Inherited white matter diseases

How should we classify white matter diseases?

Acquired
destruction of normally formed myelin

e.g., MS, ADEM, “demyelinating diseases”

Congenital
abnormal formation, destruction, or turnover of myelin

How should we differentiate inherited from acquired white matter disorders?

- Clinical findings
  motor function impairment, cognitive and behavioral involvement, seizures

- Neurophysiological studies
  NCVs, evoked potentials, EEG

- Laboratory work-up

- Neuroradiologic studies
  MRI "pattern recognition" (DWI, MRS)

The concept of symmetry

acquired
inherited

How should we categorize inherited white matter disorders?

White matter diseases = Myelinopathies

- Hypomyelination
- Hypomysis
- Dysmyelination

Delayed
Absent
Arrested
Abnormal

Not catching up
Partial

Van der Knaap et al., Radiology 1999

Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach

Impractical from a neuroimaging perspective
How should we study inherited white matter disorders on MRI?

**Diffusion-weighted MRI (DWI)**

May enhance the specificity of the MRI work-up

1. **Cytotoxic edema**
   - Cellular energetic failure
   - ↑ DWI, ↓ ADC

2. **Vasogenic edema**
   - Loss of integrity of BBB
   - ↓ DWI, ↑ ADC

3. **Intramyelin edema**
   - Myelin breakdown
   - ↑ DWI, ↓ ADC

**MRS**: 1H-MR Spectroscopy

- **N-acetylaspartate (NAA)**
  - A marker of viable neurons, reduced with neuron injury, immaturity

- **Creatine/Phosphocreatine**
  - Unknown significance, possibly energy supply

- **Choline**
  - A measure of membrane turnover, increased in infection, inflammation, neoplasm

- **Lactate**
  - Marker of anaerobic metabolism, mitochondrial dysfunction; not normally present

- **Myo-Inositol** (short TE)
  - Possibly a marker of glia

- **Glx** (short TE)
  - Glutamate release (injury)

**DWI**: specific patterns

1. 2-week-old seizures, stupor, hypotonia
2. Restricted diffusion limited to the myelinated WM of birth ("myelination map")

**MSUD**: maple syrup urine disease

- Deficient activity of branched chain 2-ketoacid dehydrogenase
- Accumulation of branched chain amino- and ketoacids in blood and urine

**MRS**: specific patterns

- **Canavan disease**
  - Deficit of aspartoacyclase enzyme, resulting in NAA accumulation

- **Creatine deficiency**
  - Deficit of creatine synthesis or transporter, resulting in Cr decrease
Lactate
Marker of anaerobic metabolism
Not specific of mitochondrial diseases!

Table 1A. The most important white and grey matter struc-
tures of the brain to be analysed in metabolic disorders
<table>
<thead>
<tr>
<th>White matter structures</th>
<th>Grey matter structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central (suck) white matter</td>
<td>Cerebral cortex</td>
</tr>
<tr>
<td>Subcortical U-fibres</td>
<td>Cingulum</td>
</tr>
<tr>
<td>External capsule</td>
<td>Putamen</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>Globus pallidus</td>
</tr>
<tr>
<td>Medial thalamic nucleus</td>
<td>Thalamus</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>Subthalamus nucleus</td>
</tr>
<tr>
<td>Anterior commissure</td>
<td>Red nucleus</td>
</tr>
<tr>
<td>Ventral midbrain</td>
<td>Substantia nigra</td>
</tr>
<tr>
<td>Central tegmental fascicul tract</td>
<td>Dentate nucleus</td>
</tr>
<tr>
<td>Caudate-white matter</td>
<td>Cortical white matter</td>
</tr>
</tbody>
</table>

From selective vulnerability...
... to pattern recognition

Disease stages

Metabolic crises

Merosin deficient CMD [MDC1A]
LAMAR 6q22-q23

Know your clinical context!
Classification of inherited white matter diseases

1. Classified leukoencephalopathies
   A. Leukoencephalopathies with known biochemical and/or molecular defect
      i. Hypomyelinating diseases
      ii. Dysmyelinating diseases
   B. Leukoencephalopathies defined on the basis of clinical and neuroradiological criteria, but still without known defect

2. Unclassified leukoencephalopathies
   Cases without a specific diagnosis despite extensive investigations

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Hypomyelinating diseases

The paradigm:
Pelizaeus-Merzbacher disease

primary disturbance in the formation of myelin

The MRI pattern:
Diffuse hypomyelination with normal white matter volume

Pelizaeus-Merzbacher Disease (PMD)
Mutations (duplication) of the proteolipid protein (PLP) gene

Clinical features:
severe failure to thrive with developmental delay
nystagmus, seizures, spasticity
Infantile form more common
Death during 2nd or 3rd decade of life

classic PMD: mutations in the PLP1 gene (Xq22)
different mutations spectrum of phenotypes

Pelizaeus-Merzbacher-like Disease (PMLD)

Clinical and imaging diagnosis: PMD

No PLP1 mutation

GJA12 (connexin 47) mutation

Higher cognitive and intellectual function and greater levels of motor performance, but earlier onset and more rapid neurologic deterioration than PMD
Hypomyelinating diseases

- PMD
- PMD-like disease
- H-ABC
- 4H syndrome
- HCC
- Salla disease
- 18q- syndrome
- Trichothiodystrophy
- ...and probably many more

Hypomyelinating leukodystrophy with (or without) Hypodontia and/or Hypogonadotropic Hypogonadism (H-LD7, 8) [4H Syndrome]

<table>
<thead>
<tr>
<th>POLR3A</th>
<th>10q22.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLR3B</td>
<td>12q23</td>
</tr>
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</table>

Saitsu et al., Am J Hum Genet 2001

Varily combined!

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HCC

Zarate et al. Nat Genet 2006; 38:1111-1113

Hypomyelination with Congenital Cataract

- Psychomotor delay
- Congenital cataract
- Peripheral neuropathy

H-ABC

van der Knaap MS. et al. AJNR 2002;23:1466-74

Hypomyelination with Atrophy of Basal ganglia and Cerebellum

- Slowly progressive spasticity
- Extrapyramidal movement disorders
- Cerebellar ataxia
- Moderate to severe cognitive deficit
- Genetic basis unknown

Dysmyelinating diseases:
- Abnormal myelin formation
- Cystic degeneration of myelin
- Myelinopathy due to axonal damage

The paradigms

Metachromatic leukodystrophy
Krabbe disease
X-linked adrenoleukodystrophy
Dysmyelinating diseases: abnormal myelin formation

Metachromatic leukodystrophy

- Caused by cerebroside sulphatase deficiency (chr. 22)
- Accumulation of sulfatides within oligodendrocytes & Schwann cells
- Late infantile, juvenile, and adult variants
- Diagnosis confirmed on serum, leukocyte, and fibroblast arylsulfatase A activity measurements
- Brain MRI: "tigroid" pattern of supratentorial leukoencephalopathy with sparing of U fibers

Krabbe disease (globoid cell leukodystrophy)

- Caused by galactocerebroside β-galactosidase deficiency (chr. 14)
- Accumulation of psychosine within white matter
- Infantile (< 2y), juvenile, and adult variants
- Diagnosis confirmed on serum, leukocyte, and fibroblast galactocerebrosidase measurements
- CT: thalamic hyperdensities
- MRI: white matter hyperintensities with early sparing of U fibers (possible tigroid pattern)

X-linked Adrenoleukodystrophy

Disorder of peroxysomal metabolism due to very-long-chain fatty acid-coenzyme A synthetase deficiency [Xq28]

Childhood cerebral form (CCALD): Males, onset 4-8 years
Hyperpigmentation (adrenal insufficiency)

Diagnostic clue: symmetric, peritrigonal WM abnormality involving the splenium
Symmetrical hyperintensity of the peritrigonal WM and splenium centrifugal and postero-anterior gradient spared “U” fiber peripheral CE

“Schaumberg Zones”
1. fully demyelinated
2. inflammation
3. active demyelination

Dysmyelinating diseases: abnormal myelin formation

X-linked Adrenoleukodystrophy
Symmetrical hyperintensity of the peritrigonal WM and splenium centrifugal and postero-anterior gradient spared “U” fiber peripheral CE

1. fully demyelinated
2. inflammation
3. active demyelination

X-ALD: Advanced imaging techniques

Dysmyelinating diseases: cystic degeneration of myelin

The paradigms

Alexander disease
Canavan disease
van der Knaap disease

Common feature: Macrocrania

Dysmyelinating diseases: cystic degeneration of myelin

Alexander disease
Fibrinoid WM degeneration due to Rosenthal fibers accumulation within astrocytes

Infantile Form
Macrocrania, seizures, developmental delay, hypotonia and death before age 1
Juvenile & adult forms also exist

Diagnostic clues:
macrocrania with symmetrical frontal WM involvement
dense periventricular rim at CT centrifugal antero-posterior gradient “U” fibers eventually involved

Alexander disease
Typical involvement of the corticospinal tracts

X-ALD

Advanced imaging techniques

2
Dysmyelinating diseases: cystic degeneration of myelin

The paradigms

Alexander disease
Canavan disease
van der Knaap disease

Common feature: Macrocrania
Caused by deficiency of aspartoacylase enzyme, resulting in NAA accumulation
- NAA probably has a role in the molecular efflux water pump system
- Excessive NAA leads to water accumulation in WM with resulting spongy degeneration

**Infantile form (3-6 months):**
- Macrocrania, hypotonia, lethargy, seizures, spasticity, optic atrophy, developmental delay

**MRI:** Diffuse leukencephalopathy involving the entire WM with centripetal gradient starting from "U" fibers

**Canavan disease:** Advanced imaging techniques

**Van der Knaap disease**
- Megalencephalic leukencephalopathy with subcortical cysts [MLC]

**MLCI 22q13.33** (60-70% of cases)
- Spongiform leukencephalopathy with discrepantly mild clinical course

Onset during first year with macrocrania, ataxia, spasticity, gait disturbances, slow mental deterioration, seizures

**Diagnostic clue:** Diffuse leukencephalopathy with WM swelling and temporal/frontal cysts

**MLC:** Advanced imaging techniques
Dysmyelinating diseases: myelinopathy due to axonal damage

**Vanishing White Matter disease**
Childhood ataxia with central hypomyelination [CACH]

5 genes: 14q24, Chr 12, 1p34.1, 3q27, 2p23.3

- Late infantile-early childhood onset with ataxia, spasticity, but only mild impaired mental capacities
- Normal initial psychomotor development, first clinical manifestation after minor trauma or infection
- Death in 2-6 years

**Diagnostic clues:** diffuse central WM cavitation superimposed on hypomyelinating pattern

**Vanishing White Matter disease**
Mitochondrial Leukoencephalopathy

**Clinical findings:** persistent ataxia following mild head trauma

**Leukoencephalopathy and Mitochondria**

**Respiratory chain defects (I, II, IV / combined)**

- PDH deficiency
  - Extensive WM involvement (swelling, cystic degeneration)
  - Common involvement of the corpus callosum
  - Basal ganglia or brainstem involvement
  - Lactate peak on MRS

**VWMD:** Advanced imaging techniques

- Diffuse WM hyperintensity on T2WI with involvement of the "U" fibers
- WM showing areas of CSF-like signal intensity on T1, PD-, and FLAIR images

© L. Meiners and P. Sjijns, Groningen, the Netherlands
Evidence of Lac in normal-appearing WM indicates global metabolic impairment.

Strong consideration for a diagnosis of mitochondrial disease.

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Thank you!

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