Joint webinar series

Pelizaeus-Merzbacher disease and related disorders

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DG 'Leukodystrophies'
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1

Pelizaeus-Merzbacher disease

XXXI.

Ueber eine eigenthümliche Form spastischer Lähmung mit Cerebralerscheinungen auf hereditärer Grundlage. (Multiple Sklerose.)

Von

1885

Dr. **Fr. Pelizaeus,**
Dirigirendem Arzt des Stahlbades und der Wasserheilanstalt Augustusbad bei Dresden.

Eine eigenartige familiär-hereditäre Erkrankungsform (Aplasia axialis extracorticalis congenita).

Von
Privatdozent Oberarzt Dr. **L. Merzbacher.**
(Aus der Klinik für Gemüts- und Nervenkrankheiten zu Tübingen.)
Mit 40 Textfiguren.

1910

(Eingegangen am 22. Juli 1910.)

2

Pelizaeus-Merzbacher disease

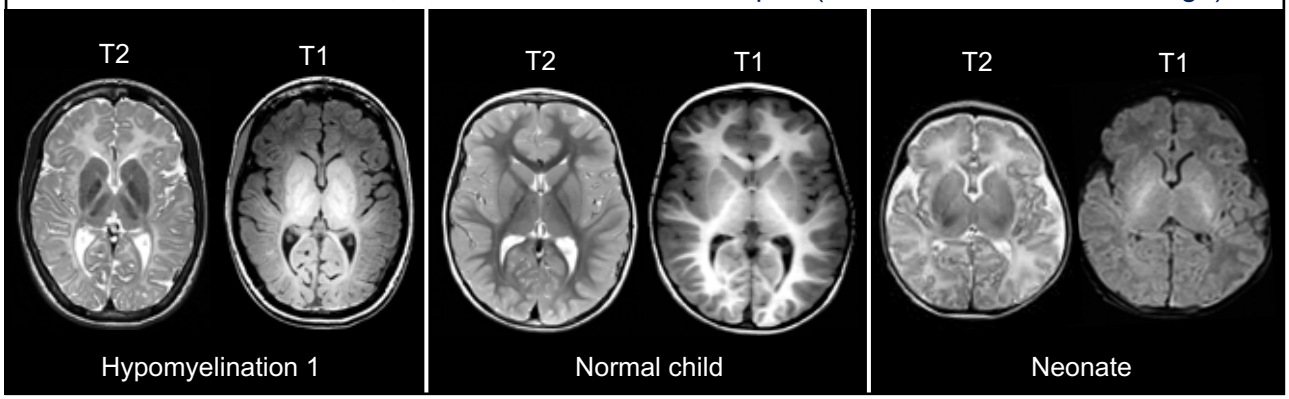
Pelizaeus and Merzbacher described

- **An X-linked disorder (males affected, mothers clinically unaffected) in one large pedigree**
- **Clinical presentation: Nystagmus with onset in infancy and improving over time, delayed motor development, ataxia and severe pyramidal syndrome**
- **Some variation**
- **Life expectancy: 25 – 35 years**
- **Normal grey matter, affected white matter with "disruption of myelin"**

3

Pelizaeus-Merzbacher disease: prototype of hypomyelinating leukodystrophies

- **Disorders of myelination**: **hypomyelination (hypomyelinating leukodystrophies)**
- **Definition**: „significant permanent deficit in myelin deposited" (van der Knaap & Valk)
- **Diagnosis**: by MRI (T2 hyperintensity of white matter (but less bright than in other leukodystrophies), T1 may be hypointense, isointense or hyperintense, depending on the amount of myelin deposited
- In children < 12 months, 2 MRIs at least 6 months apart (and the second > 12 m of age)



4

Clinical presentation

Classical presentation

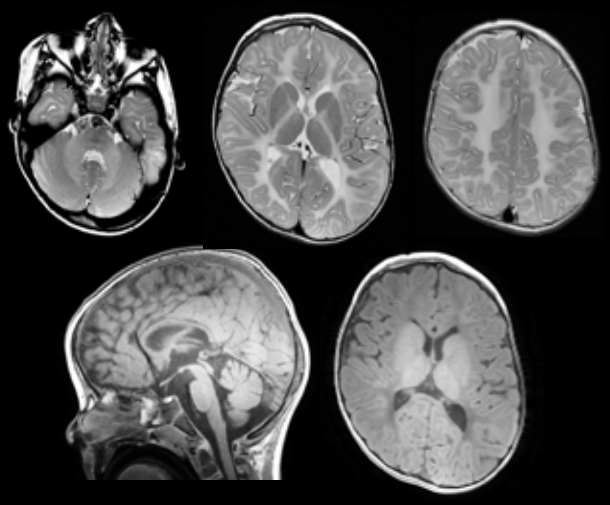
- Early-onset (« connatal ») pendular nystagmus
- Muscular hypotonia, followed by development of pyramidal signs
- Ataxia
- Dystonia
- Increasing spasticity
- Mental retardation, albeit less severe than motor impairment
- Sitting without support usually not possible, head balance usually present

Clinical course

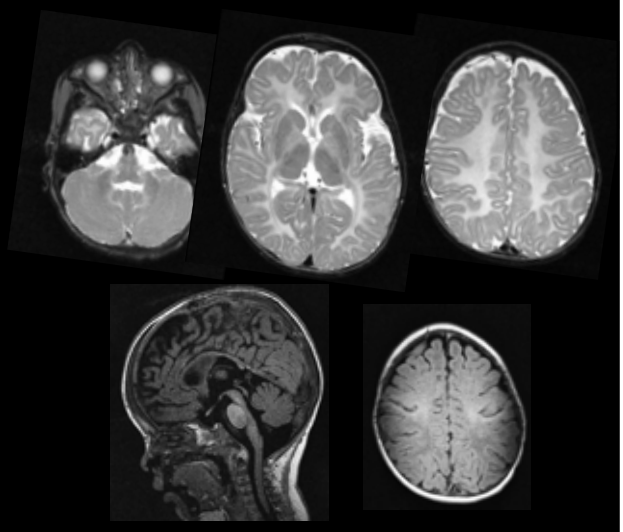
- Developmental progress in the first years
- Stable phase
- Slow deterioration (progression of spasticity, increasing dysphagia, secondary complications of severe handicap) in the second decade
- Peripheral nerve involvement rare (only with selected mutations)
- Life expectancy: difficult to predict, > 20 years

5

PMD: MRI



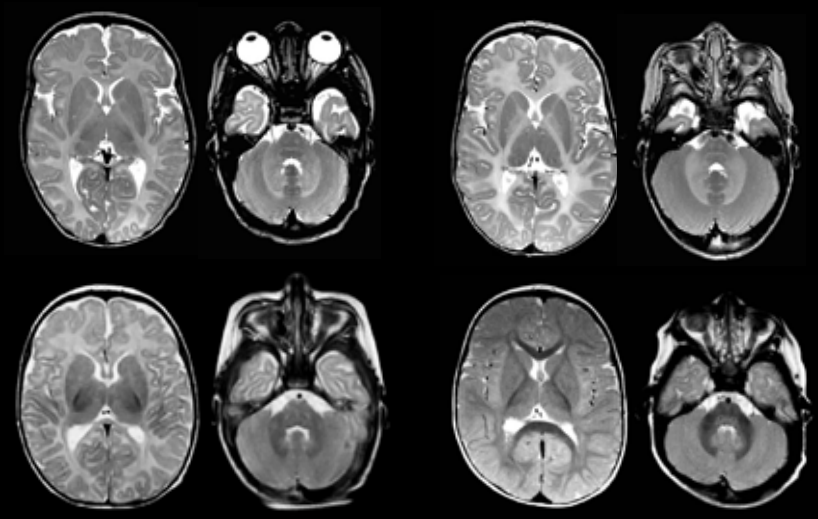
Connatal PMD, age 2.8 y



Classic PMD, age 1.2 y

6

Young infants: hypomyelination?



Pelizaeus-Merzbacher disease

Normal baby

Age 10 weeks

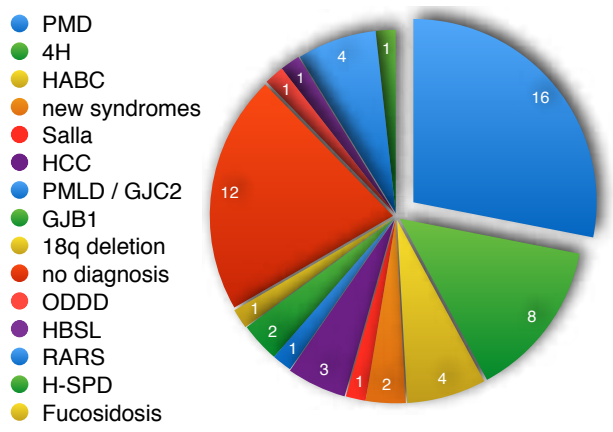
Age 12 months

7

Disorders of myelination

Hypomyelinating leukodystrophies: very heterogeneous disorders.

Pelizaeus-Merzbacher disease: the most frequent one (in the Netherlands)



The Netherlands

- 17 mio people
- 170000 births per years

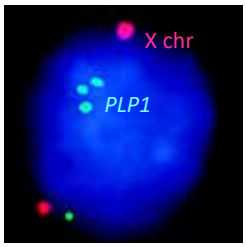
8

PMD: setting in the Netherlands

- More or less all Dutch patients referred to the Amsterdam Leukodystrophy Center
- Visits 1-4 times yearly, depending on age
- Local paediatrician / physiatrist, expert spasticity treatment in Amsterdam (including intrathecal baclofen, selective dorsal rhizotomy)
- Gastrostomy if necessary
- Orthopedic surgery if necessary (scoliosis correction, hip surgery)
- Also taking charge of adult patients

9

Genetic background: *PLP1* alterations

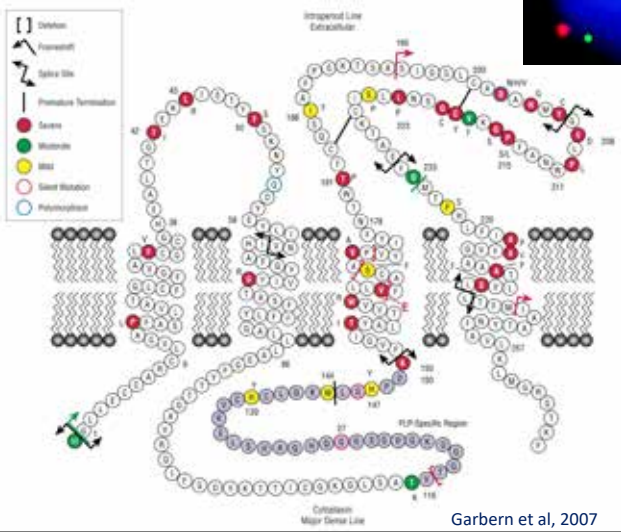


Proteolipid protein 1:

the most abundant myelin protein, expressed in oligodendrocytes

2 different isoforms (PLP1 and DM20)

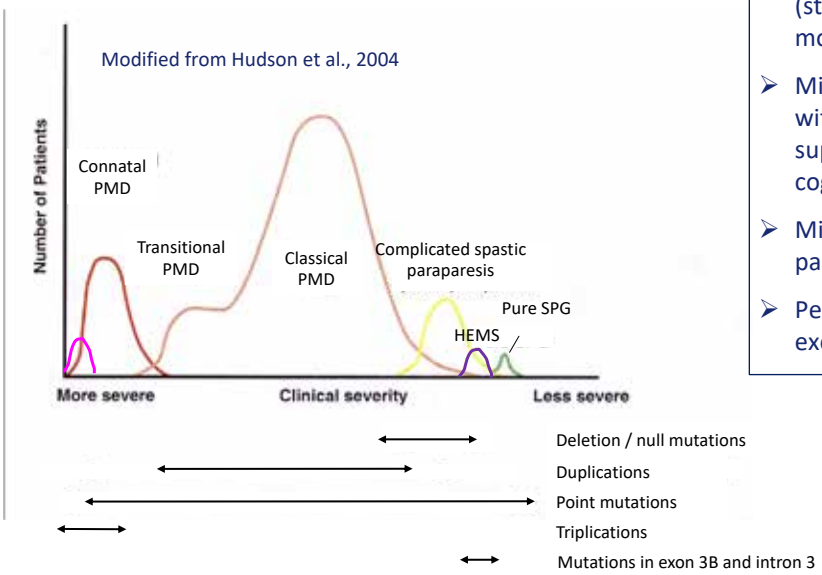
- Most frequent genetic alteration: duplications (60-70%)
- Missense mutations
- Functional null mutations
- Triplications and higher copy numbers
- Deep intronic mutations



Garbern et al, 2007

10

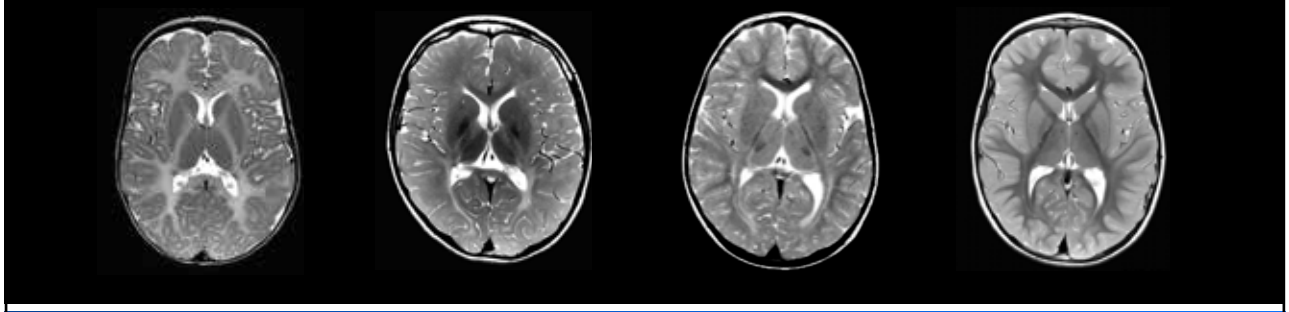
Clinical spectrum of PMD



- Severe forms: connatal PMD (stridor, severe hypotonia, no motor milestones)
- Milder forms: mild PMD (sitting without support, walking with support, better to normal cognition)
- Mildest form: X-linked spastic paraplegia
- Peripheral neuropathy: exceptional

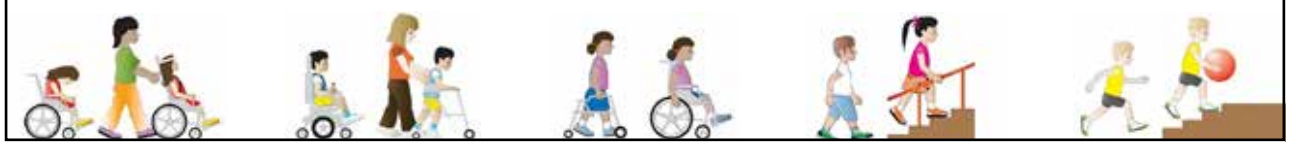
11

Clinical spectrum:
Amount of myelin correlates with clinical severity



Severe presentation — Mild presentation (pure HSP)

PLP1



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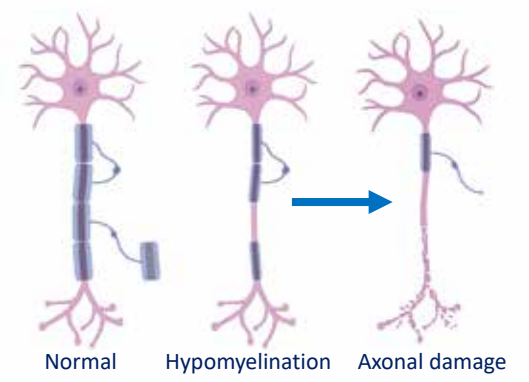
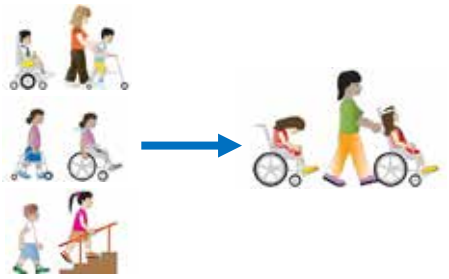




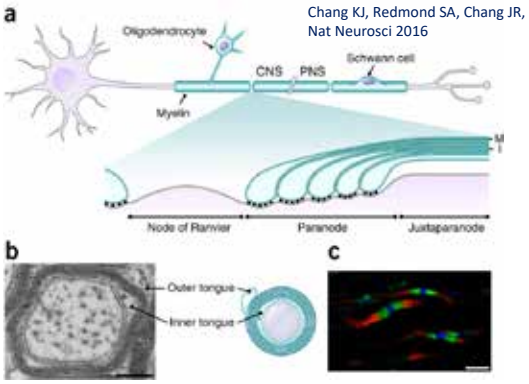
Clinical course

- **Developmental progress** in the first years
- **Stable phase**
- **Slow deterioration** (progression of spasticity, increasing dysphagia, secondary complications of severe handicap) in the second decade
- MRI: slowly progressive atrophy
- Peripheral nerve involvement rare (only with selected mutations)
- Life expectancy: difficult to predict, > 20 years

13

Functions of myelin?

- Enables rapid saltatory conduction
- Protects axons

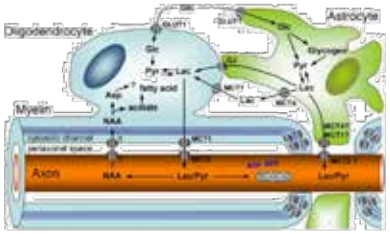


Chang KJ, Redmond SA, Chang JR, Nat Neurosci 2016

14

Functions of myelin?

- Enables rapid saltatory conduction
- Protects axons
- Provides energy substrates to the axon (lactate): metabolic coupling



Hirrlinger & Nave, 2014

15

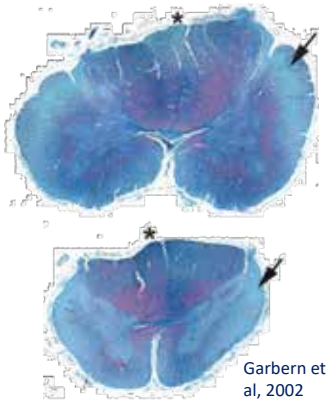
Are axons also affected in PMD?

Garbern et al, Brain 2002

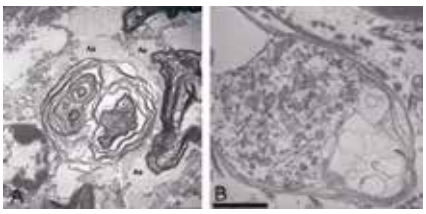
- Patients with *PLP1* null mutations and a *PLP1* null mouse model were studied.
- Length-dependent axonal degeneration
  - Histopathological changes
  - NAA reduction in ^{1}H-MR spectroscopy

Bonavita et al, Neurology 2001

- Patients with *PLP1* mutations: significantly lower NAA in ^{1}H-MRS



Garbern et al, 2002



16

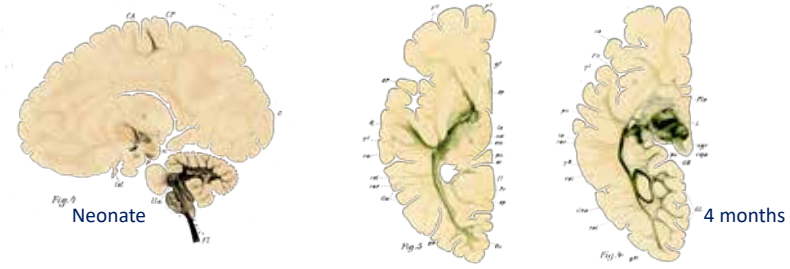
Special forms of PMD

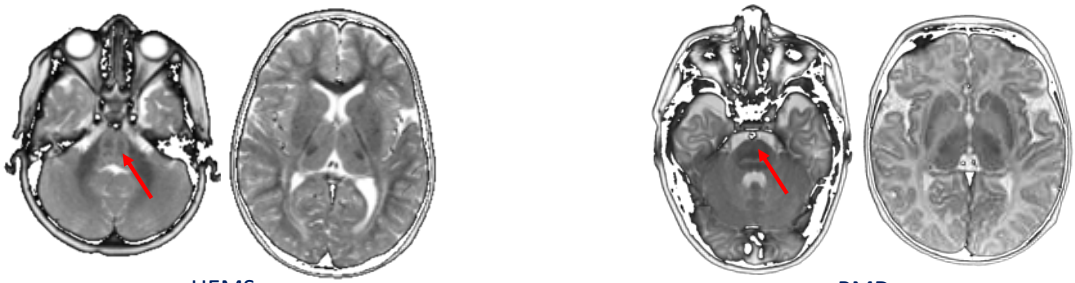
- HEMS: Hypomyelination of early myelinating structures
- *PLP1* null mutations
- Higher copy numbers (triplications…)

- Female carriers

17

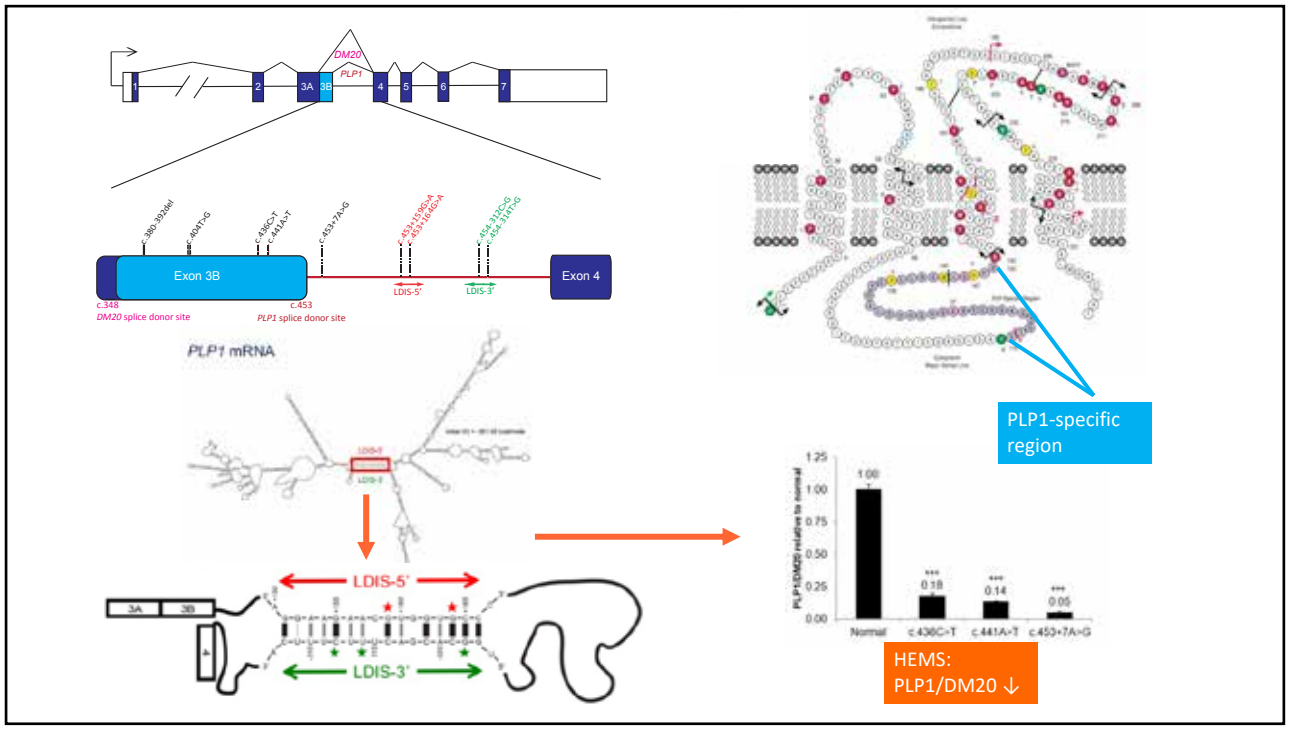
HEMS: Hypomyelination of Early Myelinating Structures





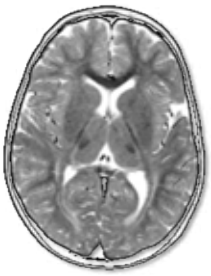
HEMS PMD

18



19

HEMS is caused by *PLP1* mutations

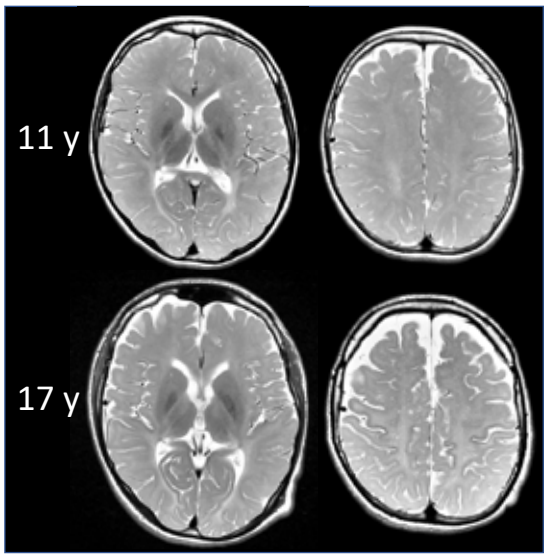


- *PLP1* mutations in HEMS are located in exon 3B and intron 3.
- They reduce *PLP1* to *DM20* ratio.
- Correct ratio seems to be important for early myelination.
- Recognizable MRI phenotype.
- Clinical presentation: complicated spastic paraplegia, fitting within PMD spectrum (mild end).
- Recognition of non-coding mutations only possible thanks to the number of patients with this MRI pattern.

20

PLP1 null syndrome

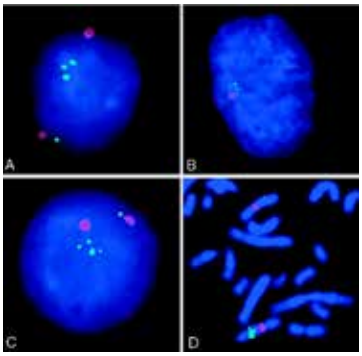
- *PLP1* deletions and functional null variants
- Often said to be a mild PLP1 form
- Peripheral neuropathy (loss of both PLP1 and DM20)
- Better cognition and language, a little better motor function (sitting without support/walking with support)
- Clear decline in the second decade:
  - Loss of mobility
  - Swallowing problems
  - Scoliosis
  - Pulmonary problems



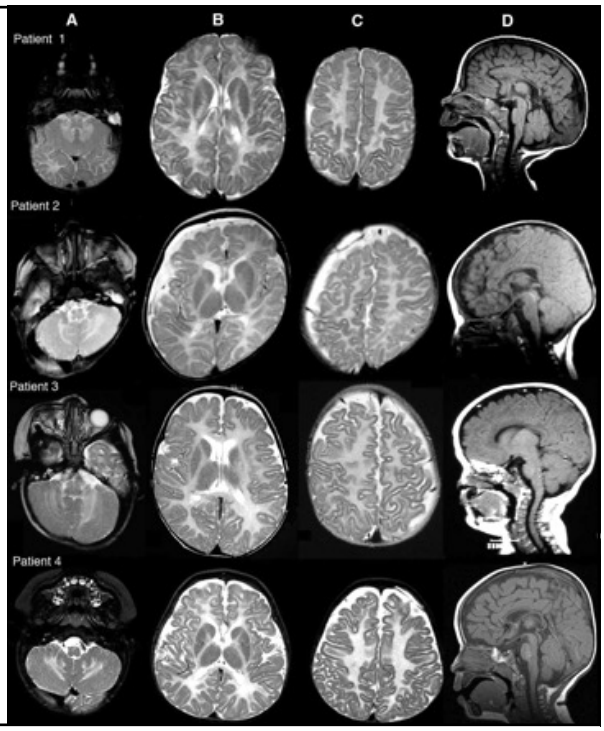
21

Higher copy numbers

- Mainly triplications
- One patient with *PLP1* quintuplication described
- Severe (connatal) PMD variant
- Clearly reduced life expectancy



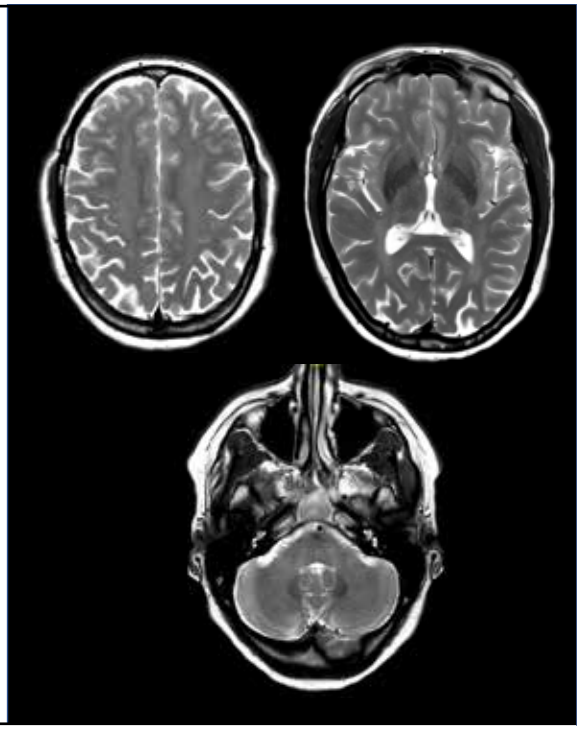
Wolf et al, Brain 2005



22

Female carriers

- Carriers of severe *PLP1* mutations usually do not develop symptoms.
- Carriers of milder *PLP1* variants usually do develop symptoms.
- Start usually at age 30-40 years.
- Often not recognized.
- Usually slowly progressive spastic paraparesis, may become wheelchair bound.
- Cognitive involvement may be present, usually mild.
- Often spastic bladder.



23

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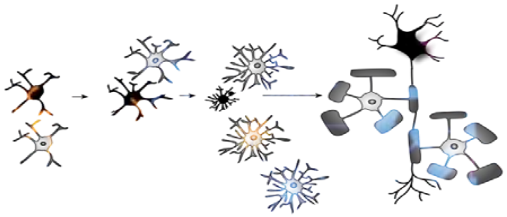
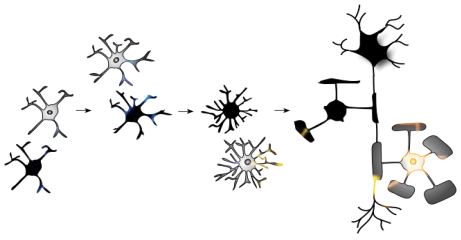


PMD female carrier: severe PLP1 variant



PMD female carrier: mild PLP1 variant

24

Treatment of PMD

Currently only symptomatic treatment

Problems of developing causal treatment

- Ultrarare disorders
- Mouse models available, but experience has shown that not all data in mouse are relevant for humans (and not all treatments that work in mice, work in humans)
- Lack of natural history data – needed to decide whether a treatment works or not
- Different mechanisms of pathology, not only one factor
- Individual treatment approaches per disease vs influencing global mechanisms (inflammation, axonal health)

25

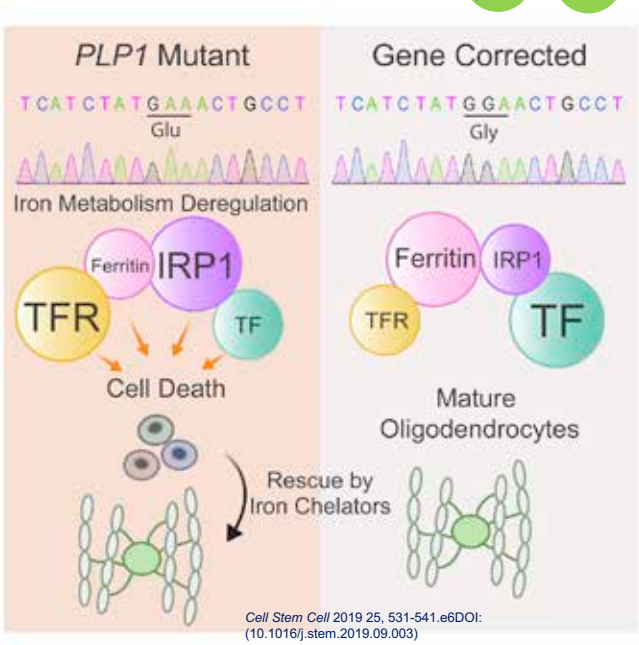
Treatment approaches for PMD

- Alternative substrates for axonal nourishment (ketogenic diet?)
- Treatment of inflammation?
- PMD: Intracerebral transplantation of neuronal precursors
- PMD: Cholesterol, Kurkumin, ketogenic diet… in animal models positive results (no studies so far)
- PMD: **decreasing gene dosage with antisense nucleotides** (taking care not to knock out PLP1 completely)

26

Deferiprone for PMD?

- Rowitch/Wernig group:
- In a study of PMD cells, changes in proteins involved in iron metabolism were found (ferroptosis) (Nobuta et al, 2019)
- Gene correction normalised these changes.
- Treatment with an iron chelator (deferiprone) was successful in
  - Cell cultures of PMD oligodendrocytes
  - PMD mice



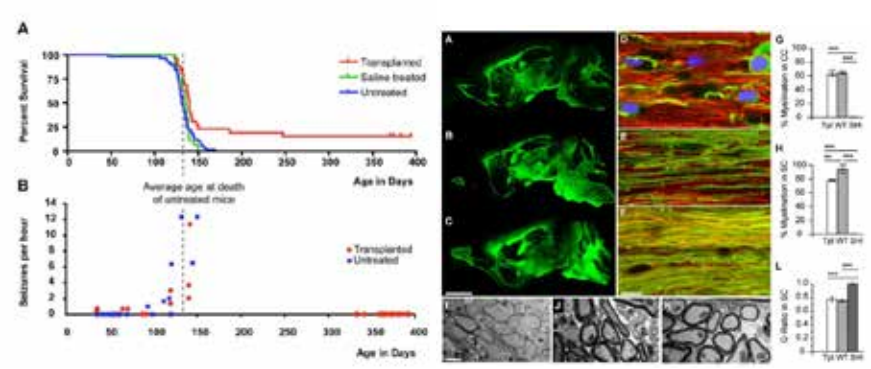
27

Iron chelators

- Are used for the treatment of certain blood disorders (leading to many blood transfusions)
- Scavenge iron
- Are used in adults and children, not all registered for young children (< 6 years of age)
- Side effects: nausea, vomiting, diarrhoea (frequent) and leukopenia / agranulocytosis (low/absent white blood cells) → risk of life-threatening bacterial infections

28

Remyelination as therapy for PMD?



Windrem et al., Cell Stem Cell 2 (6), 2008, : transplantation of shiverer mice (MBP deficient) with human glial progenitor cells

→ rescues part of the animals

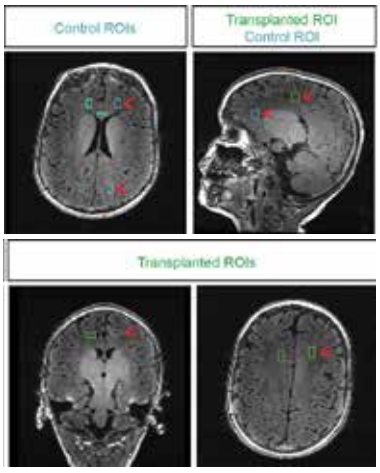
29

Remyelination as therapy for PMD?

Therapeutic trial (phase I) for Pelizaeus-Merzbacher disease (Gupta et al, Sci Transl Med 4 (155) 2012)

Intracerebral implantation of HuCNS-SCs in 4 boys

- Evaluate safety
- Detect evidence of myelin deposition with MRI in regions of interest
  - Single voxel MRS
  - DTI (FA, radial, axial and mean diffusivity)



30

Remyelination as therapy for PMD?

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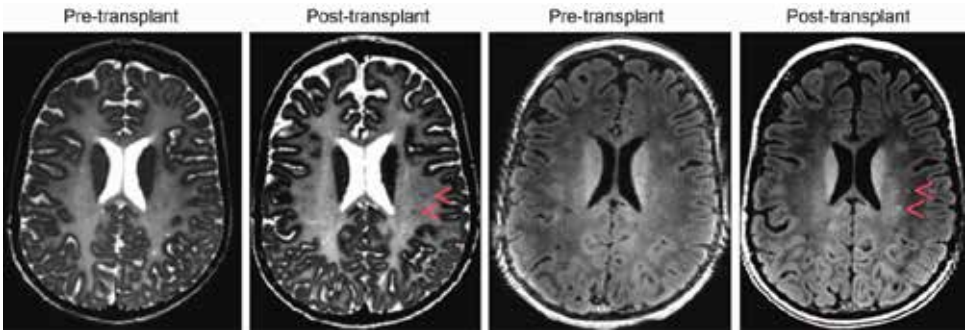


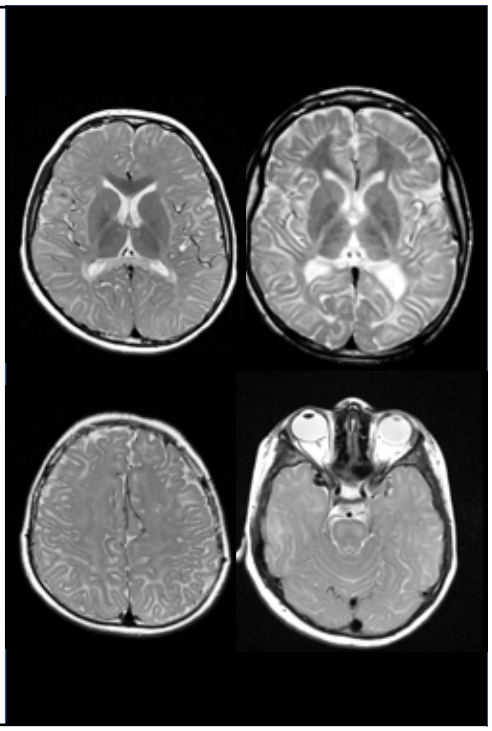
→ Evidence of increased myelin deposition on conventional imaging?

31

PMD related conditions

PMD-like disease (PMDL / PMLD)

- Autosomal recessive disease with similar manifestations as PMD
  - Congenital nystagmus
  - Ataxia and pyramidal syndrome
  - Usually a little milder, walking with support often possible
  - In addition, peripheral neuropathy
- Not synonymous with hypomyelinating leukodystrophies
- Strictly speaking: only *GJC2*-associated hypomyelination (the first gene for an AR PMD-like disorder)
- *GJC2* encodes an astrocytic connexin (Cx43), forming channels with Cx47, connecting oligodendrocytes and astrocytes
- Epilepsy frequent in PMDL due to *GJC2* variants

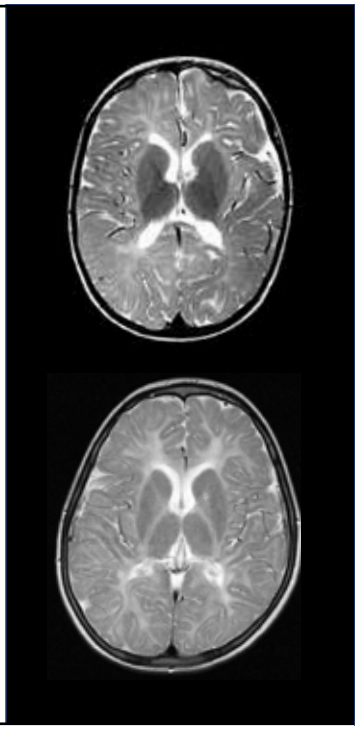


32

PMD related conditions

More disorders with similar clinical presentation as PMD

- Autosomal recessive
  - *RARS1*
  - *EPRS1*
  - *DARS1*
  - *NKX6-2*
  - *PI4KA*
- De novo
  - Certain forms of H-ABC (*TUBB4A*, without basal ganglia involvement)
  - *TMEM106B* (mild form with long stable phase)
  - *TMEM63A* (with improvement later on in many cases)



33

Summary

- PMD is a disorder with varying severity.
- More information about natural history is necessary.
- Biomarker: MRI. Unknown whether there are other good blood or CSF biomarkers.
- Female carriers often develop symptoms (with mild variants).
- Treatments are not yet available, but clinical studies are starting:
  - Deferiprone
  - In the future, gene dose reduction
  - Treatment approaches for older / milder patients: aimed at axonal health?

34