Microcephalies: MRI clues

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Microcephaly

- Reduction in brain volume
- Good correlation with occipitofrontal circumference
- OFC < 3rd centile or more than 2 SD below the mean for sex, age, and ethnicity.

Roche et al. [Pediatrics 1987;79:706-712]
**Incidence and neurological outcome in microcephaly**

- **Intellectual deficiency and microcephaly**
  - 11% ID in OFC < -2 SD and 51% in OFC < -3 SD

- **Risk of ID is increased when microcephaly + IUGR**

- **Risk of cerebral palsy**
  - 21.4% in OFC < -2SD
  - +++ Postnatal Microcephaly (progressive) > Congenital Microcephaly

- **Risk of Epilepsy**
  - 40.9% in OFC < -2SD
  - +++ Postnatal Microcephaly (progressive) > Congenital Microcephaly

- **Risk of ophthalmological / auditory deficiency**
  - 6.4% in patients with severe microcephaly (<-3 SD)
  - ++ Syndromal microcephalies

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Abdel-Salam et al. 2000
Watemberg et al. 2002
Microcephaly: Major neurological sign

The phenotype of microcephaly is variable and the spectrum of associated disorders is large, with more than 900 disorders comprising the clinical sign ‘microcephaly’

- 1- Classifications
- 2- Diagnostic approach
- 3- MRI clues
Microcephaly: Aetiological classification

Any condition that affects important processes of brain growth, such as progenitor cell proliferation, cell differentiation, and cell death, can induce microcephaly.

- Non syndromal
- Syndromal
  - + extracranial malformations and/or
    - facial dysmorphism
    - Vision impairment
    - Hearing impairment

Genetics
Metabolic
Exogenic
Craniostenosis

Teratogens
Perinatal damage
Fetal infections
Microcephaly: classification according to the onset

**Primary congenital**
- Evident at birth

**Secondary (acquired)**
- Postnatal
  - normal OFC at birth and then the relative OFC drops to a value < 2SD below the mean.
- Prenatal
  - normal OFC at 2\(^{nd}\) trimester and then the relative OFC drops to a value < 2SD below the mean

These terms do not imply distinct aetiologies. Both primary and secondary microcephaly can be acquired or genetic.
Evaluation of patients with microcephaly

Does newborn have clinical features, other organ involvement, vision/hearing impairments, or family history to suggest a specific disease or syndrome?

Yes
- Do specific testing for that condition

No
- Is the microcephaly proportionate with weight and height?
  - Yes
    - Proportionate microcephaly. Does the child have neurologic signs or symptoms or a family history of childhood neurologic disease?
      - Yes
      - Observe and consider MRI, genetic, or metabolic testing if there are new neurologic signs or symptoms or worsening microcephaly.
      - No
  - Proportionate microcephaly.

Obtain Neuroimaging

- CT often non-specific but does have a strong prognostic value if abnormalities
- MRI more sensitive, gold standard
- Repeated MRI > 2 years recommended given complete myelination at this age.
- In severe microcephaly < 3SD, abnormal findings on MRI is 80% vs. 43% less severe
Microcephaly: MRI clues

- ASPM
- WDR62
- FOXG1
- KIF11
- PNPK
- PHGDH
- Maternal PKU
- ZivaV
Congenital Microcephaly with a Simplified Gyral Pattern: Associated Findings and Their Significance

Grading system for sulcation

- **Mildly simplified**
  - width of gyri < depth of sulci

- **Moderately simplified**
  - width of gyri = depth of sulci

- **Severely simplified**
  - width of gyri > depth of sulci

A strong correlation between the degree of microcephaly, the volume of white matter, and the presence of a simplified gyral pattern.

No correlation with the abnormalities of the corpus callosum, size and structure of posterior fossa contents, and myelination.

Diagnostic work-up in microcephaly

- Isolated
- Progressive microcephaly
- Metabolic
- Craniostenosis

- Teratogens
- Perinatal damage
- Fetal infections

- Clastic events
- + Posterior Fossa Abnormalities
- + Ocular abnormalities
Fetal infection CMV

Fetal MRI at 32sd WG: vacuolization of the temporal horn and heterogeneous WM

OFC at birth 31 cm

MR imaging findings of fetal CMV infection

1st trimester
- ventriculomegaly with severe loss of volume,
- lissencephaly,
- periventricular and cortical calcification

Mid 2nd trimester
- schizencephaly
- periventricular calcification

3rd trimester
- patchy periventricular white matter lesions
- normal gyration

Fink K R et al. Radiographics 2010;30:1779-1796
Fetal infection Zika Virus

brain circumference (-4.5 SD), at 23+5 GW,
### Microcephaly and Zika virus: neonatal neuroradiological aspects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly</td>
<td>100%</td>
</tr>
<tr>
<td>Skull telescoped with overriding of bones</td>
<td>100%</td>
</tr>
<tr>
<td>Decreased cerebral mantle</td>
<td>100%</td>
</tr>
<tr>
<td>Increased subarachnoid space</td>
<td>100%</td>
</tr>
<tr>
<td>Lissencephaly</td>
<td>100%</td>
</tr>
<tr>
<td>Ventriculomegaly</td>
<td>100%</td>
</tr>
<tr>
<td>Brain stem atrophy</td>
<td>0</td>
</tr>
<tr>
<td>Cerebellar atrophy</td>
<td>0</td>
</tr>
<tr>
<td>Spinal atrophy</td>
<td>0</td>
</tr>
<tr>
<td>Schizencephaly</td>
<td>0</td>
</tr>
</tbody>
</table>
Risk of microcephaly is about 1% if the mother is infected by ZIKV in the first trimester of pregnancy

• This risk seems low compared to other viral infections associated to birth defects
  – 13% of Primary CMV infections
  – 38%-100% for Congenital rubella syndrome if the mother is infected during the first trimester
  – 10% Parvovirus B19

• However, the rate of contamination is very high (66-73%)
  – Vs 1-4% for CMV, <10/year for Rubella, or 0.6-1.2% for Parvovirus

Cauchemez S, Lancet. 2016 May 21;387(10033):2125-2132
After neuroimaging, there is no universal testing recommended. Further studies directed by the presence of signs or symptoms:

- Maternal PKU
- Amish lethal microcephaly
- Phosphoglycerate Dehydrogenase Deficiency

In patients with MIC and DD, the prevalence of an underlying metabolic disorder ranges from 1–5%.
Maternal PKU

- Microcephaly
- Delayed myelination.
- Hypoplasia of the corpus callosum

+ other malformations, including CHD, craniofacial abnormalities, intrauterine and postnatal growth retardation
Amish Lethal microcephaly:

- Metabolic disorder related to a mitochondrial deoxynucleotide carrier ($DNC/SLC25A19$)
- 2-ketoglutaric aciduria and lactic acidosis
- Extremely profound microcephaly (−6 SD), lissencephaly and PCH


Amish microcephaly: Long-term survival and biochemical characterization, Volume: 152A, Issue: 7, Pages: 1747-1751,
Phosphoglycerate dehydrogenase deficiency (PHGDH)

- Severe developmental delay
- Epilepsy
- Intrauterine growth retardation
- Low serine levels in plasma and CSF

• Extreme end of the spectrum: a lethal MCA syndrome
• Defective somatic growth
• Microlissencephaly and cerebellar hypoplasia
• Colloidon-like Icthyosis

• Genetic testing: next step after neuroimaging
• WES is becoming more widely available in the evaluation of microcephaly.
• Use of this technology found an etiology in 29% of previously evaluated and undiagnosed cases of microcephaly

Autosomal Recessive primary microcephaly (MCPH):

- Primary i.e evident by 32th WG, present at birth and non progressive
- Incidence
  - 1 per million (Eastern countries)
  - 1/100,000 in consanguineous populations (Pakistan)
- Microcephaly is the outcome of a smaller but architecturally normal brain
- Genetic heterogeneity with 23 MCPH loci
  - 2 major genes *ASPM and WDR62*
  - Responsible for 55-60% of the mutated genes

MCPH-5 : ASPM

- The most common form of MCPH World-wide
- Protein-truncating mutations

US at 30 GW
Sloping forehead

MRI 31 GW : Delayed gyration (arrow)

Simplified Gyral pattern

Bond J, Nat Genet. 2002;32:316–320; Mahmood Orphanet J Rare Dis. 2011; Letard P Hum Mutat. 2018
MCPH-5 : ASPM

- Mutations distributed throughout the gene without any observed association of phenotypic severity with mutation position or type
- Late-onset seizures 10%
- Borderline-normal to severe ID.
- Mild motor delay 50% patients.
- Delayed Language development
MCPH2: WDR62

- Protein-truncating distributed throughout the gene
- Mutations include missense, deletions and premature terminations

variety of severe cortical malformations
- microcephaly,
- pachygyria with cortical thickening
- hypoplasia of the corpus callosum

Nicholas, Nat Genet 2010

Nature. 2010 Sep 9;467(7312):207-10. Bilgüvar K1
MCPH2: WDR62

Additional cortical abnormalities
- lissencephaly
- polymicrogyria
- Schizencephaly

Traditionally regarded as distinct entities

Conclusion

- Common clinical situation
- A wide spectrum of evolution and aetiologies
- Diagnostic work-up starts with an evaluation of the evolution of MIC and associated neurological and non neurological features
- In cases of severe MIC or with neurological features not explained by clastic or toxic events, MRI may give some clues
- Among the monogenic causes of primary Ar MIC, ASPM and WDR62 related MIC are the most common with distinct MRI patterns
Acknowledgements

- Charles Joris, Nathalie Boddaert, and Pascale Sonigo Pediatric Radiology Necker Enfants Malades
- Molecular Biology–Necker- Julie Steffann and coll., Necker Enfants Malades
- Anais Brassier and Pascale de Lonlay, Metabolic Unit Necker Enfants Malades
- Josseline Kaplan and Catherine Edelson (KIF11 observations)
- INSERM U1163 Imagine Institute – Team Pierani
  - Mara Cavallin, Nancy Vegas, Camille Maillard (*), Amandine Bery,
- COST network members
- Clinicians from AndiRare and Defiscience Networks who share many observations on MCD