, **before major neuronal migrations** (abnormality of morphogenesis).
  - *cleft extends* from pial surface (subarachnoid space) to lateral ventricle.
  - **lining gray matter** is abnormal (often *polymicrogyria* pattern).
    - cortex lining cleft is not continuous at ependymal end of cleft (vs. primitive sylvian fissure seen in some brain malformations – has continuous abnormally thick cortex beneath prominent cleft).

- cleft borders may be surrounded by abnormal brain (esp. *microgyria*).
- forms:
  - a) **closed lip** (type 1) - growing edges come into contact.
  - b) **open lip** (type 2) - widely patent cleft - result of involvement of greater brain volume (worse prognosis).
- unilateral or bilateral.
- usually located in central region.
- clinically:
  - 1) contralateral **hemiparesis** (spastic quadriplegia when clefts are bilateral)
  - 2) temporal lobe **seizures**
  - 3) severe **mental retardation, microcephaly**.
- CT clearly demonstrates size and extent of cleft.
- treatment – seizure control (e.g. **anterior temporal lobectomy** for unilateral schizencephaly)

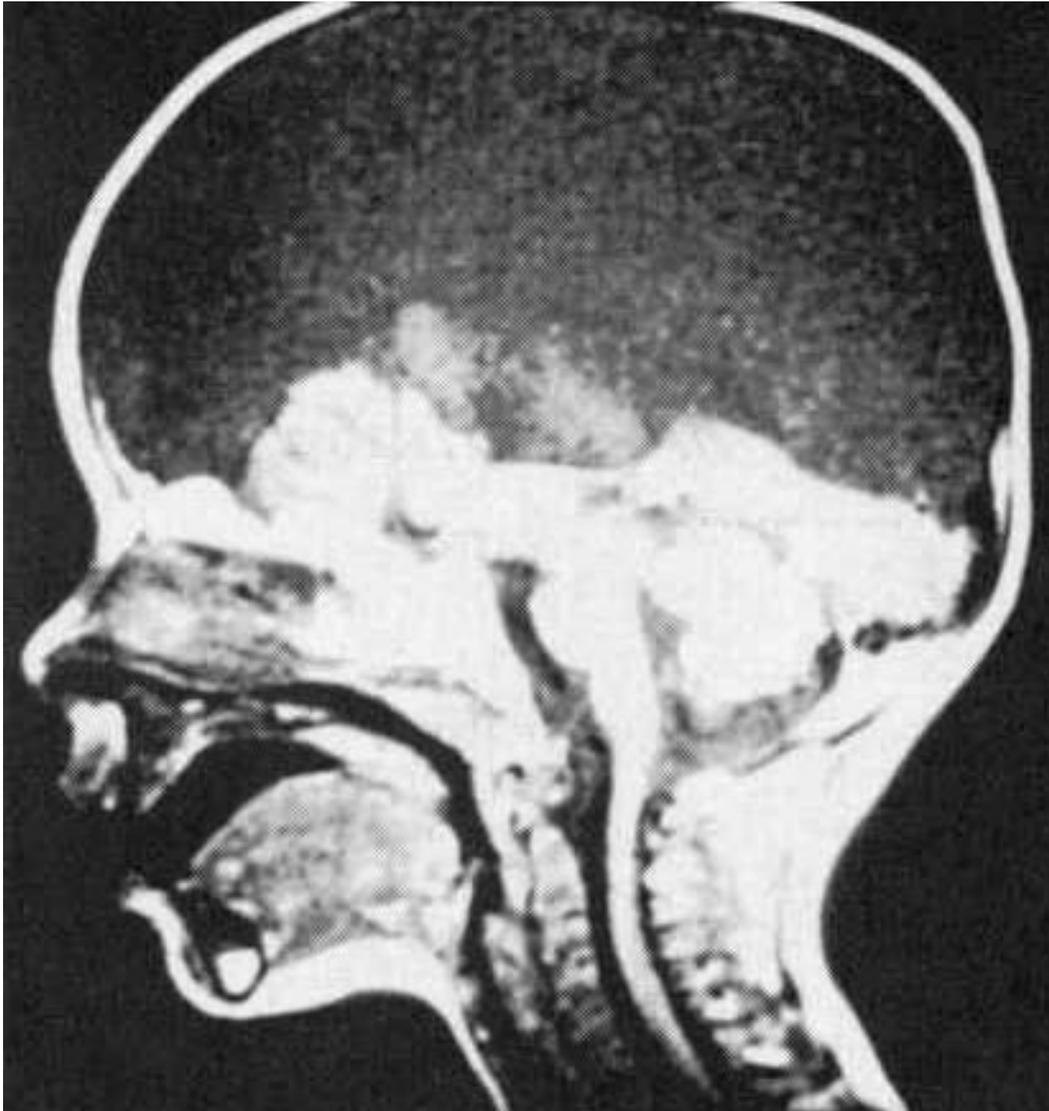
## PORENCEPHALY

- **cyst in cerebral hemisphere** that *communicates* with lateral ventricle and / or subarachnoid space; lined with **white matter** (vs. *SCHIZENCEPHALY* – lined with gray matter).
  - most frequently located in region of sylvian fissure.
  - etiology – **perinatal (pre- or post-natal) insult** (i.e. destructive process after brain has formed) – ischemia, intraventricular hemorrhage with parenchymal extension, inflammatory disease.
  - clinically (few patients develop only minor neurologic signs and have normal intelligence): seizures, spastic quadriplegia, mental retardation, optic atrophy.
  - diagnosis is confirmed by **CT** or **ultrasound**.
  - treatment – seizure control (e.g. **anterior temporal lobectomy** for unilateral porencephaly); progressive hydrocephalus may require shunt.

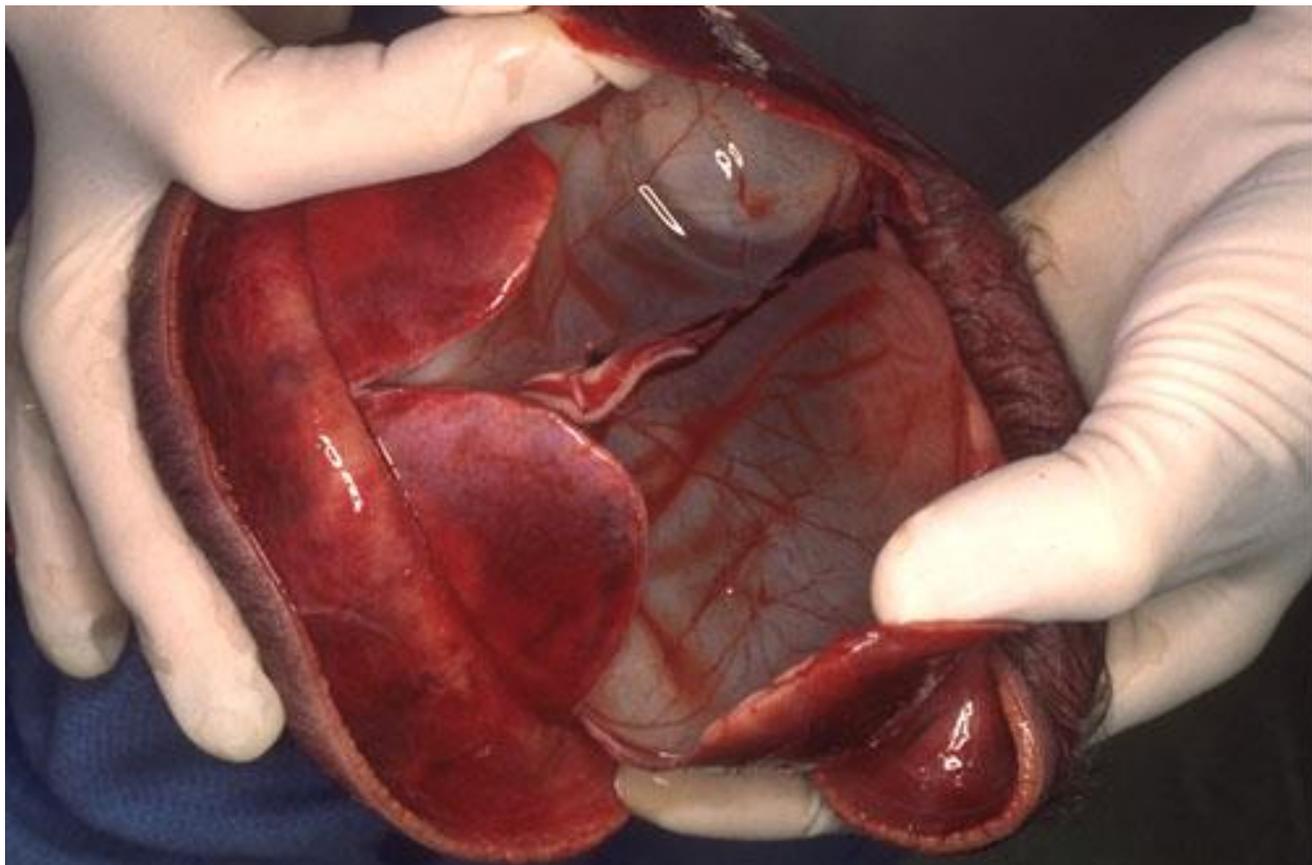
## HYDRANENCEPHALY

- **extreme form of porencephaly** - **cerebral hemispheres are almost totally absent** (or represented by membranous sacs with remnants of frontal, temporal, or occipital cortex dispersed over membrane).
  - **basal ganglia, cerebellum** and **brain stem** are intact.
  - **cranial vault** (meninges, bones, and skin) is normal.
  - etiology - **bilateral occlusion of internal carotid arteries** during early fetal development.
  - clinically (findings are subtle):
    - externally, head appears normal or enlarged, but **when transilluminated, light shines completely through!!!** (may be confused with hydrocephalus)
    - infant **fails to develop normally** (irritable, feeds poorly, seizures, spastic quadriplegia, little or no cognitive development).
  - diagnosis is confirmed by CT or ultrasound.
  - treatment is supportive; shunting if head growth is excessive.

**Hydranencephaly** - MRI shows brain stem and spinal cord with remnants of cerebellum and cerebral cortex; remainder of cranium is filled with CSF:



**Hydranencephaly** (3<sup>rd</sup> trimester stillborn fetus) - skull is opened - all that is left is thin rim of cortex or glial tissue with meninges surrounding a fluid-filled cavity:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

## MEGALENCEPHALY (s. MACROENCEPHALY)

- **enlarged brain volume** (white and gray matter volume↑):

- a) brain weight **2.5 standard deviations** above mean for sex and age.
  - b) brain weight > **1600 g**.
- diffuse broadening of cerebral gyri.
  - normal-sized ventricles.
  - brain is usually microscopically normal.

### ETIOLOGY

#### A. Isolated:

- a) **sporadic**
- b) **autosomal dominant (familial megalencephaly)** - majority of cases are neurologically normal! (delayed motor milestones and hypotonia but normal or near-normal intelligence)
- c) **autosomal recessive**

#### B. Part of recognized syndrome:

##### 1. Neurocutaneous syndromes:

- 1) neurofibromatosis 1
- 2) tuberous sclerosis
- 3) proteus syndrome
- 4) Klippel-Trenaunay-Weber syndrome
- 5) Riley-Smith syndrome
- 6) Shapiro-Shulman syndrome
- 7) linear sebaceous nevus syndrome

2. **Generalized overgrowth syndromes:**
  - 1) Sotos' syndrome (s. cerebral gigantism)
  - 2) Ruvalcaba-Myhre-Smith syndrome
  - 3) Beckwith-Wiedemann syndrome
  - 4) Weaver's syndrome
  - 5) Bannayan-Zonana syndrome
3. **Metabolic disorders** (i.e. neuronal storage disorders):
  - 1) leukodystrophies (Alexander's disease, Canavan's disease)
  - 2) GM<sub>1</sub> and GM<sub>2</sub> gangliosidosis
  - 3) glutaricaciduria type 1
  - 4) mucopolysaccharidoses

### CLINICAL FEATURES

- **progressive brain enlargement** with **deterioration of neurologic function**.

**Sotos' syndrome (s. cerebral gigantism)** - primary megalencephaly (may be autosomal dominant) with:

- 1) macrocephaly, dolichocephaly
- 2) acromegaly (hypertelorism, macroglossia, prognathism)
- 3) progressive mental retardation, seizures

**FG syndrome** - megalencephaly with:

- 1) facial dysmorphism
- 2) imperforate anus
- 3) joint and hand deformities
- 4) occasional hydrocephalus, agenesis of corpus callosum, intestinal abnormalities, sensorineural deafness, cardiac and genitourinary defects.

## HEMIMEGALENCEPHALY

- **abnormally large one cerebral hemisphere**.

- **MACROSCOPICALLY** - regions of pachygyria / polymicrogyria, thickened cerebral cortex, frequent heterotopia in cerebral white matter.
- **MICROSCOPICALLY** - **marked disorganization** (neurons abnormally spaced and disorganized in orientation).

### ETIOLOGY

- A. **Isolated**
- B. **Part of recognized syndrome** (most commonly - *Beckwith-Wiedemann syndrome*, *linear sebaceous nevus syndrome*).

Association of hemimegalencephaly with **Wilms' tumor of kidney!**

### CLINICAL FEATURES

- 1) intractable focal seizures or infantile spasms during first year of life → **mental retardation**.
  - 2) **body asymmetries** (esp. skull and face), hemihypertrophy.
  - 3) **asymmetries of motor development** (subtle ÷ frank hemiparesis).
- patients with well-controlled partial seizures and normal development & intelligence have been reported.

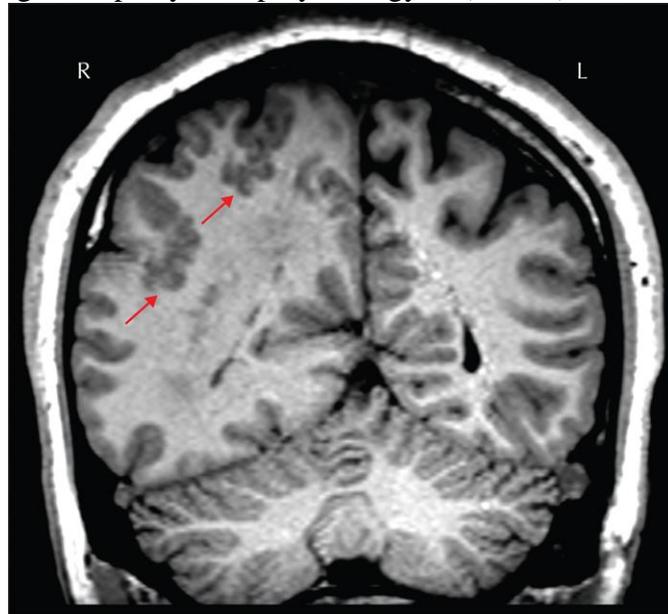
**DIAGNOSIS**

**MRI** - larger hemisphere;

- thickening of cortical mantle and poor demarcation from subcortical white matter.
- coarse gyrations with wide sulci.
- underlying white matter with defective or delayed myelination - hyperintense on T2 images, and dark on CT.

**EEG** - fast rhythmical pattern in  $\alpha \div \beta$  range, burst-suppression patterns, spike-wave or repetitive triphasic complexes.

Right hemimegalencephaly with polymicrogyria (arrows):

**TREATMENT**

- difficulties of medical seizure control (ongoing seizures have adverse effects for developmental outcome) → **early anatomic or functional hemispherectomy**.

**MICROENCEPHALY**

- disturbed normal neuronal proliferation → **brain of abnormally low weight**.

A. **Isolated** (very rare)

B. **Component of other malformations** (lissencephaly, pachygyria, fetal alcohol syndrome).

Micrencephaly accompanies microcephaly!

**Posterior Fossa anomalies**

- anomalies of **brainstem & cerebellum** development.

**JOUBERT'S syndrome** see p. Mov50 >>

**MÖBIUS' syndrome** see p. CN7 >>

**DIAGNOSIS**

Imaging posterior fossa is best done with **MRI!**

- diagnosis of cerebellar / pontine hypoplasias can be difficult in mild cases (requires *age-matched controls*).
- **screening for additional malformations** may lead to syndrome diagnosis (*ultrasound of heart and internal organs, skeletal radiographic survey, and ophthalmological evaluation* are recommended).

**CHIARI malformations**

- collection of various (different etiopathophysiology) *posterior fossa / hindbrain malformations* (described by Chiari in 1890s), each characterized by **displacement of cerebellum**.

- **Julius Arnold** (1835–1915) discussed a patient with hindbrain herniation and myelodysplasia in 1894.
- in 1891 and 1896, **Dr. Hans Chiari** (1851–1916), professor of pathologic anatomy at the German University in Prague, used autopsy specimens to describe hindbrain herniation in four congenital anomalies later termed the Chiari malformations (types I to IV)
- no unifying pathophysiology.
- more frequently recognized with increased use of MRI.
- important feature – *disturbed CSF flow across foramen magnum* (best demonstrated by **cine MRI**) → *development of hydromyelia* due to a “water hammer” effect caused by blockage of the foramen of Magendie.
- main treatment – only for symptomatic cases – restoring normal CSF dynamics across craniocervical junction.

| Associated anomaly       | Chiari 0 | Chiari I | Chiari 1.5 | Chiari II           |
|--------------------------|----------|----------|------------|---------------------|
| Hydrocephalus            |          | 7-9%     | ±          | +                   |
| Supratentorial anomalies |          |          |            | +                   |
| Cerebellar herniation    |          | Tonsills | Tonsills   | Vermis, hemispheres |
| Brainstem herniation     |          |          | +          | +                   |
| Syringomyelia            | 100%     | 30-75%   | +          | 40-95%              |
| Myelomeningocele         |          |          |            | +                   |

Chiari 0 may have crowded posterior fossa without hindbrain herniation

Chiari III - foramen magnum / high cervical encephalocele

Chiari IV - cerebellar hypoplasia or aplasia

**CHIARI I malformation**

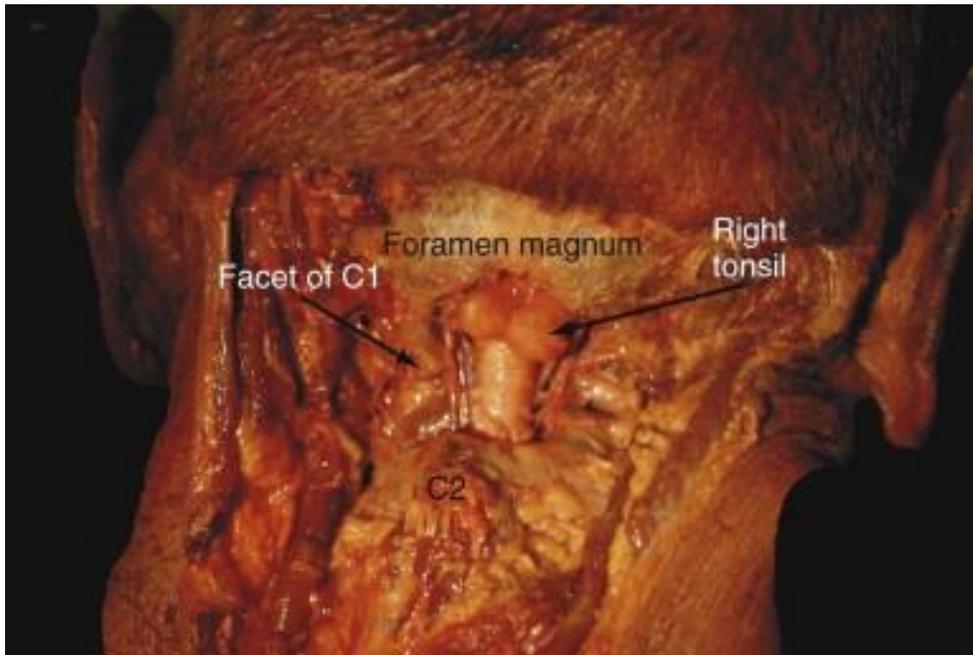
- **displacement of cerebellar TONSILS\*** over cervical spinal cord, i.e. ectopia of cerebellar tonsils at least **5 mm below plane of foramen magnum** [McCrae’s basion-opisthion line].

\*vs. cerebellar VERMIS & INFERIOR HEMISPHERES plus BRAINSTEM – in Chiari II

- EMBRYOLOGIC ORIGIN at later stage than more severe Chiari II malformation.
- PATHOGENESIS is unknown (obstruction of caudal portion of fourth ventricle during fetal development?).

N.B. tonsillar displacement may be in ACQUIRED HERNIATION – raised ICP (tumors, venous hypertension), lowered intraspinal pressure (lumboperitoneal shunts), conditions that diminish posterior fossa volume (craniosynostosis, basilar invagination) – cause **tonsillar coning**.

- Chiari I lesion used to be distinguished from coning, by **shape of herniated tonsils**, which were said to be **rounded in coning** and **pointed in Chiari**, but it is now clear that there are no grounds for distinguishing between two conditions.
- in 50% cases, **medulla oblongata shows elongation**, obex of 4<sup>th</sup> ventricle coming to lie in cervical canal (where it may or may not be overlain by cerebellar tonsils); elongation is sufficient to produce **kink on posterior surface of medulla oblongata** (tail of 4<sup>th</sup> ventricle rolls down over upper segments of spinal cord).
  - N.B. Chiari I does not have brainstem herniation (if yes, it is Chiari II)
- **syringomyelia coexists in 30-75% cases!** (due to CSF flow obstruction at craniocervical junction).
- not associated with myelomeningocele or hydrocephalus.
- normal posterior fossa.
- associated with **skull base anomalies** (most frequently basilar impression), **craniocervical junction anomalies** (Klippel-Feil anomaly, atlanto-occipital assimilation).



Source of picture: H. Richard Winn "Youmans Neurological Surgery", 6th ed. (2011); Saunders; ISBN-13: 978-1416053163 >>

## CLINICAL FEATURES

N.B. clinical picture is broad and varied! 15-30% patients are **asymptomatic**

- usually **manifests** in teen ÷ early adult years (or even later).
  - average age at presentation is 41 years (range: 12-73 yrs).
  - slight female preponderance (female:male = 1.3:1).
- **initial complaint** is often nondermatomal **neck pain**, **headaches** accentuated by Valsalva (straining, sneezing, cough) or neck extension.
- impairment of **brain stem** and **cerebellar tonsils**:
  - a) medullary compression at level of foramen magnum
  - b) extension of syrinx into brain stem (syringobulbia)

- **eye movement abnormalities** (oscillopsia, various forms of nystagmus\*).
  - \*esp. characteristic *downbeating nystagmus accentuated by lateral downgaze* - alert to potential problem at craniocervical/pontomedullary junction.
- **lower cranial nerve impairment** (dysphagia, aspiration, sleep apnea, stridor, feeding difficulties); syringobulbia may involve up to cranial nerve V.
- imbalance and **vertigo** with truncal **ataxia**.
- impairment of **cervical spinal cord**:
  - **myelopathy**
  - **hydrosyringomyelia (central cord syndrome)**: upper extremity numbness and loss of pain and temperature sensation, lower extremity spasticity, progressive levoscoliosis\* (relatively common manifestation!), etc. see p. Spin5 >>
    - \*adolescent idiopathic scoliosis is dextroscoliosis

**DIAGNOSIS**

Diagnosis requires **absence of** intracranial mass lesion, Dandy-Walker malformation, or hydrocephalus, all of which may cause tonsillar displacement secondary to raised ICP

**Plain films** are usually normal.

**MRI** (**imaging modality of choice**, esp. sagittal images): for MRI samples see p. Spin5 >>

T2 + CINE + CISS (FIESTA) through foramen magnum ± screening panspinal MRI

- 1) **compressed tonsils extending through foramen magnum into cervical subarachnoid space** (i.e. tongue of pointed tonsils extending over cervical spinal cord).
  - 2) **elongation and kinking of medulla oblongata**.
  - 3) **vermis** is intact (no displacement).
  - 4) **obstructed CSF flow** at foramen magnum.
- routine MRI discovers numbers of asymptomatic Chiari I and syringomyelia cases.
  - **significance of low-lying tonsils**:
    - *tonsils normally retract upward with age*, so their location must be interpreted in age-dependent context:

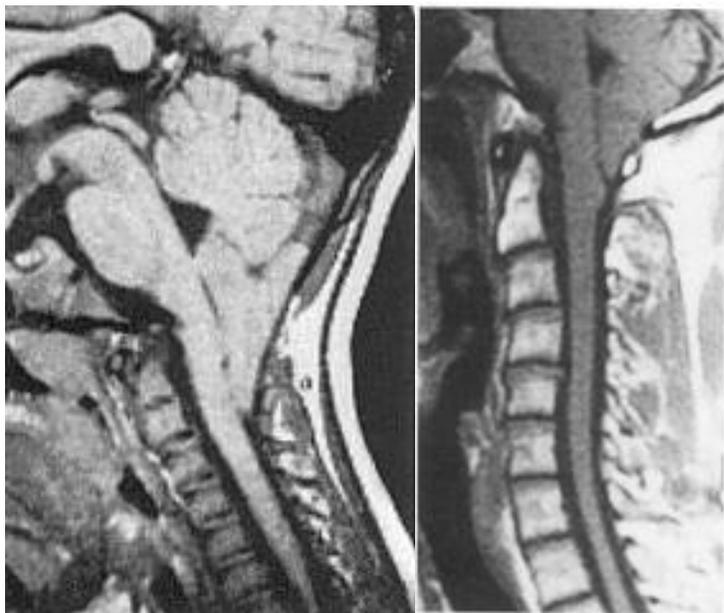
0-10 yrs ≤ 6 mm below level of foramen magnum; 10-30 yrs, ≤ 5 mm; after 30 yrs, ≤ 4 mm.

- 30% cases with significant displacements (5-10 mm) are asymptomatic.
- herniations > 12 mm are almost invariably symptomatic.

Tonsillar position relative to foramen magnum at various ages:

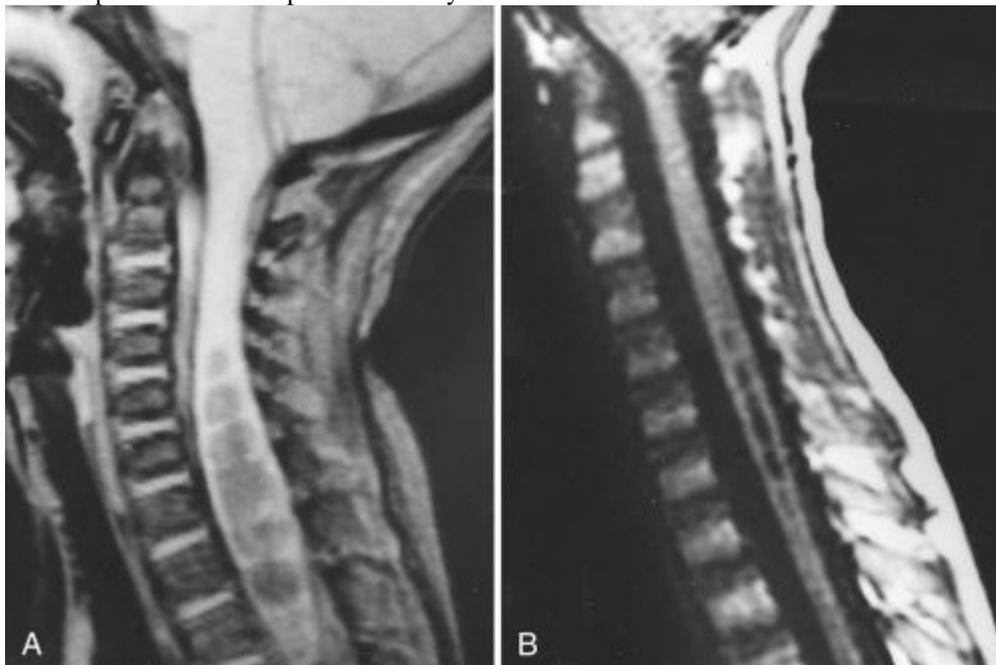
| Age (years) | Normal (mm)* | 2 S.D.† (mm) |
|-------------|--------------|--------------|
| 0-9         | -1.5         | -6           |
| 10-19       | -0.4         | -5           |
| 20-29       | -1.1         |              |
| 30-39       | 0.0          | -4           |
| 40-49       | 0.1          |              |
| 50-59       | 0.2          |              |
| 60-69       | 0.2          |              |
| 70-79       | 0.6          |              |
| 80-89       | 1.3          | -3           |

\* negative number indicates distance below FM  
 † S.D. = standard deviation. Descent > 2 S.D. beyond normal is suggested as a criteria for tonsillar ectopia



A. Child with Chiari I malformation and preoperative syrinx.

B. Postoperative MRI - improvement of syrinx:



Source of picture: H. Richard Winn "Youmans Neurological Surgery", 6th ed. (2011); Saunders; ISBN-13: 978-1416053163 >>

## TREATMENT

- **decompressing structures trapped in foramen magnum** (i.e. posterior fossa decompression):

- 1) wide **suboccipital craniectomy**
- 2) **cervical laminectomies** to level below herniated tonsils (usually involving C1).
- 3) **management of dura:**
  - a) **duraplasty (dural patch grafting)**; dura is opened; arachnoid is densely adherent to anomalous structures - dissection of these adhesions (under high-power magnification).
  - b) superficial dural **splitting**
  - c) do **nothing** → higher reoperation rates (12.6% vs 2.1%) but lower rate of CSF-related complications (1.8% vs 18.5%)

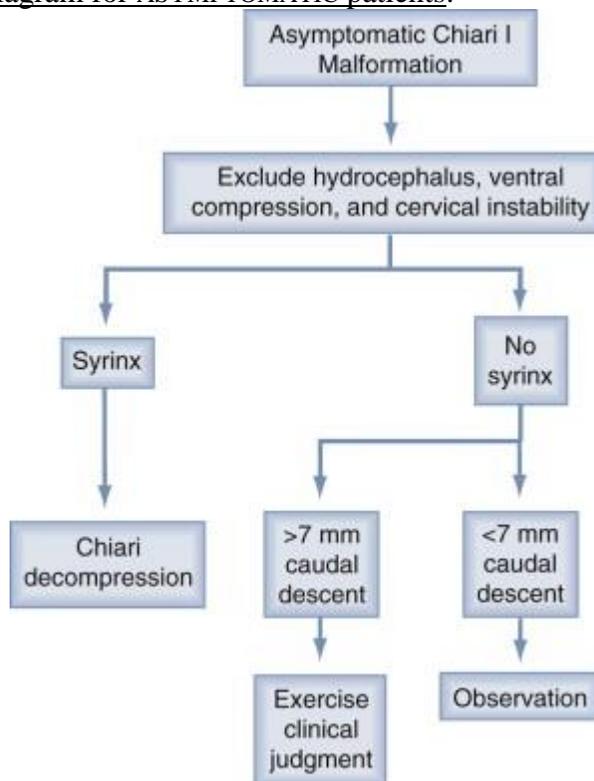
Historical procedures that have been appended to the above (by current recommendations these are usually not warranted):

- plugging of obex with muscle or Teflon.
- Silastic stent placement into 4th ventricle (to improve CSF outflow into basal cisterns and subarachnoid space → resolution of hydromyelia)
- drainage of syrinx if present (fenestration, usually through dorsal root entry zone, with or without stent or shunt);  
     *syrinx cavities* may shrink / resolve postoperatively without further intervention (very large syrinx cavities require drainage into subarachnoid space)
- 4th ventricular shunting, terminal ventriculostomy, opening foramen of Magendie if obstructed if **hydrocephalus** coexists, it should be resolved before consideration of Chiari decompression.

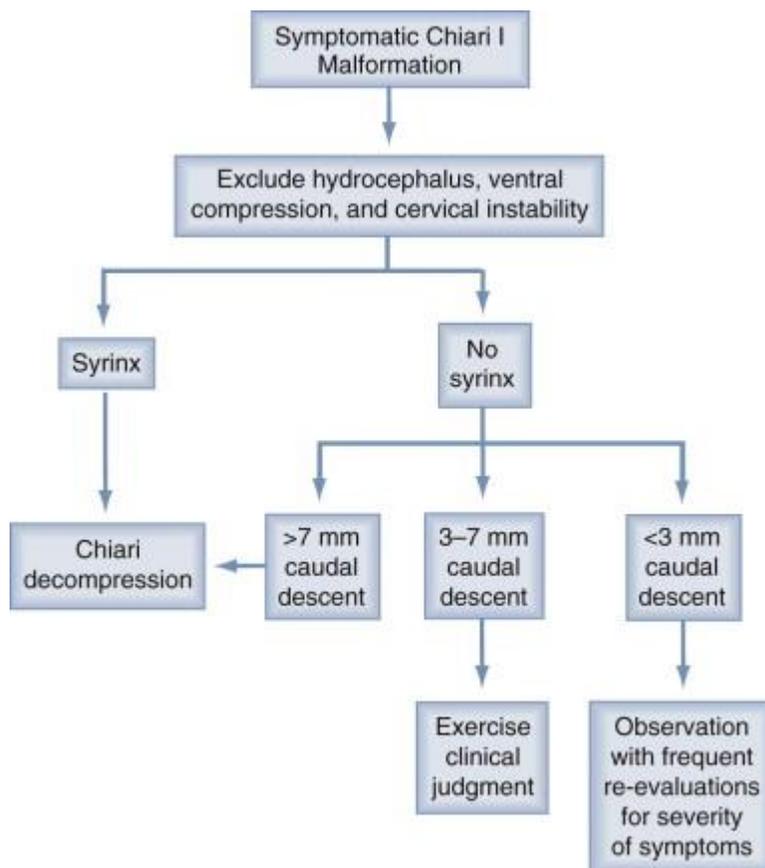
### Indications for surgery

- A. **Syrinx** (however, < 2 mm asymptomatic syringes can be safely followed with serial examinations and imaging q6mos)
- B. **Symptoms**:
  - a) lifestyle-limiting **occipital Valsalva-induced headaches** refractory to multidisciplinary management.
  - b) objective **brainstem dysfunction** (esp. respiratory or cranial nerve dysfunction)
  - c) progressive scoliosis.

Flow diagram for ASYMPTOMATIC patients:



Flow diagram for SYMPTOMATIC patients:



### Surgical Details

- see p. Op300 >>

### Postoperatively

- may place into ICU overnight
- may continue dexamethasone for 4 8hrs

### Follow up

- patients with **preoperative syrinx** receive follow-up MRI in 6 to 12 months:
  - if symptoms improve or syrinx decreases in size significantly (usually by third month postop) → **no further imaging**
  - if syrinx improves minimally → **additional imaging** (as long as syrinx progressively shrinks and no additional symptoms or signs occur, no matter how slowly, continue to follow patient conservatively with imaging).
  - if syrinx fails to improve or symptoms referable to persistent syrinx are present → **second surgery** (reexploration is preferred to myelotomy and syringosubarachnoid drainage).

### Complications

- **CSF leak**: keep HOB up, suture wound if leak is external → lumbar drain → revision → VP shunt.  
Full discussion – see p. S64 >>
- **aseptic meningitis** (from subdural blood) - treated with 7-10 days of high-dose steroids, including a steroid taper;
  - recurrent aseptic meningitis occasionally responds to serial lumbar puncture in combination with steroid administration.

- in patients who initially improved clinically and radiographically with decompression, and then worsened, most likely explanation is **reclosure of outlet foramen** - will respond to repeat decompression and possibly resection of portion of tonsil.
- **cerebellar slump / ptosis** - complication unique to posterior fossa craniectomies - results from extending craniectomy so far laterally that *cerebellum herniates through craniectomy defect*.
  - can cause headaches (different from typical Chiari I headaches), obstruction of CSF flow with syrinx formation, and variety of motor, sensory, and cranial nerve deficits.
  - cranioplasty to buttress cerebellum into place is most definitive treatment. Simple shunting is not adequate!
- 1-9% pediatric patients develop **hydrocephalus** (may be accompanied by syrinx worsening); needs shunting (vs. acetazolamide, temporary EVD, or ETV that might be effective in a very few selected cases); redo decompressions and intradural explorations usually fail to control HCP.

### PROGNOSIS

- prognosis is worse if symptoms preoperatively lasted > 2 years.

**Table 8-12 Long-term follow-up after surgery for Chiari I malformation (69 patients, 4 years mean F/U<sup>65</sup>)**

|                                      |     |
|--------------------------------------|-----|
| early improvement of pre-op symptoms | 82% |
| percent of above that relapsed*      | 21% |
| early improvement of pre-op signs    | 70% |
| no change from pre-op status         | 16% |
| worse than pre-op                    | 0   |

\* these patients deteriorated to pre-op status (none deteriorated further) within 2-3 years of surgery; relapse occurred in 30% with foramen magnum compression syndrome, and in 21% with central cord syndrome

### Incidental CM-I followed with watchful waiting

*When Does an Incidental Chiari I Malformation Require Surgery? A 10-Year Prospective Study on the Evolution and Natural History* Hepzibha Alexander, Deki Tsering, John S Myseros, MD, Suresh N Magge, MD, Chima Oluigbo, MD, Carlos E Sanchez, MD, Robert F Keating, MD *Neurosurgery*, Volume 66, Issue Supplement\_1, September 2019, nyz310\_201, [https://doi.org/10.1093/neuros/nyz310\\_201](https://doi.org/10.1093/neuros/nyz310_201) Published: 20 August 2019

- relatively benign natural history, however, careful and longterm follow-up, particularly during the first 3 yr after diagnosis is critical - 9.9% of patients are likely to experience a change in clinical or radiographic status necessitating surgical intervention.

### OBSTETRIC CONCERNS

- CM-1 is of a significant clinical concern in pregnant patients, first because of physiological increase in CSF pressure associated with pregnancy, and second because delivery represents a vulnerable period with acute increase in ICP (pain + “pushing” during labor increases CSF pressure by approximately 20–51 mmHg).

- Meadows *et al.* study: asymptomatic or minimally symptomatic advanced CM-1 can lead to catastrophic consequences during labor and delivery.

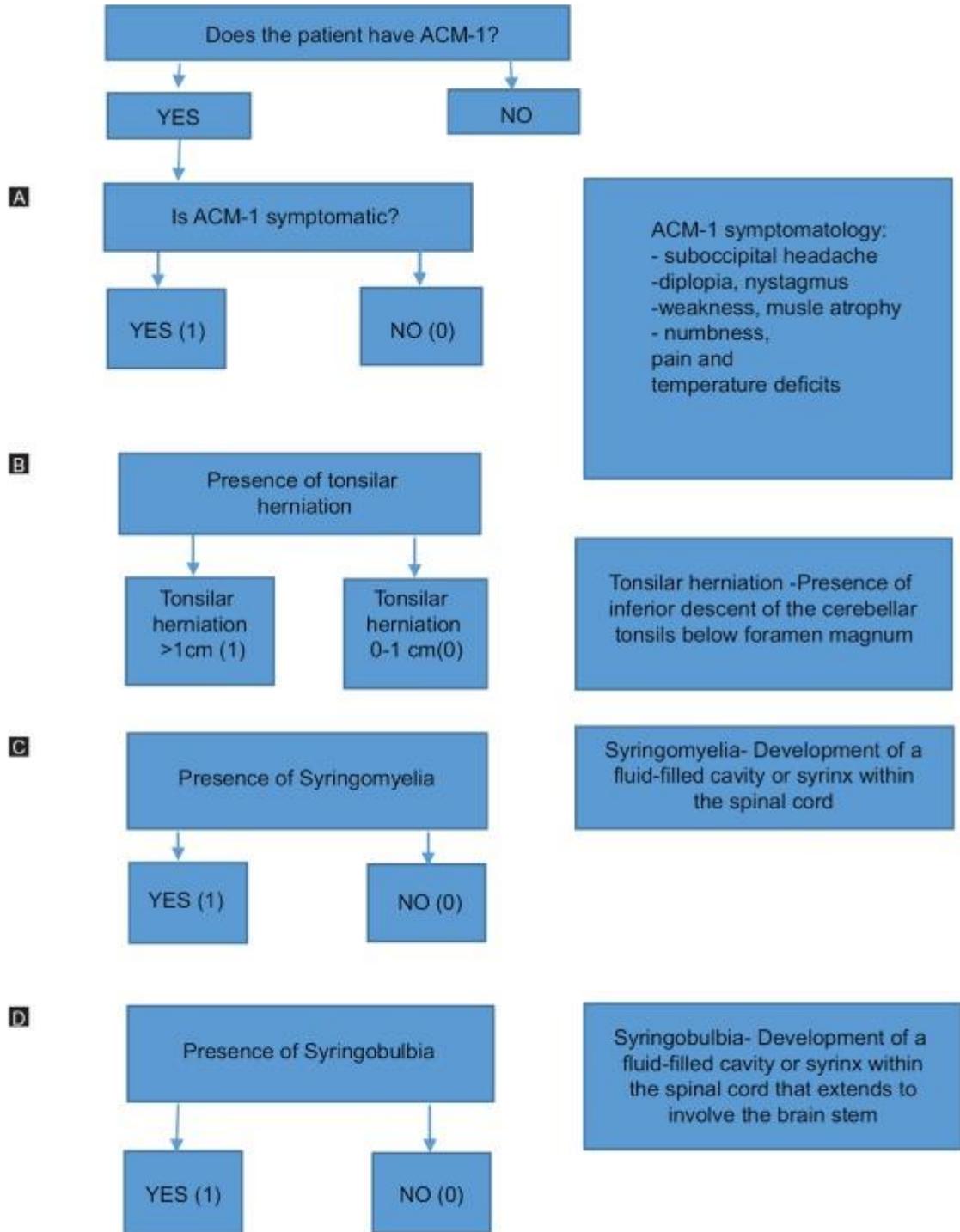
### Retrospective Review

*D. Andrew Wilkinson et al. Obstetric Management and Maternal Outcomes of Childbirth Among Patients With Chiari Malformation Type I. Neurosurgery 0:1–8, 2019*

- 866 patients with CM-I diagnosis who had 1048 hospitalizations for delivery, including 103 deliveries to 83 patients who underwent performance of CM-I decompression (CMD) either before or after childbirth.
- among 400 births that occurred after CM-I diagnosis, rates of C-section were higher (42.3% vs 36.2%, OR 1.29, 95% CI 1.00-1.66, P = .05) and rates of epidural analgesia were lower (45.3% vs 55.4%, OR 0.67, 95% CI 0.52-0.85, P = .001) compared to 648 births before CM-I diagnosis.
- rates of serious maternal morbidity among women with CM-I were similar to those for 11 000 normal controls.

Most pregnant patients with Chiari *should not be treated differently* than women without Chiari—and specifically Chiari malformation is not a contraindication to vaginal delivery or epidural anesthesia!

Ghaly Obstetric Guide to Arnold-Chiari malformation type 1 (GOGAC-1)



1 point - multidisciplinary meeting on the site  
 2 points- neurosurgery consult and multidisciplinary meeting on the site  
 >3 points- neurosurgery consult and preparation for C-section

Ghaly general anesthesia recommendations for cesarean section in parturients with ACM-1

---

Notify Neurosurgery service and open communication  
Anesthesia time-out, add ACM-1 concerns to the surgery standards time out  
Avoiding blood pressure fluctuation and ICP elevation with measures to reduce the ICP throughout the procedure  
Prophylactic antacid protocol  
ASA monitors and preoxygenation  
Simultaneous surgical field preparation  
Adequate topicalization and awake fiberoptic intubation  
Consider hyperventilation and osmодиурезис  
Post-intubation neurological assessment  
Propofol IV 1 mg/kg for induction followed by balanced anesthesia with volatile anesthetic, Sevoflurane 0.5 MAC and additional IV infusions of Propofol and Remifentanyl  
Postdelivery osmодиурезис (Lasix 0.5 mg/kg, Mannitol) and hyperventilation (CO<sup>2</sup> 30-35 mmHg)  
Immediate delivery of the baby  
Ensure smooth emergence: avoid increase in ICP  
Confirm full NMB reversal  
Prior extubation neurological assessment  
Standby neurosurgeon on call

---

### Management of parturients with CM-1 during delivery

#### General anesthesia in CM-1 parturients

- general anesthesia **avoids the risk of dural puncture in patients with increased ICP.**
- general anesthesia **can help manage the sudden increases in ICP** intraoperatively by hyperventilating the patient, keeping the airway secure, and controlling blood pressure.
- **laryngeal manipulation and endotracheal intubation** can lead to abrupt increases in ICP with serious consequences; for this reason, some authors prefer **awake intubation** with local airway anesthesia to prevent serious complications from occurring, whereas others prefer laryngoscopy intubation using a **modified rapid sequence technique**, and opioids.
- be aware of **difficult airway** – may lead to hypoxia and damage to the spinal cord.
- may have an **increased sensitivity to neuromuscular blocking agents**; some anesthesiologists prefer to avoid them altogether, whereas others closely monitor neuromuscular function for prolonged effects and then provide complete reversal.

#### Spinal anesthesia in CM-1 parturients

- may lead to post-dural puncture headache.

#### Epidural anesthesia for parturients with CM-1

- although successful deliveries were accomplished with this method of anesthesia, the potential risks of inadvertent dural puncture can lead to serious complications.

#### Other CM-1 particularities

- postoperative pain should be addressed!

## CHIARI II malformation (s. ARNOLD-CHIARI malformation)

- elongation and downward displacement of **brain stem, 4<sup>th</sup> ventricle, and cerebellum** (small posterior fossa)

N.B. term ARNOLD-CHIARI malformation is used specifically in reference to hindbrain herniation in **myelodysplastic** patients

- clear associations can be made with Chiari II, myelomeningocele, and folate deficiency.
- **cerebellar vermis** and inferior poles of **cerebellar hemispheres**\* extend downward through foramen magnum in tongue-like processes and are often adherent to adjacent medulla; more than half is usually below level of foramen magnum. \*vs. just **tonsils** – in Chiari I
  - **inferior vermis** is everted rather than inverted, so nodulus becomes most inferior part of cerebellum.
  - **tentorial incisura** is enlarged and cerebellum herniates upwards into supratentorial space.
- **pons, medulla, 4<sup>th</sup> ventricle** are elongated and partially located in spinal canal;
  - **posterior fossa** is small (vs. Chiari I – normal size); **foramen magnum** is enlarged, low attachment of tentorium
  - **medulla** is flattened anteroposteriorly and elongated (→ characteristic **“Z” kinking of cervicomedullary junction** - caused by caudal displacement of medulla in conjunction with spinal cord that is held in relative immobility by dentate ligament)
  - **4<sup>th</sup> ventricle** is typically small (as coronal cleft).
  - **lower cranial nerves** are stretched.
  - crowding and high position (with respect to midbrain) of **superior cerebellar vermis** give it heart-shaped appearance where it surrounds beaked tectum of midbrain
- cerebral falx is partially absent or fenestrated (→ interdigitation of medial gyri across midline).

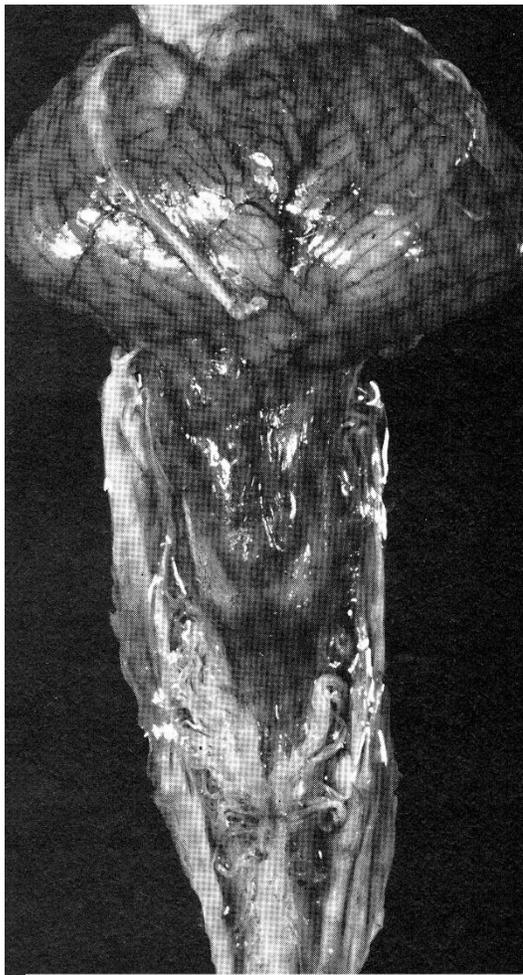
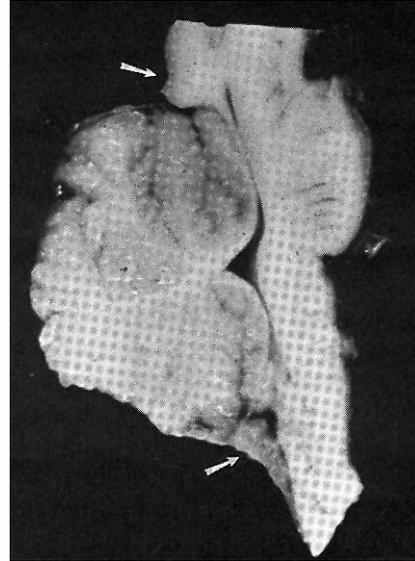
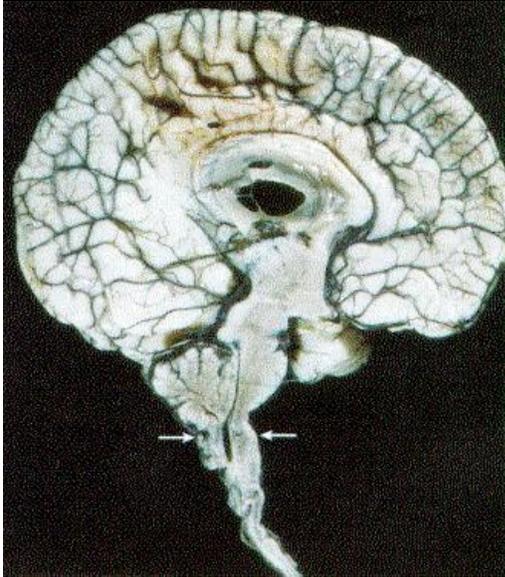
### Associated disorders:

- **almost always (> 98%) associated with lumbosacral neural tube defects** (incidence of Chiari II parallels incidence of myelomeningoceles\*).
  - \*Chiari II is present in 95% children with myelomeningoceles
- progressive **hydrocephalus** is present in most cases (due to blockage of 4<sup>th</sup> ventricular outlets).
- other associated defects
  - rounded defect in skull bones (**craniolacunia**, Lückenschädel)
  - callosal agenesis / dysgenesis
  - enlarged massa intermedia (interthalamic adhesion)
  - polygyria
  - **beaked tectum of midbrain** (fusion of colliculi into single backward pointed peak)
  - basilar impression, missing posterior C1 arch
  - **syringomyelia** (40-95%)

meningomyelocele + hydrocephalus + craniolacunia

Small posterior fossa contents, downward displacement of cerebellar vermis, and deformity of medulla (arrows indicate approximate level of foramen magnum):

Note beaked tectum (arrow) and position of cerebellar vermis extending to about C3 (arrow):



Arnold-Chiari malformation. Cerebellar tonsils are displaced into cervical canal.



Source of picture: H. Richard Winn "Youmans Neurological Surgery", 6th ed. (2011); Saunders; ISBN-13: 978-1416053163 >>

**PATHOGENESIS**

- a) **cord adhesions at site of spinal defect** - prevent cord from ascending in normal manner and pull brain stem and cerebellum downward into cervical canal.
- b) failure of neural tube closure with CSF drainage into amniotic fluid → **collapse of primitive ventricular system** → decrease in inductive influences on overlying axial mesenchyme → skull development defect (i.e. incomplete distention of 4<sup>th</sup> ventricle fails to stimulate growth of skull base → smaller posterior fossa, which is unable to respond during later phase of rapid cerebellar growth → herniation of neural tissue from posterior fossa → impaired CSF flow → hydrocephalus).

– these hypotheses do not explain cases without spinal defect.

### CLINICAL FEATURES

- manifest in **first few months of life\*** (vs. Chiari I):

\*those who survive this high risk period have better prognosis (onset is rarely delayed until adult life)

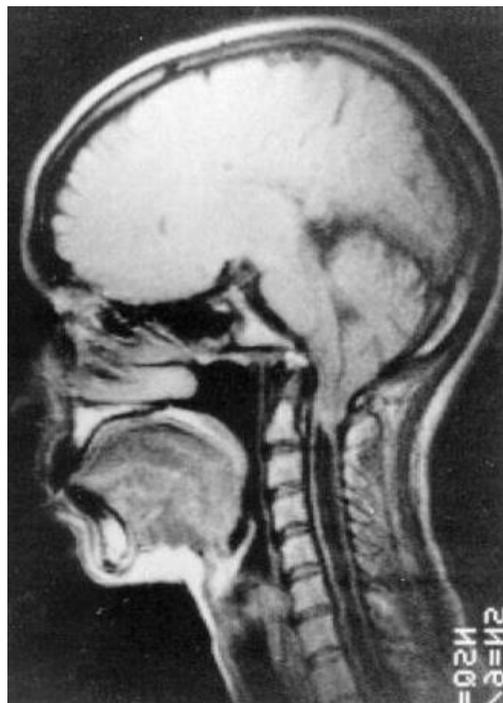
- 1) injury to **cerebellum, medulla, and lower cranial nerves** - progressive ataxia, leg weakness, visual complaints, dysphagia, drooling, nasal regurgitation, stridor, vocal cord paralysis, opisthotonos, *life-threatening apneic spells* (leading causes of death in children with myelomeningocele). see Chiari I >>
- 2) hydrocephalus
- 3) spina bifida

### DIAGNOSIS

**Plain radiographs** - small posterior fossa and widened cervical canal.

**CT with contrast / MRI** - cerebellar vermis protruding downward into cervical canal.

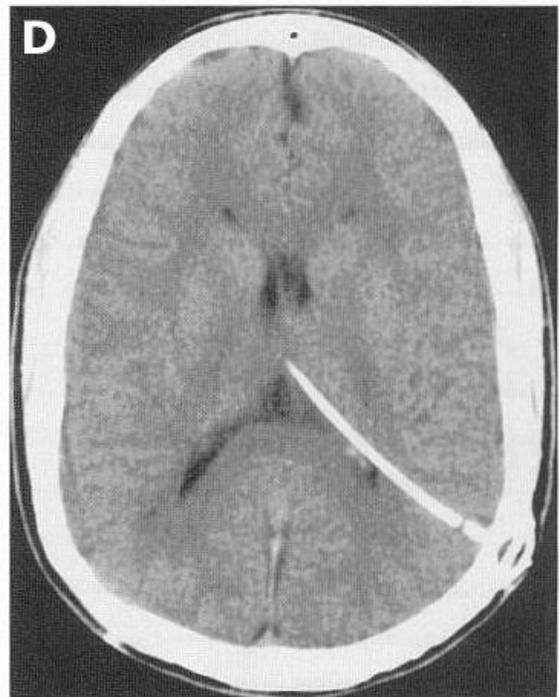
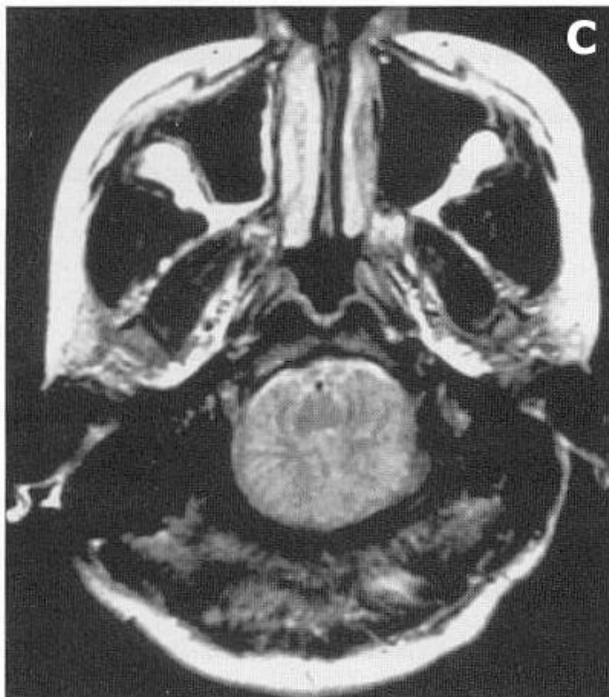
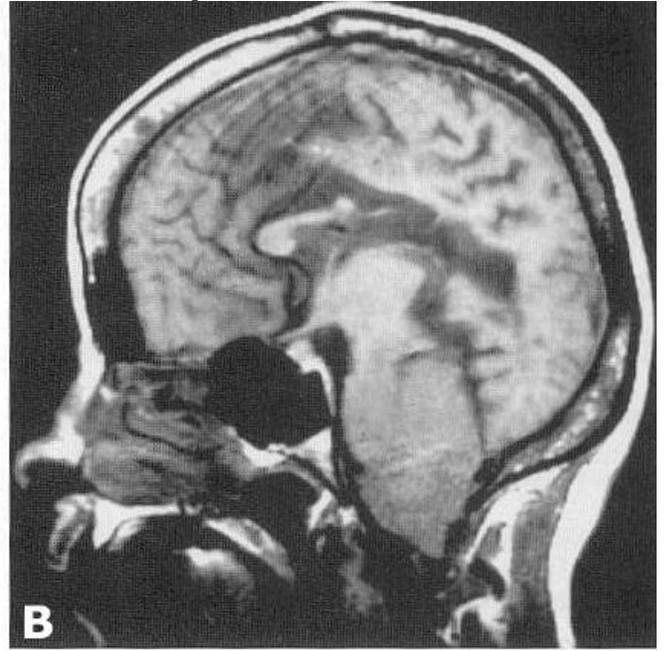
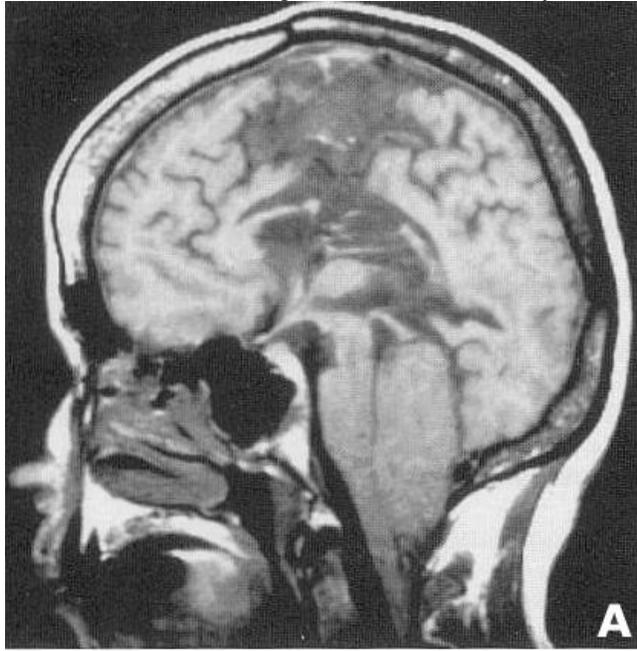
T<sub>1</sub>-MRI - small and elongated 4<sup>th</sup> ventricle, low position of obex of 4<sup>th</sup> ventricle (below plane of foramen magnum), cerebellar tonsillar ectopia, short clivus, wide foramen magnum, kinked cervical medullary junction, and prominent superior vermis; large hydromyelia in cervical cord:

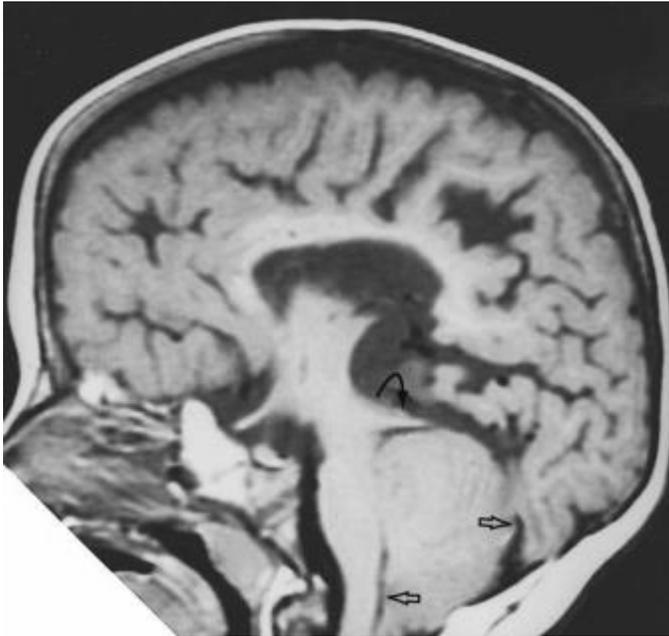


**A and B** (midline and paramedian sagittal T<sub>1</sub>-MRI): very low position of medulla, cerebellum, and 4<sup>th</sup> ventricle; very low position of transverse sinus (flow void visible just above foramen magnum) and beaked appearance of midbrain tectum.

C (axial T2-MRI): inferior cerebellar hemispheres surrounding upper medulla at level of foramen magnum.

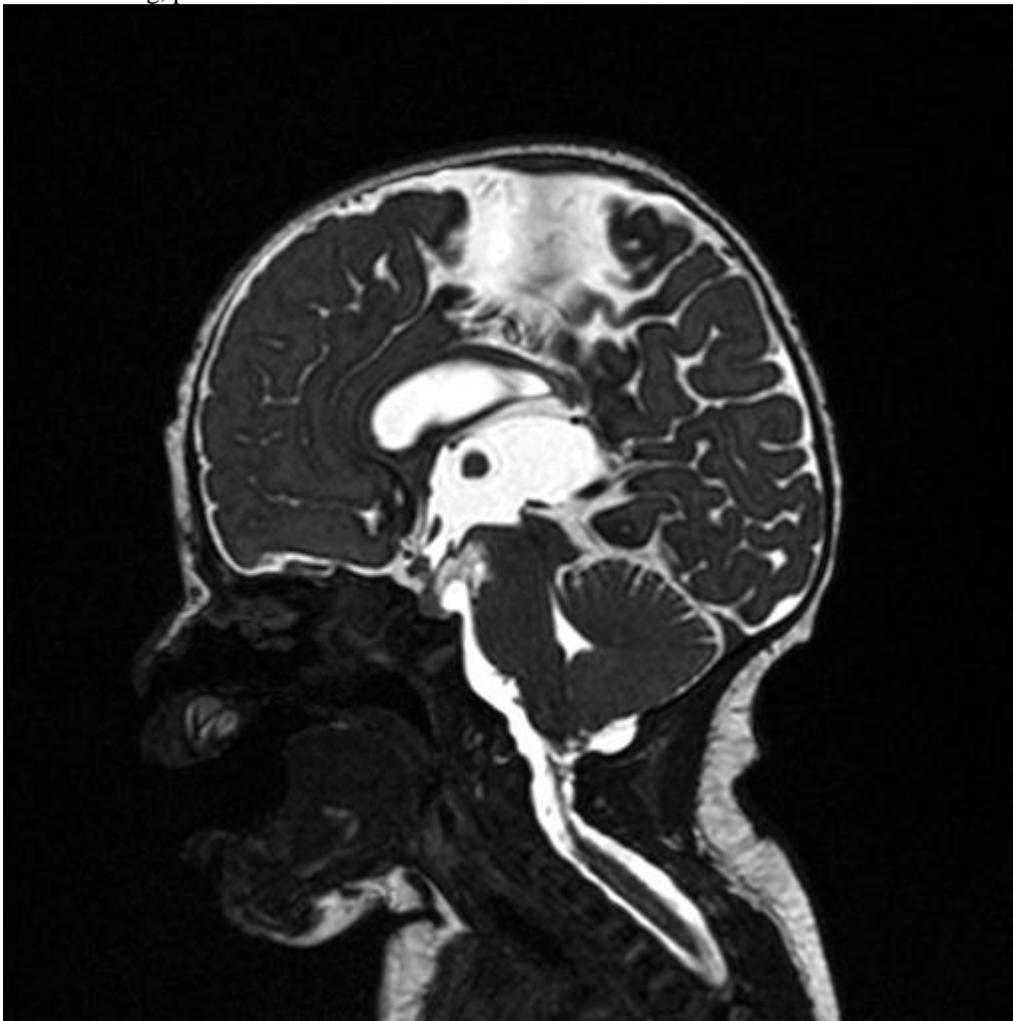
D (axial CT): mild interdigitation of sulci anteriorly (absent falx) and ventriculoperitoneal shunt catheter:





Source of picture: H. Richard Winn "Youmans Neurological Surgery", 6th ed. (2011); Saunders; ISBN-13: 978-1416053163 >>

Tectal beaking, prominent massa intermedia:



Source of picture: V. Palys

PRENATAL DIAGNOSIS (possible early in pregnancy) – by **ultrasound**:

- 1) **large lateral ventricle** in which choroid plexus is seen to move (*'dangling choroid plexus'*).

- 2) *frontolateral skull* is **flattened** on both sides → specific head shape ('*lemon sign*').
- 3) *posterior fossa* is small, *cerebellum* is not surrounded by CSF and is **abnormally shaped** like banana ('*banana sign*').

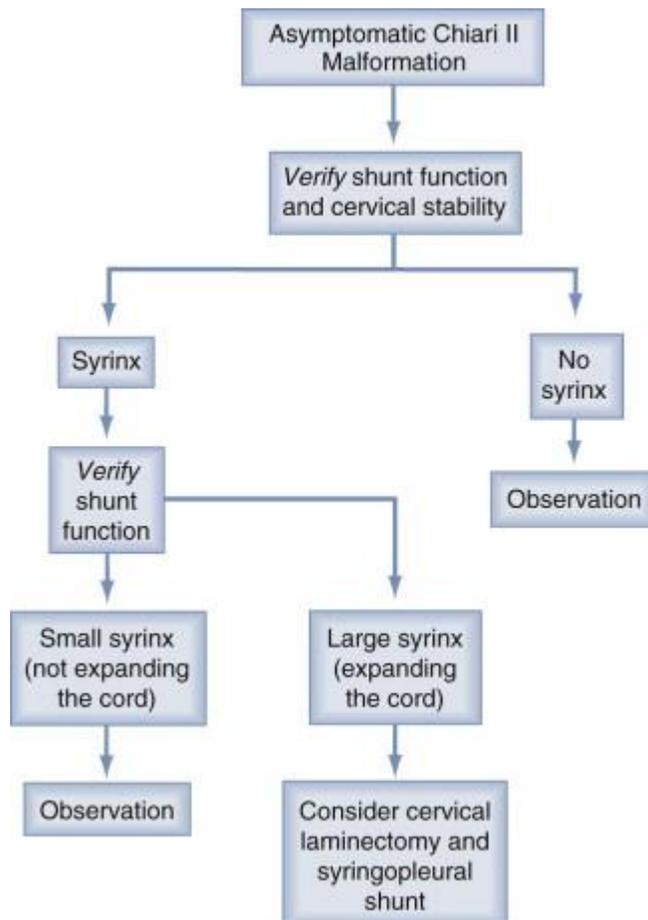
N.B. ventricles are normally large in fetus < 20 weeks' gestation! (excessive ventricular size is required to identify abnormality)

## TREATMENT

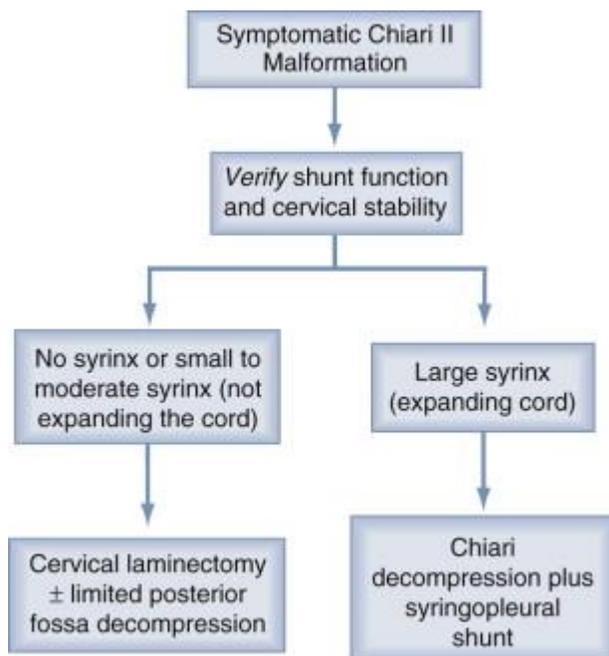
1. **Ventriculoperitoneal shunt** (to relieve hydrocephalus) – first step in management (properly functioning shunt can often obviate need for decompression of hindbrain herniation)
2. Early **posterior fossa decompression** see Chiari I >>  
**Restoration of normal CSF dynamic flow** (from fourth ventricle to subarachnoid space) and **relief of direct brainstem compression** are goals of surgery
3. **Cele excision**

## Indications for Surgery

Flow diagram for asymptomatic patients:



Flow diagram for symptomatic patients:



**Expedient brain stem decompression** should be carried out when any of the following critical warning signs develop:

- a) neurogenic dysphagia
- b) stridor
- c) apneic spells

### Pre-operative mandatory testing

- 1) **BAEPs**
- 2) **swallow** study (frequently need PEG)
- 3) direct **vocal cord** visualization by otolaryngologist
- 4) assessment of **pulmonary function** including obstructive and central apnea (sleep study) as well as hypercapnic ventilatory drive by pulmonary specialist.
- 5) **MRI** (esp. position of confluence of sinuses, cerebellar vermis, cervicomedullary kink, and choroid plexus)

### Surgery Details

- Chiari II anomaly is challenging surgical entity (vs. Chiari I operation, which can be performed by any experienced neurosurgeon with good knowledge of anatomy of region); main challenge is **variable anatomy**:
  - cerebellar tissue usually extends into lower cervical spine; it may be very adherent to medulla, and occasionally two tissues may even seem indistinguishable or fused.
  - **confluence of sinuses can be as low as rim of foramen magnum**, and dura may contain large venous sinuses.
- foramen magnum is generally enlarged and patient is unlikely to benefit if it is made even larger (plus, concern for delayed cervical instability and postlaminectomy kyphosis); extent of bony opening should encompass cerebellar hindbrain hernia but need not include medullary kink or occipital bone, especially if confluence of sinuses is low lying.
- dense arachnoidal adhesions are common, as is striking superficial hypervascularity.

- choroid plexus is identified by its yellow-orange color and granular appearance; it maintains its early embryologic extraventricular location and marks entrance into fourth ventricle.
- interface between vermis and medulla is usually densely adherent and difficult to separate.  
DO NOT attempt to dissect tonsils from underlying medulla!!!
- procedure is not thought to be finished until *avascular floor of fourth ventricle is well visualized* (tip of vermis is coagulated to maintain opening out of fourth ventricle to subarachnoid space).
- dura is grafted and wound closed in routine fashion.

### Postoperatively

- close post-op **respiratory monitoring** for obstruction and reduced ventilatory drive!!!
- **surveillance CT scan** is performed at 3 months to evaluate ventricular size.
- any **clinical relapse** is managed as *presumed shunt malfunction* before any direct surgical approach to persisting syrinx (direct shunting of persisting symptomatic syringes is frequently not necessary).

### **PROGNOSIS**

- 68% - complete or near complete resolution of symptoms, 12% - mild to moderate residual deficits, 20% - no improvement (in general, neonates fare worse than older children)
- **respiratory arrest** is the most common cause of mortality.

### **CHIARI III malformation**

- **displacement** of cerebellum ± brainstem **into occipital encephalocele**.
- rare malformation!
- **poor prognosis** - seizures and respiratory insufficiency  
(vs. **cervical myelomeningoceles** - may look the same superficially but more favorable prognosis)

### **CHIARI IV malformation**

- **cerebellar a(hypo)plasia**
- posterior fossa is relatively normal in size
- absence of any hindbrain herniation.

More appropriate classified in category of *posterior fossa cysts*.

### **CHIARI 0 malformation**

- isolated **syringomyelia** (without tonsillar herniation) that **responds to posterior fossa decompression**
- MRI of entire neuraxis – to rule out other causes of syrinx.
- pathophysiology resulting in syrinx formation is poorly understood.

## CHIARI 1.5 malformation

- herniation of cerebellar **tonsils** + additional component of brainstem descent.

## DANDY-WALKER malformation

- developmental failure of roof of 4<sup>th</sup> ventricle (imperforation of Magendie and Luschka foramina):

- 1) **cystlike dilation of 4<sup>th</sup> ventricle** (“large posterior fossa cyst”)
- 2) **partially\* (75%) / completely absent cerebellar vermis**  
\*absent inferior portion; superior portion is anteriorly rotated
- 3) **enlarged posterior fossa** with elevated tentorial insertion (upward displacement of transverse sinuses).

- **obstructive hydrocephalus** ( $\approx 90\%$ ) as secondary complication (most cases show no clear obstruction of CSF flow; true lack of patency of foramen of Magendie and Luschka is rare).
- possible ectopia of certain brainstem nuclei.

## ETIOLOGY

A) **isolated** malformation

- associated with maternal exposure to **retinoic acid** and **warfarin**.

B) **part of syndrome** (e.g. Meckel-Gruber syndrome, Walker-Warburg syndrome).

Carefully search for associated abnormalities! (esp. heart, kidneys, musculoskeletal)

## CLINICAL FEATURES

- patients without associated anomalies may have relatively **normal intelligence and development**.
- **initial presentation** (may occur as late as **adulthood!**):
  - 1) rapid **increase in head size** and prominent occiput.
  - 2) **headache**
  - 3) **hydrocephalus**
  - 4) progressive pressure effects on brain stem and cerebellum → **ataxia** and **brain stem dysfunction**.
    - owing to pressure fluctuations in posterior fossa, these symptoms can occur intermittently.
    - despite of vermian aplasia, congenital ataxia is not typical feature.

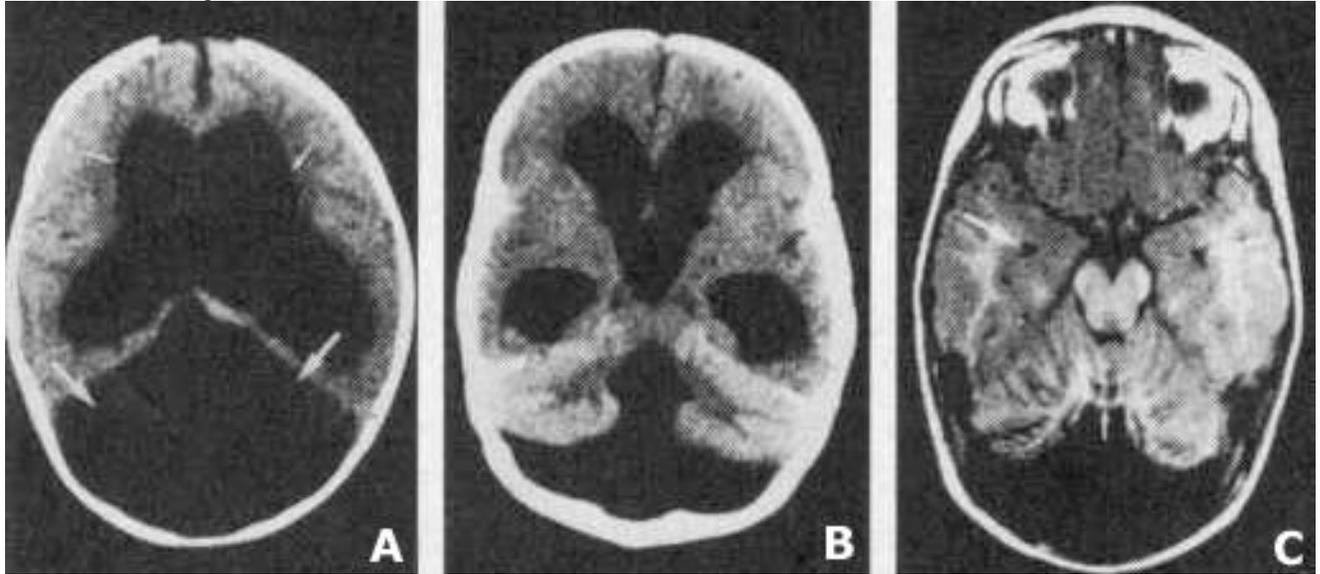
## DIAGNOSIS

PRENATAL DIAGNOSIS (possible early in pregnancy) – by **ultrasound**  
**MRI** (imaging modality of choice)

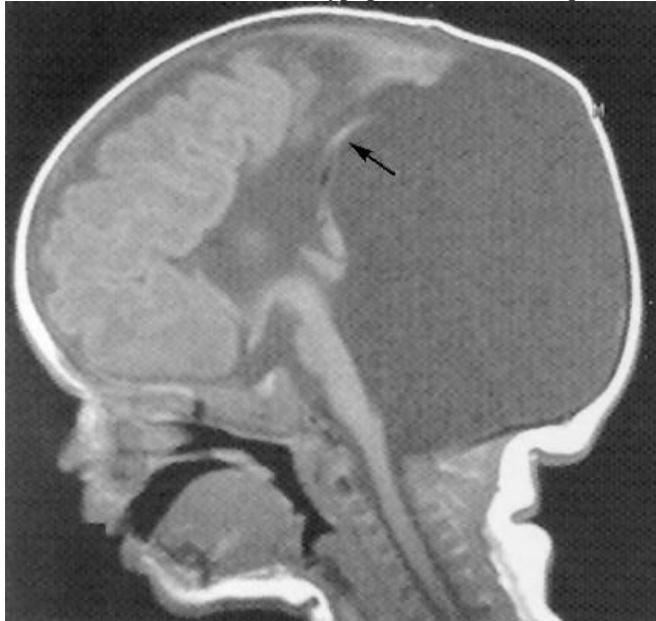
A. Preoperative CT - large posterior fossa cyst (*large arrows*) and dilated lateral ventricles (*small arrows*).

B. Same patient (lower axial CT) - splaying of cerebellar hemispheres by dilated 4<sup>th</sup> ventricle.

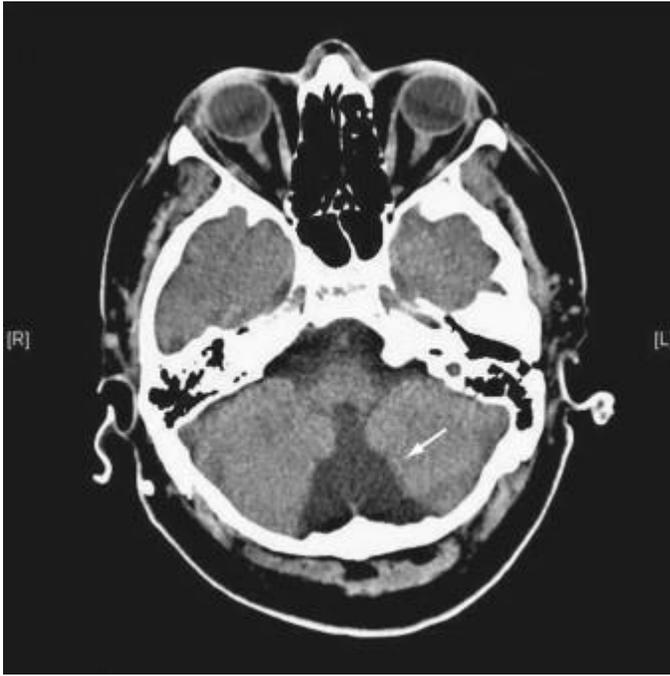
C. Postoperative MRI - decreased size of Dandy-Walker cyst and temporal horns (*arrows*); incomplete vermis (*small arrow*) now becomes recognizable:



Newborn girl born with large head (midline sagittal T1-MRI): large cystic area expanding posterior fossa and elevating tentorium (*arrow*); vermis is hypoplastic and rotated posteriorly and upwards:



Source of picture: Ronald G. Grainger, David J. Allison "Grainger & Allison's Diagnostic Radiology: A Textbook of Medical Imaging", 4<sup>th</sup> ed. (2001); Churchill Livingstone, Inc.; ISBN-13: 978-0443064326 >>



Differential diagnosis - *cysts in posterior fossa* (4<sup>th</sup> ventricle is compressed!): arachnoid cysts, mega-cisterna magna, cystic tumors.

### TREATMENT

- shunting of *hydrocephalus* and *posterior fossa cyst* via **double ventriculoperitoneal and cystoperitoneal shunt**.

- intrauterine diversion of intraventricular CSF is possible.

## MEGA CISTERNA MAGNA

- **enlarged cisterna magna** (but vermis is intact).

- enlargement may extend supratentorially through weakness of tentorium.
- falx cerebelli is present in > 50% cases.
- may have same embryological origin as Dandy–Walker malformation.

### CLINICAL FEATURES

- in most cases asymptomatic (any developmental delay is related to additional supratentorial malformations).

### DIAGNOSIS

- in difficult cases intrathecal contrast medium may be needed to establish diagnosis.

## VERMIAN–CEREBELLAR HYPOPLASIA

- **congenital cerebellar hypoplasia**.

- genetically heterogeneous.
- have been associated with number of other syndromes (e.g. Joubert's syndrome, Walker-Warburg syndrome, muscle-eye-brain disease).
- prenatal CMV infection also needs to be investigated.

## OTHER

### INTRACRANIAL ARACHNOID CYSTS

- **arachnoid-lined cavities** filled with fluid similar in composition to CSF.

- may communicate to varying degrees with surrounding subarachnoid space.
- most are **congenital**, pathogenesis is unknown.

#### CLINICAL FEATURES

- depend on SIZE & LOCATION;

- **displace surrounding structures** (→ seizures, focal neurologic deficits), cause **intracranial hypertension** (→ increased head circumference, full fontanelle, headache).
- most common LOCATIONS:
  1. **Sylvian fissure** → seizures, hemiparesis.
  2. **Suprasellar** → visual disturbances.
  3. **Posterior fossa** → obstructive hydrocephalus, mass effect on cerebellum and brain stem.
- causes of **sudden deterioration:**
  - 1) development of obstructive hydrocephalus
  - 2) cyst rupture
  - 3) bleeding into cyst (spontaneous or traumatic).

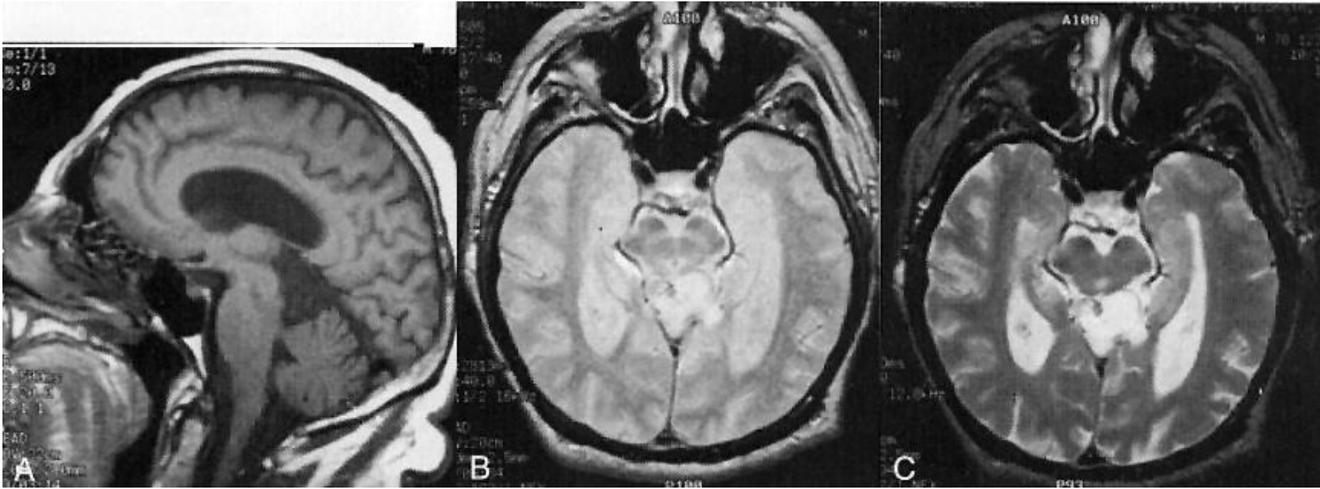
#### DIAGNOSIS

**MRI** is preferred (well-demarcated, thin-walled masses with attenuation values same as CSF).

- do not contain calcium or fat.
- margins are not enhanced following IV contrast medium.

**Plain X-ray** - compression or scalloping of inner table of calvarium.

Quadrigeminal cistern arachnoid cyst (A) sagittal T1-, (B) axial proton density, (C) axial T2-MRI:



Source of picture: John H. Juhl "Paul and Juhl's Essentials of Radiologic Imaging", 7<sup>th</sup> ed. (1998); Lippincott Williams & Wilkins; ISBN-10: 0-397-58421-0 >>

### THERAPY

- for *symptomatic* arachnoid cysts:
  - a) simple cyst shunting
  - b) cyst fenestration
  - c) cyst wall excision.

BIBLIOGRAPHY for ch. "Developmental Anomalies" → follow this [LINK >>](#)