Malformations of the Pediatric Brain

**Thierry A. Huisman, MD**

**Introduction**
- Fetal pathology/malformation
  - Congenital
  - Acquired

**Introduction**
- Congenital (fetal) pathology
  - Malformations: erroneous development of the central nervous system (CNS)
    - Examples:
      - Rhomboencephalosynapsis
      - X-linked bandheterotopia
      - Anomalies of the corpus callosum
      - Encephaloceles
      - Anomalies of neuronal migration
      - Holoprosencephaly
      - Chiari-Malformations
      - Joubert syndrome
- Acquired (fetal) pathology
  - Destruction of initially correctly developed structures
    - Ischaemia
    - Intrauterine ischaemia
    - Diffuse hypoxia (placental insufficiency)
    - Hemorrhage
    - Infections

**Problems**
- Sounds easy
- Gets more and more complicated, the more you think about it
- Problems, problems, problems…….

**Problem 1**
- Discrete, “destructive events“ during neurulation can result in erroneous development of the CNS
- Overlap “congenital pathology“ and “acquired pathology“
- Identical lesions, may have different etiologies (e.g., disorders of migration: focal ischaemia, hypoperfusion, infection, chromosomal)

**Figures 1 A, B, C & D**
- Axial T2-weighted image (A) demonstrates fused cerebellar hemispheres consistent with rhomboencephalosynapsis. A FLAIR image (C) shows a band of cortex isointense heterotopic gray matter within the subcortical white matter.

**Figure 2 A, B, C & D**
- Axial fetal T2-weighted image and matching postnatal T2-weighted image show chronic left hemispheric watershed ischemic lesions.
Problem 2  [Figure 4]
- Identical "destructive events" can result in spectrum of fetal pathologies
- Timing of the event is a key feature

Problem 3  [Figure 5]
- Spectrum of similar kinds of malformations
- Variable expression versus variable timing?

Problem 4  [Figure 6]
- Associated findings in malformations

Figure 4 A to G
Multiple MR images demonstrate various degrees of central nervous system disruption: Focal insular cortical pachygyria, bilateral closed/open lip schizencephaly and (T1- and T2-weighted images) anencephaly (clockwise).

Figure 5 A, B, C & D
Multiple T2-weighted images demonstrate various degrees of "cystic" posterior fossa abnormalities: Classic Dandy Walker malformation, mild Dandy Walker malformation; Blake pouch cyst, and retrocerebellar arachnoid cyst (clockwise).

Figure 6 A, B & C
Sagittal, coronal, and axial T2-weighted images of a fetus with a Dandy Walker malformation (clockwise). Next to the cystic enlargement of the IV ventricle, a large right hemispheric porencephalic cyst is demonstrated.
Problem 5
- An increasing number of gene defects are identified in congenital and so-called acquired fetal pathologies
- Holoprosencephaly: mutations of at least three genes: Shh, ZIC2, and SIX3

Problem 6
- In addition, it is progressively recognized that
  - A predisposition for malformations is encoded in the chromosomes
  - A trigger is necessary to induce the cascade of events
- Triggers start to get identified but are yet poorly/partially understood

Problem 7
- Pathology can be present intrauterine, but is not recognized
  - Asymptomatic
  - Too small to be identified
- Can get symptomatic later in life
  - Spontaneous progress (e.g., Sturge-Weber)
  - "Trigger" induces progression (e.g., AVM)

In Summary
- We start to get some insight in fetal pathologies
- Much is (yet) unknown
- Much is not (yet) fully understood
- Much is not (yet) recognized
- Most probably, in fetal pathologies there is a multifactorial, overlapping genetical etiology that interacts with the environment triggers and may show a variable degree of expression

Classification of Malformations
- Disorders of organogenesis
  - Disorders of neural tube closure
    - Chiari, Dandy Walker, corpus callosum agenesis
  - Disorders of sulcation and migration
    - Agyria, schizencephaly, heterotopias, pachygyria
  - Disorders of diverticulation or brain cleavage
    - Holoprosencephaly, septooptic dysplasia
  - Disorders of size
    - Micro- and macrocephaly
  - Destructive lesions
    - Hydrancephaly, porencephaly, Hypoxia,

- Disorders of histiogenesis
  - Neurocutaneous syndromes
  - Vascular lesions
  - Congenital neoplasms

Disorders of Organogenesis
- Focus on
  - Posterior fossa malformations
    - Chiari I, II, III
    - Dandy Walker Spectrum
    - Rhombencephalosynapsis
    - Joubert Syndrome
  - Callosal dysgenesis
  - Diverticulation and cleavage disorders
  - Malformations of cortical development

Chiari Malformations
- Chiari I
  - Tonsillar ectopia + deformation
  - 5 mm below foramen magnum
  - Asymptomatic 15%-50%
  - Vague, ambiguous symptoms related to hindbrain compression: headache, neck pain, numbness, weakness, coordination issues, nystagmus, ataxia
  - Often delay in diagnosis
  - Likely related to disorder of paraxial mesoderm with hypoplasia of the occipital somites
  - Ball-valve obstruction at foramen of magnum ~> increased systolic CSF waves ~> increased bulk flow of CSF through dilated perivascular spaces ~> syringohydromyelia/hydrocephalus
  - SHM most frequent in cervical cord, may be holocordal (scoliosis 28%)
  - Treatment: Posterior fossa decompression, shunting
Chiari Malformations

- Chiari II
  - Complex malformation of a "too small posterior fossa"
  - Almost always associated with neural tube closure defect e.g., "open" myelomeningocele (MMC)
  - High incidence of associated cerebral malformations
  - Internal disorder of fibers/neuronal networking

Figure 8
Sagittal T2-weighted image shows a Chiari I malformation with low positioning of the cerebellar tonsils.

Figure 9 A & B
Serial T1-weighted images of a child with Chiari I malformation demonstrates resolution of the cervical hydromyelia after posterior fossa decompression.

Figure 10
Sagittal T2-weighted image of the neuroaxis shows simultaneous appearance of a Chiari II malformation and a lumbar non skin covered myelomeningocele. Image courtesy of P. Tortori-Donati.

Figure 11 A to F
Multiplanar T2-weighted images demonstrate characteristic stigmata of Chiari II malformation.

Figure 12 A to F
Multiple T2- and T1-weighted images show additional, variable imaging findings related to Chiari II malformation.
Do not Underestimate Ultrasound

[Figure 13]

Coronal and sagittal ultrasound (US) images and matching computer tomography (CT) images demonstrate Chiari II stigmata.

Which Combination of “Fruits” are Typically Seen on Prenatal Ultrasound?

[Figure 14]

- Apple and pear
- Lemon and banana
- Pear and lemon
- Grapes and banana
- Apple and lemon

What is Chiari III?

- Chiari II plus low occipital and/or high cervical meningo-encephalocele
- Chiari II plus low occipital and/or high cervical meningo-encephalocele
- (Chiari I) + (Chiari II) = (Chiari III)
- (Chiari IV) – (Chiari I) = (Chiari III)

Chiari Malformations

- Chiari III
  - Chiari II plus low occipital and/or high cervical meningo-encephalocele
  - Very rare, high/early mortality rate
  - Severe neurological deficits in survivors

[Figure 15]

Multiplanar T2-weighted images show an occipital meningo-encephalocele, small posterior fossa and hydrocephalus compatible with Chiari III.

Chiari Malformations

- Chiari variants
  - Chiari 0: term loosely used to describe people who have Chiari-like symptoms, but have little to no tonsillar herniation...
  - Chiari IV: Cerebellar hypoplasia and MMC

Chiari “IV”

[Figure 16]

Sagittal T1 and axial and sagittal T2-weighted images reveal a small disrupted cerebellum and brainstem secondary to an open lumbar myelomeningocele.

Figure 13 A to H

Coronal and sagittal ultrasound (US) images and matching computer tomography (CT) images demonstrate Chiari II stigmata.

Figure 14 A, B, C & D

Axial prenatal Ultrasound images of the posterior fossa reveal the “lemon” and “banana”.

Figure 15 A, B & C

Multiplanar T2-weighted images show an occipital meningo-encephalocele, small posterior fossa and hydrocephalus compatible with Chiari III.

Figure 16 A, B & C

Sagittal T1 and axial and sagittal T2-weighted images reveal a small disrupted cerebellum and brainstem secondary to an open lumbar myelomeningocele.
Dandy Walker Malformation
- Cystic dilatation of IV-ventricle, associated with varying degrees of vermian hypoplasia
- Associated findings in 60% of patients
  - Hydrocephalus, corpus callosum dysgenesis, polymicrogyria, cephaloceles, polydactyly, cardiac anomalies
- Cognitive performance depends on associated malformations (35%-50% normal intelligence)
- Spectrum of expression (DW spectrum)

Dandy Walker Malformation
[Figures 17 & 18]
- Cystic dilatation IV ventricle
- Vermian hypoplasia
- IV ventricle choroid plexus absent
- Normal or enlarged posterior fossa
- Elevated torcula
- Falx cerebelli usually absent
- Vermian remnant may be rotated upward

Again, Do Not Forget the Ultrasound
[Figure 19]
Ultrasound images and matching T1- and T2-weighted images demonstrate a hypoplastic vermis, cystic dilatation of the IV ventricle and supratentorial hydrocephalus related to a Dandy Walker malformation.

Dandy Walker Malformation
- Metencephalic roof
  - Velum medullare anterior invaded by neurons ~> cerebellum
  - Velum medullare posterior expands and disappears ~> outlets
- Defective VMA + VMP;
  - Dandy Walker malformation
- Defective VMP
  - Blake’s pouch cyst
  - Mega cisterna magna

Blake’s Pouch Cyst
[Figure 20]
- Velum medullare posterior outpouching, inferior to plexus
- Pouch does not rupture
- No Foramen of Magendie
- Posterior fossa may be enlarged
- IV ventricle choroid plexus may be displaced
- Torcula normal to elevated
- Falx cerebelli present
- Rarely associated malformations

Malformations of the Pediatric Brain
Neuroradiology
1450
**Mega Cisterna Magna**  
- Large retrocerebellar space  
- Normal vermis and cerebellum  
- Differential diagnosis arachnoid cyst  
- IV ventricle choroid plexus in normal location  
- Posterior fossa usually normal to large  
- Torcular normal to elevated  
- Rarely associated malformations

**Rhomboencephalosynapsis**  
- Single lobed cerebellum  
- Fusion of both cerebellar hemispheres, dentate nuclei, and superior cerebellar peduncles  
- Vermian agenesis  
- Failure of induction and differentiation of midline structures (genetic defect)  
- Often associated malformations  
- Ataxia, developmental delay

**Joubert Syndrome**  
- Congenital vermian hypo-or aplasia  
- Episodic hyperpnea, abnormal eye movements, rhythmic tongue protrusion, ataxia, mental retardation  
- Associated lesions: cerebellooculo-renal syndrome  
- Autosomal recessive  
- Molar tooth brainstem, bat-wing, or umbrella shaped IV-ventricle

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**Figure 21 A & B**  
*Sagittal T2-weighted images of a child with a mega cisterna magna and a second child with a retrocerebellar arachnoid cyst.*

**Figure 22 A to G**  
*Multiplanar T2-weighted images demonstrate characteristic imaging features of a child with a rhomboencephalosynapsis.*

**Figure 23 A to F**  
*Multiplanar T2 and T1-weighted images of a patient with Joubert syndrome demonstrating molar tooth appearance of the midbrain, umbrella shaped fourth ventricle, absent vermis, and horizontal course of the cerebellar peduncles.*

**Figure 24 A & B**  
*Color-coded fractional anisotropy maps of a Joubert patient and a matching healthy volunteer; The decussation of the fibers along the floor of the interpeduncular cistern is missing.*
Malformations of the Pediatric Brain

Disorders of Organogenesis: Callosal Dysgenesis
- Posterior fossa malformations
- Callosal dysgenesis
- Diverticulation and cleavage disorders
- Malformations of cortical development

Corpus Callosum

Callosal Dysgenesis
- Partial or complete
- In 50% associated with other CNS malformations (DW-malformation, Chiari-II, septooptic dysplasia)
- Seizures, developmental delay, microcephaly, hypothalamic-pituitary malfunction, hypertelorism
- No inverted cingulate gyrus
- No cingulate sulcus
- Radiating medial gyri

Figure 25 A & B
Color-coded tractography of the cortico-spinal tracts in a Joubert patient and a healthy volunteer demonstrate the diminished crossing of the cortico-spinal tracts.

Figure 26
Sagittal T2-weighted image of a normal corpus callosum.

Figure 27 A, B, C & D
Sagittal T2-weighted images of various normal variants of the corpus callosum.

Figure 28
Sagittal T2-weighted image shows complete absence of the corpus callosum.

Callosal Dysgenesis
- No inverted cingulate gyrus
- No cingulate sulcus
- Radiating medial gyri
- Trident shape of lateral ventricles (Probst Bundle)
- No inversion of cingulate gyrus
- III-ventricle extending interheminispheric
- Vertical hippocampi (no duck)
- Fissure between hemispheres
- III-ventricle may extend interheminispheric
- Parallel course of lateral ventricles, Colpocephaly
- Probst bundles
Corpus Callosum [Figure 32]
- Differentiation between
  - Malformation
  - Destruction
  - Stretching

**Do Not Forget Ultrasonography** [Figure 31]

**Corpus Callosum Agenesis** [Figures 33 to 35]

**Figure 29 A, B, C & D**
Coronal T2-weighted images of a child with a corpus callosum agenesis and a healthy control.

**Figure 30 A & B**
Color-coded fractional anisotropy maps of a Joubert patient and a matching healthy volunteer: The decussation of the fibers along the floor of the interpeduncular cistern is missing.

**Figure 31 A to F**
Coronal and sagittal US images of a neonate with a complete corpus callosum agenesis and an incidentally noted germinal matrix hemorrhage.

**Figure 32 A to E**
Sagittal and coronal T2-weighted images of two children with a corpus callosum (CC) malformation (top row images); a third child with secondary destruction (second row images) and fourth child with thinned corpus callosum due to hydrocephalus (bottom right image).

**Figure 33 A, B & C**
Multiplanar T2-weighted images fetal MRI of a child with a syndromal corpus callosum agenesis.
Complex or Syndromal Malformations

Disorders of Organogenesis: Diverticulation and Cleavage Disorders
- Also known as disorders of ventral induction
- Holoprosencephaly
- Septooptic dysplasia

Holoprosencephaly
- Failure to cleave prosencephalon
- Spectrum of malformation
- Brain + face (face predicts brain)
- Hypothalamic-pituitary dysfunction, seizures, mental retardation, dystonia, cyclopia, microcephaly, fused metopica

Holoprosencephaly
- Alobar
  - Small holosphere, monoventricle, fused thalami, no III-ventricle, no interhemispheric fissure, no falx or corpus callosum, no temporal horn. Azygous anterior cerebral artery
- Semilobar
  - Partially formed falx cerebri and interhemispheric fissure (posterior). Anterior brain fused. Thalami partially separated, small III-ventricle, rudimentary temporal horns. No septum pellucidum. Callosal splenium present without callosal body (!) Hypoplastic olfactory bulb, optic nerves
- Lobar
  - Lobar brain, hypoplastic frontal lobes, some frontal horn formation, falx cerebri extends frontally, temporal horns
Semilobar Holoprosencephaly

[Figures 37 to 39]

Figure 37 A to G
Multiplanar T2-weighted images of a child with semilobar holoprosencephaly. The frontal lobes are fused, a hypoplastic falx is noted in the posterior region. Axial fractional anisotropy map shows the extension of white matter tracts across the midline.

Figure 38 A & B
Axial MRA of a child with holoprosencephaly with malformed circle of Willis. Left image: Azgous or unpaired anterior cerebral artery (arrow.) Right image: normal anatomy.

Figure 39 A to E
Multiplanar prenatal T2-weighted images demonstrate a semilobar holoprosencephaly with a single supratentorial monoventricle.

Septooptic Dysplasia

[Figure 40]
- Mild form of lobar holoprosencephaly
- Absent septum pellucidum
- Hypoplastic optic nerves and chiasm
- Hypoplastic olfactory bulb
- 60% have associated brain malformations
- Pituitary dysfunction, visual loss, nystagmus, anosmia, slight mental retardation

Figure 40 A, B & C
Optic nerve and chiasm hypoplasia. Coronal T2-weighted images show a classical septo-optic dysplasia with box-like configuration of the anterior lateral ventricles and small hypoplastic optic nerves.
Ruptured Septum Pellucidum

[Figure 41]

Multiplanar T2-weighted images of a child with Dandy Walker malformation and hydrocephalus with ruptured septum pellucidum.

Disorders of Organogenesis: Malformations of Cortical Development

Neuronal Migration  [Figures 42 & 43]

- Programmed combination
  - Neuronal migration
  - Gyration/sulcation

Gyration/Sulcation  [Figure 44]

- Programmed development
- ↑ Gyri/sulci
- ↑ Depth
- ↑ Complexity

Figure 42 A, B, C & D

Axial and coronal prenatal T2-weighted images of a 17-week and 23-week gestational age fetus demonstrates the ongoing brain maturation.

Figure 43 A to F

Axial and coronal prenatal T2-weighted images of a 17-week and 23-week gestational age fetus demonstrates the ongoing brain maturation.

Figure 44 A, B, C & D

Axial and sagittal prenatal T2-weighted images of 25–37 weeks gestational age fetuses demonstrates the ongoing brain maturation.
Malformations of Cortical Development

- Occur between two and four months of gestation
- Schizencephaly
  - Open lip versus closed lip
- Lissencephaly
- Gray matter abnormalities
  - Pachygyria, polymicrogyria
  - Neuronal heterotopias
- Megaencephaly

Schizencephaly

- Clefts extending from the brain surface to the ventricle lined by polymicrogyric cortex
- Closed lip versus open lip
- Septum pellucidum absent in 80% of cases
- Clinically seizures, hemisyndromes, mental retardation
- No septum pellucidum
- Vessels!!!!!
Lissencephaly  
Figure 49
- Type 1 lissencephaly
- Arrested neuronal migration
- 4-layer cortex with smooth brain surface
- Genetics or infection
- Seizures and developmental delay
- Type 2, congenital muscular dystrophy, Walker-Warburg

Lissencephaly, Bandheterotopia  
Figure 50
- Bandheterotopia
- Overlying cortex may be shallow or near normal
- X-linked
- Less severe form
- Less seizures, cognitive function may be normal

Heterotopic Gray Matter
- Arrested neurons along migration path from germinal matrix to cortex
- Inherited or acquired
- Subependymal nodules
- Band heterotopia
- Overlying cortex may be affected
- Seizures, mental retardation or normal
Heterotopic Gray Matter: Spectrum

[Figure 51]

Figure 51 A to F

T1- and T2-weighted images demonstrates various degrees of periventricular cortex isointense heterotopias in three different children.

Disclosure

- I have nothing to disclose
- No relevant financial relations interfering with my presentation
- No reference of any unlabeled or unapproved use of drugs