Myelination, Leukodystrophies and Hypomyelinating Disorders

Florian Eichler, M.D.
Massachusetts General Hospital
Harvard Medical School
Myelin

- Lipid bilayer enhanced by intrinsic and extrinsic proteins
- 50% less proteins than RBC membrane
- Two genes make up 80% of total protein:
  - Proteolipid protein (PLP)
  - Myelin basic protein (MBP)
- Lipids:
  - Galactose containing glycolipids
  - High cholesterol content
What is the Sequence of Myelination?

1920
7-month-old human fetus (Flechsig 1921)
Normal Myelination Pattern

Flechsig 1920:

- Projection before Association Pathways
- Peripheral before Central
- Sensory before Motor

- Fundamental Law of Myelogenesis: “equally important nerve fibers develop simultaneously, but those of dissimilar importance develop one after another in a succession defined by an imperative law”
Normal Myelination Pattern

<table>
<thead>
<tr>
<th>Fetal age Lunar months</th>
<th>Months of first year</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 5 6 7 8 9 10</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12</td>
<td>2 3</td>
</tr>
</tbody>
</table>

1. MOTOR ROOTS
2. SENSORY ROOTS
3. STATO-ACOUSTIC SYSTEM TECTUM AND TEGMENTUM
4. MEDIAL LEMNISCUS
5. IAK INNER DIVISION INFERIOR CEREBELLAR PEDUNCLE
6. AAK OUTER DIV. INF. CEREB. PEDUNCLE
7. SUP CEREBELLAR PED
8. MID CEREBELLAR PED
9. RETICULAR FORMATION
10. BR INF COL BRACHIA SUP. COL., OPTIC NERVE AND TRACT
11. HI and VICO d’AZYR
12. ANSA and PI
13. H2 and PE
14. OPTIC RAD
15. SOMESTHETIC RAD
16. ACOSTIC RAD
17. NON-SPECIFIC
18. STRIATUM
19. PYRAMIDAL TRACTS
20. FRONTO-PONTINE TRACT
21. FORNIX
22. CINGULUM
23. GREAT CEREBRAL COMMISSUR

Lecours, 1967
MRI reveals Myelination Pattern at Birth

Myelin in post limb of IC, GP and thalamus, central parts of cerebellar WM.
Statoacoustic Organ fully myelinated before birth

Yakovlev and Lecours, 1967
Statoacoustic Organ fully myelinated before birth

Concurrent Functional Changes:

- Unique effectiveness of rocking stimulation in quieting a newborn
- Effect of upright posture upon alertness
- Vestibular reflexes elicited at birth (Peiper)
Normal Myelination Pattern
Pyramidal Tract Myelinates Rapidly in First Year

4 months
Pyramidal Tract Myelination

• “The longer the axon the more the cell has to gain by becoming myelinated”

Concurrent Functional Changes:

• In the first year of life the infant gains dramatically in neuromuscular function
Pyramidal Tract Myelinates Rapidly in First Year

Auditory Pathways Myelinate Slower than Visual Pathways
Anterior Temporal Lobe Last to Myelinate
Normal Myelination Pattern
Auditory Pathways Myelinate Slower than Visual Pathways

Concurrent Functional Changes:

- Rapid visual maturation in the infant
- Language comprehension takes time
Normal Adult Myelination on MRI
Neuroimaging Patterns in Myelin Disorders

- Disorders with Confluent MRI lesions
- Disorders with Cavitating MRI lesions
- Disorders with Hypomyelination
- Disorders with Calcifications
Hypomyelination: harder to distinguish gray and white matter
Demyelination

Hypomyelination

Krabbe

VWMD

GM2

PMD

Hypomyelination: milder changes on T1 and T2
MRI Lesion Pattern can be Diagnostic
Leukodystrophies of Infancy

- Globoid cell leukodystrophy (GLD)
- Pelizaeus-Merzbacher disease (PMD)*
- Canavan disease (CD)*
- Megalencephalic leukoencephalopathy with cysts (MLC)
- Aicardi-Goutières syndrome (AGS)
- Sulfite Oxidase Deficiency*
Globoid Cell Leukodystrophy (Krabbe Disease)

Classic Infantile (onset 0-6m)
- hyperirritability
- frequent arching
- hyporeflexia
- rapid decline
- seizures
- death

Juvenile (onset 3-8 yrs)
- rare ocular abnormalities
- spasticity, gait difficulties
- poor balance and falls

autosomal recessive
mutations in GALC

globoid cells: galactosylceramide
Canavan Disease (CD)

- increasing head size
- not irritable
- poor head control, hypotonia
- nystagmus
- motor delay: unable to sit up but some can reach for objects

*autosomal recessive, mutations in aspartoacylase gene leading to N-acetylaspartate (NAA) accumulation*
Sulfite Oxidase Deficiency (SOD)

- newborn with:
  - respiratory distress and poor feeding
  - fluctuations in tone
  - refractory seizures
- EEG: diffuse epileptiform discharges on a burst-suppression background
- + urine sulfite dip-stick
- ↑ urine thiosulfate and sulfocysteine

 distinguish isolated SOD from molybdenum cofactor deficiency

Eichler et al, 2006
Leukodystrophies of Childhood

- Metachromatic leukodystrophy (MLD)
- X-linked adrenoleukodystrophy (X-ALD)
- Alexander disease (AD)
- Vanishing white matter disease (VWMD)
- Megalencephalic leukodystrophy with cysts (MLC)*
Metachromatic Leukodystrophy (MLD)

Late Infantile (onset 6-15 months) at diagnosis (2 years)

- initial developmental progress
- “persistent toddlers”
- pain with minimal passive movement of the limbs

Juvenile (onset 3-8 yrs):

- behavioral changes
- tremor
- gait difficulties
- seizures

*autosomal recessive, defect in ARSA (arylsulfatase A) leading to sulfatide accumulation*
Alexander Disease

Infantile (onset 0-2 years):
- Macrocephaly
- Regression
- Seizures

Juvenile (onset after 2 years):
- Headaches
- Vomiting
- MRI reveals symmetric brainstem lesions

Mutations in $GFAP$ encoding filamentous protein of astrocytes and also accumulates as part of the Rosenthal fibers

Messing, Lancet 2003
Vanishing White Matter Disease

- onset and clinical severity highly variable
- chronic and episodic neurological deterioration (motor > mental, ataxia > spasticity), no or mild epilepsy
- episodes of rapid and major deterioration following infections with fever and minor head trauma

autosomal recessive, mutations in eIF2B
Childhood Cerebral Adrenoleukodystrophy (CCALD)

- boy with hyperactivity and inattention
- gait difficulties, “bumping into walls”
- within months nonambulatory and nonverbal
- latent adrenocortical insufficiency

*X-linked recessive, mutations in ABCD1*

very long chain fatty acids (VLCFA) > 20 carbons
Leukodystrophies of Adulthood

- Metachromatic leukodystrophy (MLD)
- Adrenomyeloneuropathy (AMN)*
- Vanishing white matter disease (VWMD)
- Cerebrotendinous Xanthomatosis (CTX)*
- Hereditary Diffuse Leukodystrophy with Spheroids (HDLS)*
- Alexander Disease (AD)
Monozygotic Twins with Discordant ALD Phenotype
Adrenomyeloneuropathopathy (AMN)

- adult male with spastic paraparesis - gait difficulties and bladder and bowel problems
- slow progression
- cognitively intact

20% of adults show progression similar to childhood form (adult CALD)

Eichler et al, 2007
Cerebrotendinous Xanthomatosis

- 21 yo man with progressive coordination difficulties and dementia
- history of cataracts
- history of frequent diarrhea

- *elevated plasma cholestanol*
- *Tx: chenodeoxycholic acid*

xanthomas
Hypomyelinating Disorders
Hypomyelinating Disorders

- permanent, substantial deficit in myelin deposition in the brain
- similar appearance on brain MRI
DEMYELINATION

KRABBE

HYPOMYELINATION

GM2

VWMD

PMD

Hypomyelination: milder changes on T1 and T2
Hypomyelination Pattern Summary

- T2: hyperintense
- T1: iso-, hyper- or slightly hypointense
- Overall MRI looks like that of a young child (less well distinguished gray and white matter)
- Pattern is unchanged – myelination is “stuck” on 2 MRIs 6-12 months apart in a child > 1 year of age
Common Neurological Findings in Hypomyelinating Disorders

- Developmental delay
- Nystagmus
- Cerebellar ataxia
- Spasticity

- Usually do not reach diagnosis but specific clinical and MRI features can lead to diagnosis
Pelizaeus Merzbacher Disease (PMD) is the prototypic hypomyelinating disorder.
Pelizaeus Merzbacher Disease (PMD) – Typical Clinical Features

- Family history: X-linked inheritance
- Nystagmus, usually by 3 months
- Early hypotonia and delayed motor development
- Prominent ataxia, eventually spastic paresis
- Most never walk but learn to speak
- Scoliosis and contractures
- Usually improve to about puberty or adolescence, then variable rate of decline
PMD shows a strikingly homogeneous T2 signal intensity of the cerebral white matter.

Rearrangements or mutations in gene encoding PLP1
T2 signal intensity of the cerebral white matter can vary in hypomyelination.

Pelizaeus Merzbacher Disease

4H Syndrome
4H Syndrome – Typical Clinical Features

- Hypomyelination on MRI
- Hypogonadotropin hypogonadism
- Hypodontia
4H Syndrome shows hypomyelination, cerebellar atrophy, and low signal in anterolateral thalamus, internal capsule and optic radiations caused by recessive mutations in POLR3A: encodes largest subunit of human RNA polymerase III (AJHG, September 2011)
Fucosidosis – Typical Clinical Features

- Progressive motor and mental decline
- Coarse facial features
- Dysostosis multiplex
- Angiokeratoma
- Visceromegaly
- Seizures
Fucosidosis shows T2 hypointensity in globus pallidus and substantia nigra deficiency of alpha-fucosidase
GM2 Gangliosidosis – Typical Clinical Features

Infantile:

- Normal at birth
- Motor weakness and less responsive by 3-5 months
- Exaggerated startle response
- Myoclonic jerks
- Seizures
- Cherry red spot

Late onset: no hypomyelination, no cherry red spot!
GM2 Gangliosidosis – Typical Clinical Features

- Elevated noise sensitivity
- Exaggerated startle
- Hypotonia
- Loss of sitting
- Reduced vocalization
- Loss of moving head side to side
- Loss of reaching for an object
- Spasticity
- Seizures
- Diminished eyesight

Age at onset, mo (mean ±1 SD)

n = 92

Bley et al. Pediatrics 2011
GM2 gangliosidosis with T2 hypointensity of **corpus callosum** and hyperintensity of **basal ganglia**

deficiency of beta-galactosidase and beta-hexosaminidase
Flow chart developed for reviewing MRI scans displaying signs of hypomyelination

Steenweg M E et al. Brain 2010;133:2971-2982
- Diagnostic Testing
- Management
- Therapies
Medical Management

- prevention infections and aspirations tantamount
- prudent use of antibiotics
- gastric tube placement (swallowing studies to monitor)
- antispasmodics, pain medication (eg gabapentin)

- adrenal replacement can be lifesaving - stress dose steroids
- hypogonadism and associated low serum testosterone concentration should receive androgens.
Orthopedic disorders in children with leukodystrophies

Pelvic tilt in a patient with Krabbe disease is shown by hip radiograph (a). Bilateral coxa valga with bilateral dislocated femoral heads is demonstrated in a patient with Pelizaeus-Merzbacher (b). Severe thoracolumbar scoliosis and pelvic tilt is shown in a patient with X-linked Adrenoleukodystrophy (c).

Adang et al, Molecular Genetics and Metabolism 2017 (in press)
Enzyme Replacement and Metabolic Correction

- Enzyme replacement: in animal models of metachromatic and globoid cell leukodystrophy but so far not successful in humans.

- Lorenzo’s Oil, a combination of erucic and oleic acid, lowers plasma VLCFA levels over a six to eight week period.
  - Continuous and longstanding correction of plasma VLCFA may be able to delay and reduce the risk of cerebral disease in boys with X-ALD. Unfortunately it does not halt brain demyelination, once the process has begun.
Cell Based Therapies

Bone marrow transplantation (BMT):
- efficacious in cerebral X-ALD but less efficacious for MLD as well as other leukodystrophies
- significant risks and hazards
  - < 2/3 of X-ALD males will ever develop cerebral disease
  - not a therapy that all asymptomatic boys X-ALD should undergo
  - not as effective in advanced brain disease

Gene therapy (lentiviral vector corrects autologous cells)
- for X-ALD and MLD patients
- likely reduces risks of graft versus host complications
- improved but still unknown leukemia risk
- high percentage of transfected CD34+ cells (35-50%)
Developmental outcomes of cord blood transplantation for Krabbe disease

Wright et al, Neurology 2017
Gene Therapy for X-ALD and MLD

Mobilization

Pre-infusion Conditioning

Infusion of Modified HSCs

Subject Treatment

Apheresis

GCSF (+/- plerixafor)

Myeloablation

busulfan + cyclophosphamide

Centralized Manufacturing

Select CD34+ stem cells

Transduce with Lenti-D vector

Cryopreserve, test and release
Lentiviral Vector-mediated ABCD1 Addition to Hematopoietic Stem Cells for the Treatment of CCALD

after autologous transplantation of gene corrected CD34+ cells:

- polyclonal hematopoietic repopulation occurred
- no clonal dominance emerged

Cartier et al, Science 2009
Lentiviral Vector-mediated ABCD1 Addition to Hematopoietic Stem Cells for the Treatment of CCALD

Cartier et al
Science 2009
How to measure clinical improvement after treatment of childhood cerebral ALD?

### Neurological Function Score

<table>
<thead>
<tr>
<th>Component</th>
<th>score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing/auditory processing problems</td>
<td>1</td>
</tr>
<tr>
<td>Aphasia/apraxia</td>
<td>1</td>
</tr>
<tr>
<td>Loss of communication</td>
<td>3</td>
</tr>
<tr>
<td>Vision impairment</td>
<td>1</td>
</tr>
<tr>
<td>Cortical blindness</td>
<td>2</td>
</tr>
<tr>
<td>Swallowing dysfunctions</td>
<td>2</td>
</tr>
<tr>
<td>Tube feeding</td>
<td>2</td>
</tr>
<tr>
<td>Running difficulties</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Component</th>
<th>score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking difficulties/spasticity</td>
<td>1</td>
</tr>
<tr>
<td>Spastic gait (need assistance)</td>
<td>2</td>
</tr>
<tr>
<td>Wheelchair dependence</td>
<td>2</td>
</tr>
<tr>
<td>No voluntary movement</td>
<td>3</td>
</tr>
<tr>
<td>Episodes of incontinence</td>
<td>1</td>
</tr>
<tr>
<td>Total incontinence</td>
<td>2</td>
</tr>
<tr>
<td>Non-febrile seizures</td>
<td>1</td>
</tr>
<tr>
<td>Possible Total</td>
<td>25</td>
</tr>
</tbody>
</table>

Moser et al, Neuropediatrics 2000
Efficacy of Hematopoietic Stem Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Eichler, American Academy of Neurology 2016

gene therapy may be safe and effective alternative to allogeneic transplant, particularly in the absence of matched sibling donor
Conclusions

- Myelination indicates regional brain maturation and likely developing function

- MRI scans can give clues to the diagnosis
  - Reduces number of tests ordered
  - Most sensitive in childhood
  - MRI helps define (novel) disorders
Conclusions

- Leukodystrophies occur in all age groups
- Cause of many disorders still unknown
- Technology advances gene discovery
- Leukodystrophies are treatable disorders
  - Gene therapy (lentivirus, AAV)
  - Human CNS stem cells
  - Human trials are beginning
Demyelinization cases

What type of myelin disorder?

Diagnosis?

MLD

VWMD
What type of myelin disorder? Hypomyelination

Diagnosis? Fucosidosis
What type of myelin disorder?

HYPOMYELINATION

Diagnosis?

GM2 GANGLIOSIDOSIS
References


