Hindbrain malformations

Gisele E. Ishak. MD
• No disclosure
Goals

• Scrutinizing Midbrain and Hindbrain (MH)
• Role of DTI in MH Malformations (MHM)

• Tubulinopathies – looking beyond the cortex– “new” phenotype that should be now included in the MHM
Background

• Used to be Lag in midbrain hindbrain literature

• Recently, advances in neuroimaging and genetic sequencing → new malformations (PTCD), new phenotypes within one malformation (TUBB4 in H-ABC), improved genotype-phenotype correlation, new genetic mutations within malformations (JRDS, HME/FCD)
REVIEW ARTICLE

A developmental and genetic classification for midbrain-hindbrain malformations

A. James Barkovich,¹ Kathleen J. Millen²,³ and William B. Dobyns²,³,⁴
Update on neuroimaging phenotypes of mid-hindbrain malformations

Patrice Jissendi-Tchofo • Mariasavina Severino • Béatrice Nguema-Edzang • Cissé Toure • Gustavo Soto Ares • Anthony James Barkovich

Developmental disorders of the midbrain and hindbrain

A. James Barkovich*

Department of Radiology and Biomolecular Imaging, Neuroradiology Section, University of California at San Francisco, San Francisco, CA, USA
• Pattern recognition
• Including MH in search criteria is crucial

• MHM
  – Whole world of malformations
  – Assist in classifying Malformation of cortical development MCD (genotype – phenotype, genotype – pathology (Jissendi-Tchofo et al., 2009; Dobyns 2010, Pisanoe et al., 2012)
Diffusion Tensor Imaging

DTI Revolutionized the microstructural evaluation of WM, in particular MH fiber tracts, that may go undetected on cMRI

→ Emergence of new set of axonal guidance disorders for example:

JRDS, L1 CAM, HGPPS, PTCD, ARSACS
Decussation of MCP

Transverse pontine fibers

Pontine tegmental cap

Absence of decussation of the superior cerebellar peduncles (SCP) which are elongated with Molar tooth appearance

Corticospinal tracts (CST) and dorsal longitudinal axonal pathways

Decussation of the SCP at the level of the isthmus

Dorsal longitudinal axonal pathways

Dorsal longitudinal axonal pathways

Corticospinal tracts (CST)

Normal

Normal
ARSACS
Part II
Tubulinopathy
Tubulinopathies

- Mutations in alpha- and beta-tubulins

- Known as a major cause of malformations of cortical development (MCD)

- First discovery in 2007 of TUBA1A as a novel gene for lissencephaly
Tubulinopathies

• Increase in number of publications

• Kumar et al 2010 - 30% of patients with lissencephaly with cerebellar hypoplasia had mutations in TUBA1A, as opposed to only 1% in the classic lissencephaly cohort.
Phenotypes of tubulinopathies

- LIS +/- PCH +/- ACC (*TUBA1A, TUBB2B, TUBB3*, many refs)
- PMG +/- PCH +/- ACC (*TUBB2B, TUBA1A, TUBB*, mult refs)
- CFEOM +/- LIS/PMG (*TUBB3*, Tischfield 2010)
- AR PMG + optic nerve hypoplasia (*TUBA8*, Abdollahi 2009)
- ACC + cerebellar hypoplasia (*TUBA1A*, Kumar 2010)
- H-ABC (*TUBB4*, Simmons 2013, Ferreira 2014)

- Variable spectrum of MCD – lissencephaly, Pachygyria, PMG (Published mutation detection rates ranging from 1-13.3%)

- **Key feature described** MCD +/- PCH (cb hypoplasia rather than dysplasia)
First patient
Second patient
2 different patients
• Cohort of ten patients with a distinct and very similar MRI pattern
1. MH hypoplasia and asymmetry with ventral indentation

2. Asymmetry of Middle cerebellar peduncles

3. Distinct dysplasia of the superior vermis (“diagonal” folia on axial views) with asymmetry of the orientation of the fissures

4. Mild hypoplasia and Asymmetry of cerebellar hemispheres
Asymmetry of Inferior and middle cerebellar peduncles in 2 different patients
Hypoplasia of the vermis mainly anterior lobe
Globular contour of medulla, with indistinct demarcation between the pyramids and the olivary nuclei
CC may be variably affected, ranging from almost complete agenesis to normal
Cortical asymmetry
1. BG are asymmetrically, dysplastic with bulbous appearance with diffuse, branched, or absent anterior limb of the internal capsule
2. Lateral ventricles show an irregular contour and abnormal rounding of the frontal horns
3. Thalami are globular-shaped
Normal
Asymmetry of the CST in the supratentorial including progressively smaller tract size (black arrow) and misoriented fibers (red arrow) compared to normal. Fiber bundles are less compact or less dense compared to normal.

?? Axonal Guidance disorder
• Cohort of ten patients with a distinct and Characteristic Pattern of dysplasia/asymmetry:

- MH
- Cerebellar
- BG
- AND very subtle cortical asymmetry/disorganization.
But wait!

- Mutations in tubulin genes cause PCH with lissencephaly

*Figure: TUBA1A Kumar 2010*
But wait!

• Mutations in tubulin genes cause PCH with lissencephaly

   OR

• PMG +/- PCH

*TUBB2B*  Jaglin 2009
But wait!

- MH asymmetry and Basal ganglia dysplasia!!

TUBA1A Kumar 2010

TUBB2B Jaglin 2009
• 7/9 tested → mutations in *TUBA1A, TUBB2B* or *TUBB3*

• Small cohort, but!

• Distinct and highly recognisable pattern with a high yield of mutation detection
Conclusion

• Scrutinizing MH is very crucial
  
  1. May expand phenotypes (new phenotype of Tubulinopathy which is known for MCD)

  2. May expand pathomechanism (axonal guidance and not only migrational disorder in tubulinopathies)
Thank You