Hypomyelinating leukodystrophies

Update on Hypomyelinating Leukodystrophies
Geneviève Bernard MD, MSc, FRCPC
Associate Professor, McGill University
Pediatric Neurologist, McGill University Health Center
Junior Scientist, Research Institute of the McGill University Health Center

Objectives
1. Differentiate hypomyelination from other pathologies on MRI
2. Explain the diagnostic algorithm to hypomyelination
3. Describe the clinical and MRI characteristics of novel entities

Disclosures
1. Speaker’s honoraria
   - Genzyme
   - Actelion Pharmaceuticals
2. Scientific advisory boards
   - Actelion Pharmaceuticals
   - Shire
   - Santhera Pharmaceuticals
3. Grants
   - Shire
   - Actelion Pharmaceuticals
   - Bluebird Bio
4. Funds to organize a conference
   - Fortuna Fix
   - Allergan
   - Retrophin
   - Actelion Pharmaceuticals

CLASSIFICATION
2 categories:
Hypomyelinating
  • Insufficient myelin deposition during development
Other disorders
  • Other myelin pathologies

Hypomyelination definition
- On MRI
  - On T1 weighted images, white matter is, compared to grey matter structures:
    • Hyperintense
    • Isointense
    • Slightly hypointense
  - On T2 weighted images, white matter is, compared to grey matter structures:
    • Hyperintense

NORMAL

T1  T2  T2
Hypomyelinating Other pathologies
Hypomyelinating leukodystrophies

What makes it a hypomyelinating leukodystrophy?

- "Hypomyelination pattern" on MRI
- If child < 2 years, repeat MRI ≥ 6 months later
- No progression of myelination
- Progression of myelination
- Significant atrophy?
- Myelination delay
- Neuronal disease with secondary hypomyelination

Classification – Hypomyelinating leukodystrophies

- PLP1-related disorders (Pelizaeus-Merzbacher)
- Pelizaeus-Merzbacher-like disease (HLD2)
- Hypomyelination with Congenital Cataracts or HCC (HLD5)
- Hypomyelination with Atrophy of the Basal ganglia and Cerebellum or H-ABC (HLD6)
- POLR3-related (4H) leukodystrophy (HLD7)
- 18q- syndrome
- Free fatty acid storage disease
- Oculodentodigital dysplasia
- Cockayne and Trichotiodystrophy with hypersensitivity to sunlight

Classification – Neuronal disorders with secondary hypomyelination/slowly progressing myelination (ATROPHY)

- AIMP1-related disorders (HDL3)
- HSPD1-related disorders or Mitochondrial Hsp60 chaperonopathy (HLD4)
- Global cerebral hypomyelination (SLC25A12)
- GPR56-related disorders
- Serine synthesis defects
- Neuronal ceroid lipofuscinosis
- Early-onset GM1 and GM2
- Mitochondrial disorders
- Fumarate hydratase deficiency
- Band-like intracranial calcification with simplified gyration and polymicrogyria (OCULN gene)
- Neuronalopathic form of malignant infantile osteopetrosis
- CNTNAP1 hypomyelination, neuropathy +/- arthrogryposis
- Etc.

Classification – Myelination delay

- Allan-Herndon-Dudley syndrome (MCT8 or SLC16A2)
- SOX10-related disorders
- Others
  - Chromosomal abnormalities
    - E.g. Down syndrome
  - Inborn errors of metabolism
    - E.g. creatine deficiency syndromes, biotinidase deficiency, Zellweger spectrum, SLCL2A2-related mitochondrial DNA depletion syndrome
  - Acquired causes
    - E.g. hypoxic-ischemic insults, congenital infections, hypophosphatemia, hypothyroidism, malnutrition
  - Etc.

The Hypomyelinating Leukodystrophies

CLINICAL UPDATE
Hypomyelinating leukodystrophies

H-ABC

Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (HLD6)
- 7 patients
- MRI pattern
- Clinical features
  - Abnormal psychomotor development
  - Extrapyramidal movement disorders
  - Ataxia
  - Spasticity

- Vast majority of cases are sporadic

TUBB4A disease spectrum

- 16 patients from 14 families, majority of Roma ethnicity
- Severe H-ABC phenotype
  - No development
  - Epileptic encephalopathy
  - Microcephaly
- Typical MRI features
- Autosomal recessive
- UFM1 encodes ubiquitin-fold modifier 1
  - Member of the ubiquitin-like family involved in posttranslational modification of proteins
**POLR3-RELATED (4H) LEUKODYSTROPHY**

Caused by recessive mutations in **POLR3A**, **POLR3B** or **POLR1C**

CLINICAL FEATURES

- Neurological – cerebellar > pyramidal/extrapyramidal > cognitive
- Non neurological (non obligatory) – dental, hormonal, ophthalmological

Genotype-phenotype correlations

- Difficult re numerous mutations / combinations of mutations
- In general, **POLR3A** patients have a more severe disease course
  - Age at wheelchair
  - Survival
- **POLR3A** patients with the combination of the c.1771-7C>G and non-sense mutation have a very severe disease course and a specific MRI pattern
- **POLR3B** patients have an earlier onset of disease
  - The common c.1568T>A **POLR3B** mutation is milder
    - Homozygous state can be clinically asymptomatic until at least early adulthood
- **POLR1C** patient may craniofacial abnormalities reminiscent of Treacher-Collins Syndrome
- Intrafamilial variability is rare but can be very prominent

Typical MRI features

- Hypomyelination
- Relative preservation (T2 hypointensities) of:
  - Dentate nucleus
  - Optic radiation
  - Anterolateral nucleus of the thalamus
  - Globus pallidus
  - Corticospinal tracts at the level of the posterior limb of the internal capsule
- Cerebellar atrophy
- Thinning of the corpus callosum

**POLR3-related (4H) leukodystrophy**

- 4H syndrome (Hypomyelination, Hypodontia, Hypogonadotropic Hypogonadism)
- ADDH (Ataxia, Delayed Dentition, Hypomyelination)
- TACH (Tremor-Ataxia with Central Hypomyelination)
- Leukodystrophy with oligodontia
- HCAHC (Hypomyelination with Cerebellar Atrophy and Hypoplasia of the Corpus Callosum)

Caused by recessive mutations in **POLR3A**, **POLR3B** or **POLR1C**

The American Journal of Human Genetics 81, 2, September 2007 - POLR3A

Recessive mutations in POLR3B cause a leuadystrophy by impairing biogenesis of RNA polymerase III

Clinical spectrum of 4H leukodystrophy caused by **POLR3A** and **POLR3B** mutations
Hypomyelinating leukodystrophies

Scoring system (0-54)

To quantify:
1. hypomyelination
2. atrophy

Validation – 5 different raters – 40 MRIs from 36 patients
Excellent interrater reliability
MRI scores correlated with gross motor disability (GMFCS)

Brain area – white matter

<table>
<thead>
<tr>
<th>Area</th>
<th>T1W</th>
<th>T2W</th>
<th>T1W + T2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal white matter</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Subcortical</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Frontoparietal border area</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Subcortical</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Parieto-occipital white matter</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Subcortical</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Thalamic region</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Insular gyri</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Subcortical</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Motor cortex</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Subcortical</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Subcortical</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Splenium</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Middle cerebellar peduncles</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Subcortical</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0-2</td>
<td>0-2</td>
<td>0-4</td>
</tr>
<tr>
<td>Total white matter score</td>
<td>0-22</td>
<td>0-22</td>
<td>0-44</td>
</tr>
</tbody>
</table>

Brain area – atrophy

<table>
<thead>
<tr>
<th>Area</th>
<th>T1W</th>
<th>T2W</th>
<th>T1W + T2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial (bicaudate ratio)</td>
<td>0-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>0-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem (pons diameter)</td>
<td>0-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>0-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar hemispheres</td>
<td>0-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy score</td>
<td>0-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score (white matter and atrophy)</td>
<td>0-54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HEMS
Hypomyelination of early myelinating structures

• Clinical
  – Boys
  – Onset 6-20 months
  – Relatively stable or slowly progressive course
• MRI: hypomyelination of early myelinating structures
• Genetics: PLP1 intronic mutations

Novel Hypomyelinating Leukoencephalopathy Affecting Early Myelinating Structures: Clinical Course in Two Brothers

Altered PLP1 splicing causes hypomyelination of early myelinating structures
Hypomyelinating leukodystrophies

H-SMD
X-linked Hypomyelination with Spondylometaphyseal Dysplasia

Clinical features
- Onset: 8-36 months
- Neurologically:
  - Motor regression
  - Spasticity
  - Tremor
  - Ataxia, dysarthria, nystagmus
  - Cognitive involvement
  - Vision loss
- Hearing loss (rare)
- Seizures (rare)
- Systemic features
  - Pulmonary hypertension
  - Spondylometaphyseal dysplasia
- Slowly progressive course

Genetics
- X-linked recessive
- Mutations in AIFM1
  - Some are synonymous
  - Some are intronic

Spondylometaphyseal Dysplasia
- Hands: brachydactyly, clinodactyly, flat and shortened metacarpals and phalanges
- Long bones: changes in metaphyses and physis
- Vertebral abnormalities
- Pelvic abnormalities
- Diffuse osteopenia

Miyake et al., Neurogenetics 2017

Spondyloepimetaphyseal dysplasia: a new X-linked variant with mental retardation

Spondyloepimetaphyseal dysplasia with neurodegeneration associated with AIFM1 mutation – a novel phenotype of the mitochondrial disease

A new type of leukoencephalopathy with metaphyseal chondrodysplasia maps to Xq45-q57

Genetics

Spondylometaphyseal Dysplasia

Miyake et al., Neurogenetics 2017

Clinical features
- Onset: 8-36 months
- Neurologically:
  - Motor regression
  - Spasticity
  - Tremor
  - Ataxia, dysarthria, nystagmus
  - Cognitive involvement
  - Vision loss
- Hearing loss (rare)
- Seizures (rare)
- Systemic features
  - Pulmonary hypertension
  - Spondylometaphyseal dysplasia
- Slowly progressive course

Genetics
- X-linked recessive
- Mutations in AIFM1
  - Some are synonymous
  - Some are intronic

Spondylometaphyseal Dysplasia

Miyake et al., Neurogenetics 2017

Clinical features
- Onset: 8-36 months
- Neurologically:
  - Motor regression
  - Spasticity
  - Tremor
  - Ataxia, dysarthria, nystagmus
  - Cognitive involvement
  - Vision loss
- Hearing loss (rare)
- Seizures (rare)
- Systemic features
  - Pulmonary hypertension
  - Spondylometaphyseal dysplasia
- Slowly progressive course

Genetics
- X-linked recessive
- Mutations in AIFM1
  - Some are synonymous
  - Some are intronic

Spondylometaphyseal Dysplasia

Miyake et al., Neurogenetics 2017

Clinical features
- Onset: 8-36 months
- Neurologically:
  - Motor regression
  - Spasticity
  - Tremor
  - Ataxia, dysarthria, nystagmus
  - Cognitive involvement
  - Vision loss
- Hearing loss (rare)
- Seizures (rare)
- Systemic features
  - Pulmonary hypertension
  - Spondylometaphyseal dysplasia
- Slowly progressive course

Genetics
- X-linked recessive
- Mutations in AIFM1
  - Some are synonymous
  - Some are intronic

Spondylometaphyseal Dysplasia

Miyake et al., Neurogenetics 2017

Clinical features
- Onset: 8-36 months
- Neurologically:
  - Motor regression
  - Spasticity
  - Tremor
  - Ataxia, dysarthria, nystagmus
  - Cognitive involvement
  - Vision loss
- Hearing loss (rare)
- Seizures (rare)
- Systemic features
  - Pulmonary hypertension
  - Spondylometaphyseal dysplasia
- Slowly progressive course

Genetics
- X-linked recessive
- Mutations in AIFM1
  - Some are synonymous
  - Some are intronic

Spondylometaphyseal Dysplasia

Miyake et al., Neurogenetics 2017

Clinical features
- Onset: 8-36 months
- Neurologically:
  - Motor regression
  - Spasticity
  - Tremor
  - Ataxia, dysarthria, nystagmus
  - Cognitive involvement
  - Vision loss
- Hearing loss (rare)
- Seizures (rare)
- Systemic features
  - Pulmonary hypertension
  - Spondylometaphyseal dysplasia
- Slowly progressive course

Genetics
- X-linked recessive
- Mutations in AIFM1
  - Some are synonymous
  - Some are intronic

Spondylometaphyseal Dysplasia

Miyake et al., Neurogenetics 2017

Clinical features
- Onset: 8-36 months
- Neurologically:
  - Motor regression
  - Spasticity
  - Tremor
  - Ataxia, dysarthria, nystagmus
  - Cognitive involvement
  - Vision loss
- Hearing loss (rare)
- Seizures (rare)
- Systemic features
  - Pulmonary hypertension
  - Spondylometaphyseal dysplasia
- Slowly progressive course

Genetics
- X-linked recessive
- Mutations in AIFM1
  - Some are synonymous
  - Some are intronic
THANK YOU!