Joint webinar series

# Introduction into Leukodystrophies

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## Learning objectives

By the end of this webinar you will be able to:

- know the current definition of a leukodystrophy
- understand the basic principles of MRI pattern recognition
- propose a diagnostic plan for a patient with a leukodystrophy
- recognize the most important treatable leukodystrophies
- know about important aspects regarding patient care



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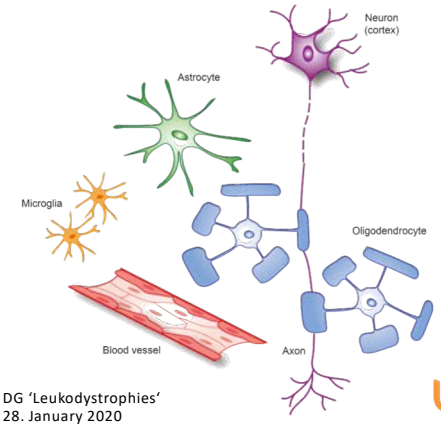
## Leukodystrophy - definition

A leukodystrophy is a genetic disorder primarily affecting brain white matter.




- All white matter components may be affected.
- All modes of inheritance are possible:
  - *Autosomal dominant*
  - *De novo*
  - *Autosomal recessive*
  - *X-linked*
  - *Mitochondrial*
- Age of onset: prenatal to adulthood.



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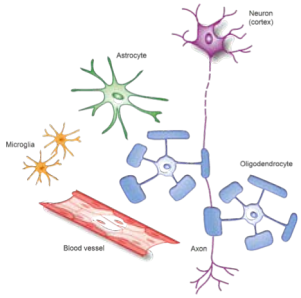
## Leukodystrophies - classification

The most recent classification from 2017 (van der Knaap and Bugiani, Acta Neuropathologica)

1. Myelin disorders (hypomyelination, demyelination, myelin vacuolization)
2. Astrocytopathies
3. Leuko-axonopathies
4. Microgliopathies
5. Leuko-vasculopathies



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## Leukodystrophies – symptoms and signs

Frequent symptoms and signs in a leukodystrophy patient

- Spasticity
- Ataxia
- Nystagmus
- Extrapyramidal movement disorder
- Dysphagia
- (mild) intellectual disability

In patients with late onset

- Slowly progressive dementia
- Psychiatric symptoms

May occur without other neurological signs and symptoms.

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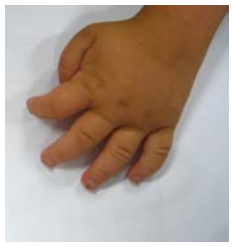
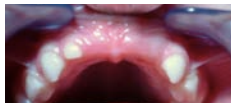
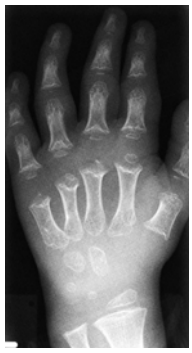
## Leukodystrophies – symptoms and signs beyond the brain

Frequent extraneurological symptoms and signs in a leukodystrophy patient

- Dental involvement
- Ocular involvement
- Skeletal involvement
- Endocrine involvement
- Skin involvement
- Hearing loss







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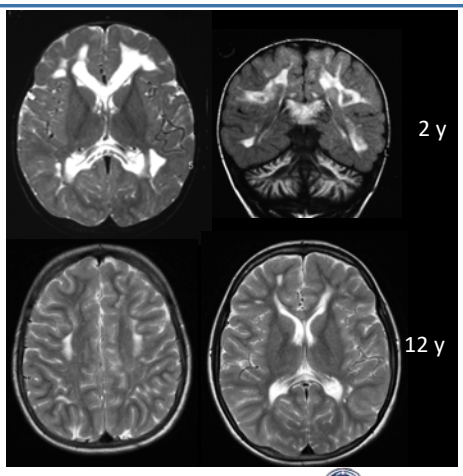
## Leukodystrophies – always progressive?

Improvement can be seen in several leukodystrophies.

*Examples*

- Mitochondrial LDs
- Dominant form of Megalencephalic leukodystrophy with subcortical cysts (MLC2b)
- Transient hypomyelination (*TMEM63A*-associated)

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## Leukodystrophies – the MRI

MRI – the diagnostic tool for a leukodystrophy!

Most helpful for a diagnosis: MRI pattern recognition (MS van der Knaap).

But:

- May be normal in a presymptomatic patient
- May improve or even normalize
- May be non-characteristic, certainly in adult patients

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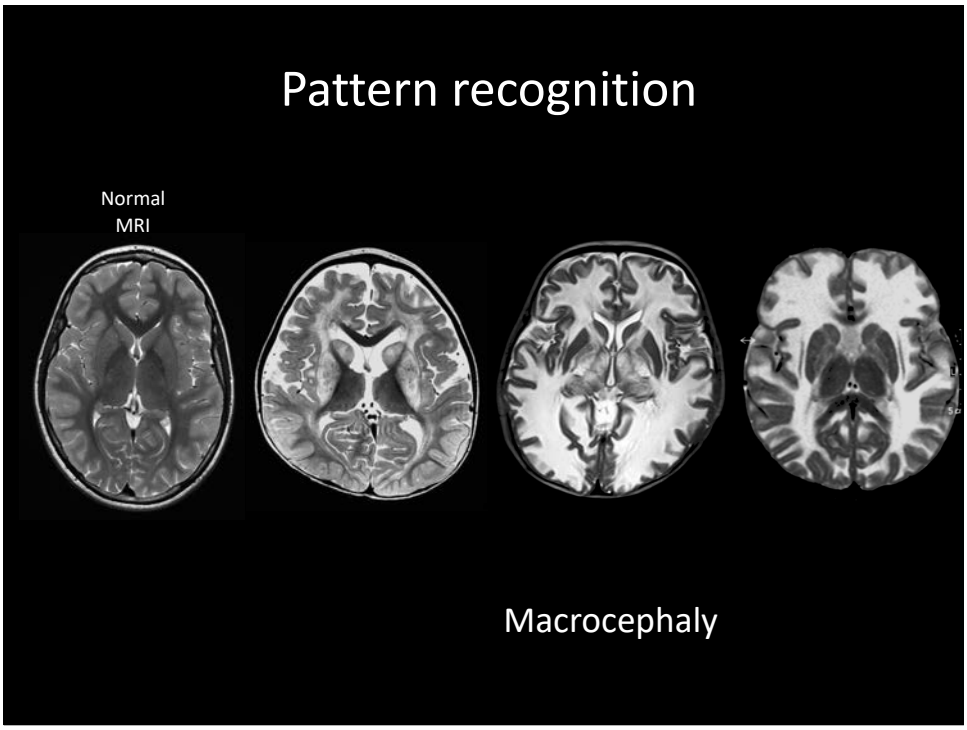
Pattern recognition
Normal
MRI
Macrocephaly

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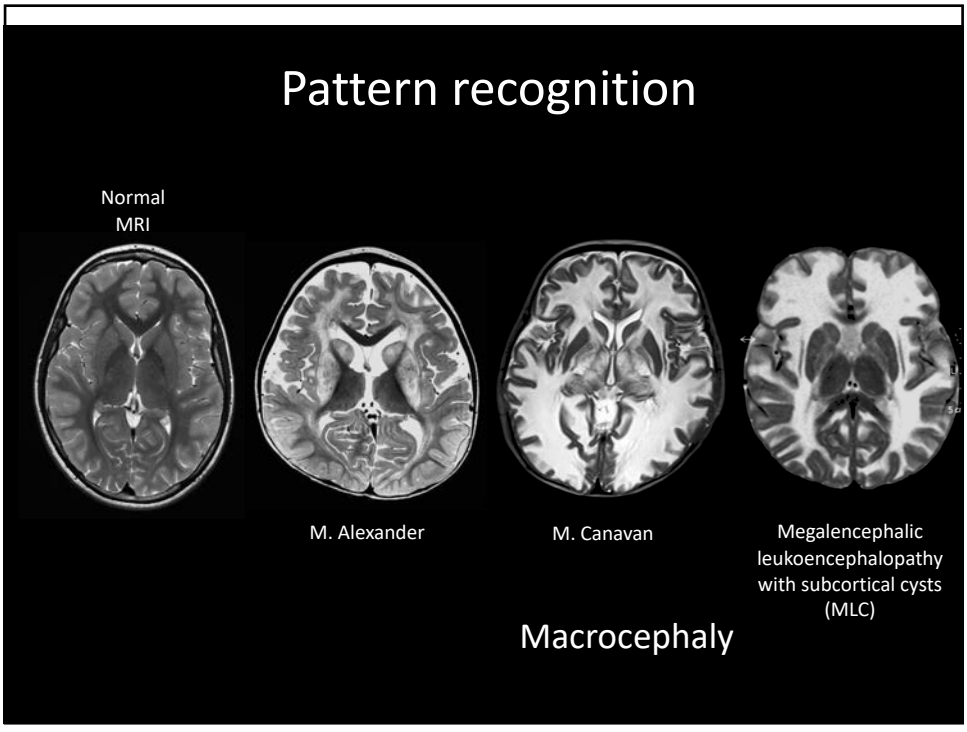
Pattern recognition
Normal
MRI
M. Alexander
M. Canavan
Megalencephalic leukoencephalopathy with subcortical cysts (MLC)
Macrocephaly

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## Leukodystrophies – the MRI

**First question: Is it a leukodystrophy?**

Differential diagnosis

- Other genetic disorders: Grey matter disorders
- Acquired disorders
  - Intoxications
  - Deficiencies
  - Infections
  - Inflammatory disorders
  - Neoplasms

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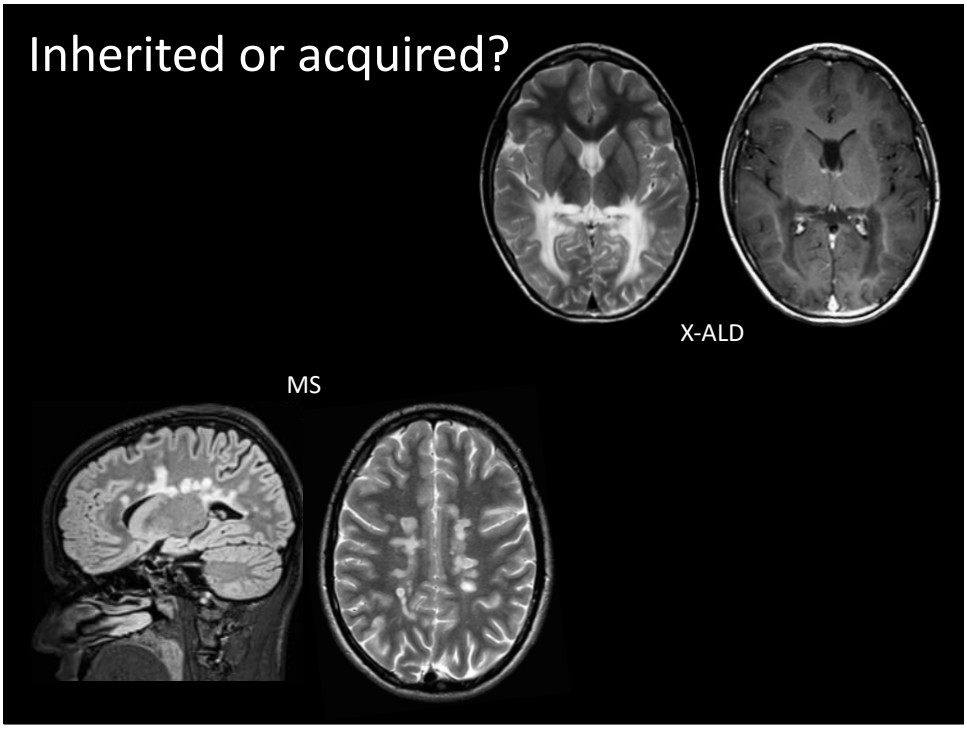


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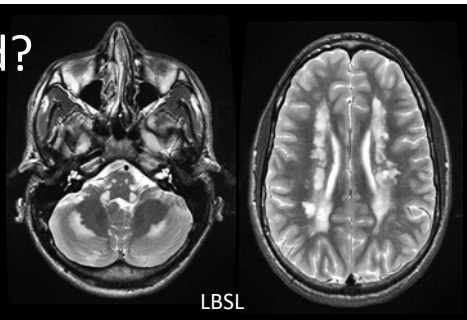
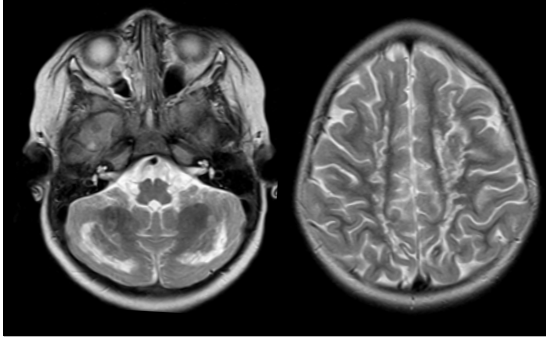
# Inherited or acquired?



LBSL
(Leukoencephalopathy with brain stem and spinal cord involvement and elevated lactate)

Rotavirus encephalitis



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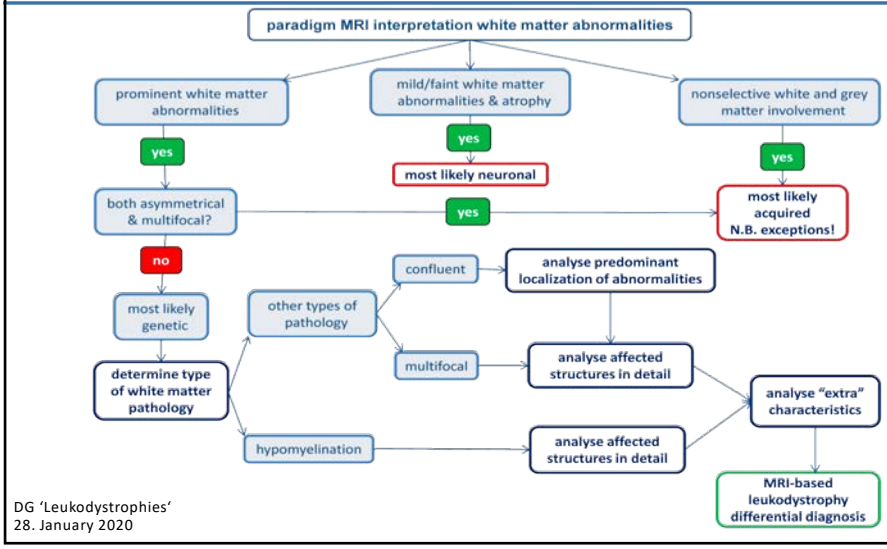
## How to analyse MRI images?

Van der Knaap et al, Lancet Neurology 2019

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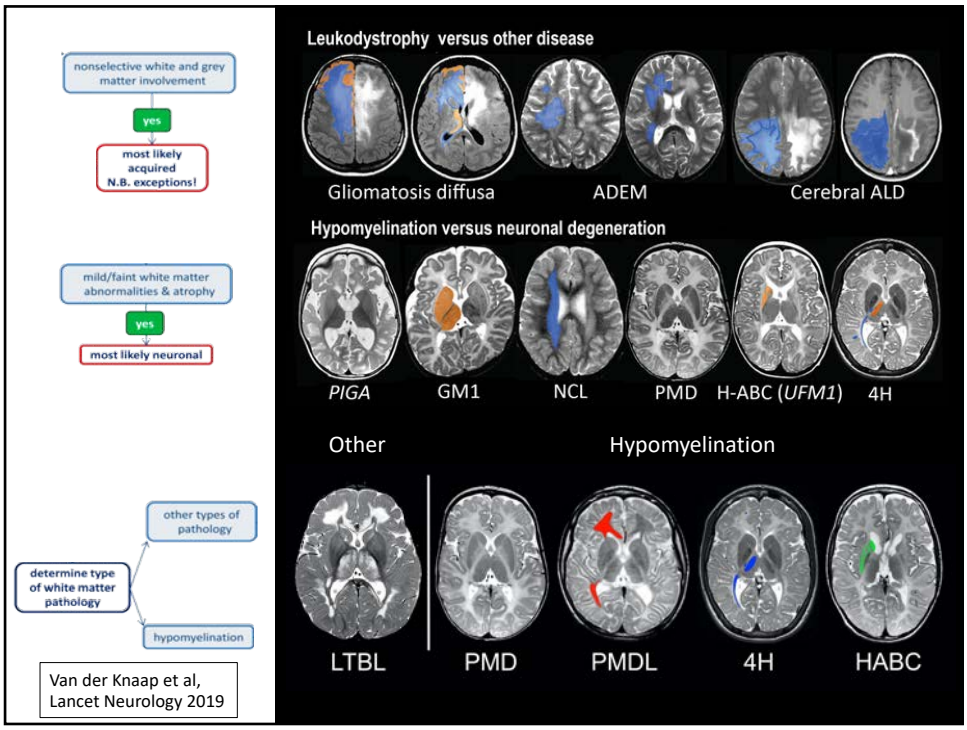
nonselective white and grey matter involvement
yes
most likely acquired N.B. exceptions!
mild/faint white matter abnormalities & atrophy
yes
most likely neuronal
determine type of white matter pathology
other types of pathology
hypomyelination
Van der Knaap et al, Lancet Neurology 2019
Leukodystrophy versus other disease
Gliomatosis diffusa
ADEM
Cerebral ALD
Hypomyelination versus neuronal degeneration
PIGA
GM1
NCL
PMD
H-ABC (UFM1)
4H
Other
Hypomyelination
LTBL
PMD
PMDL
4H
HABC

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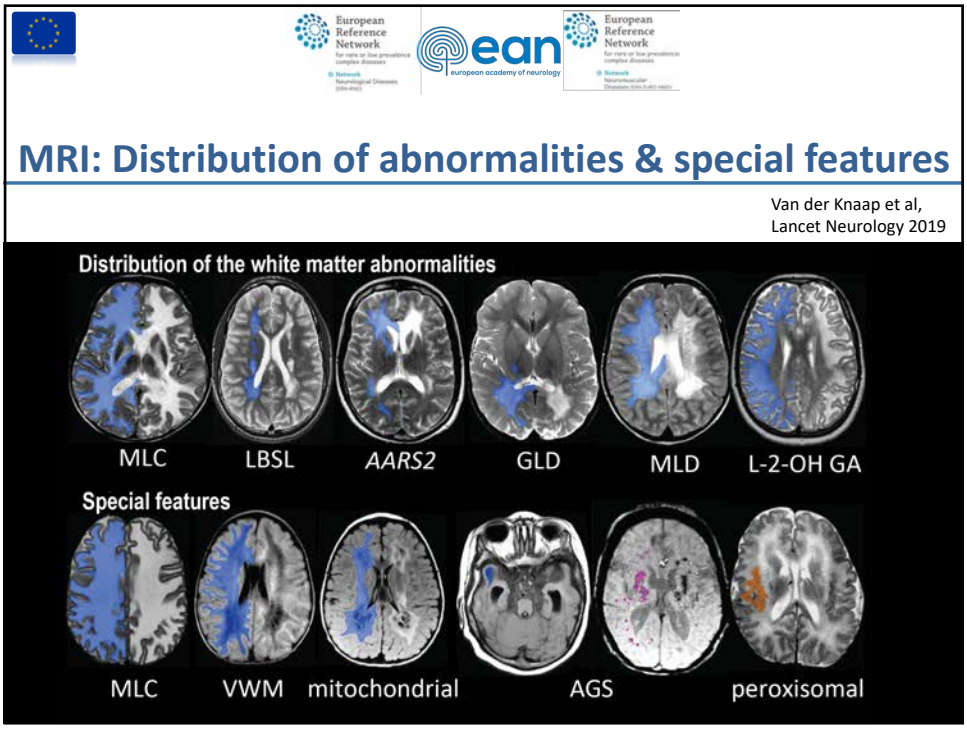
MRI: Distribution of abnormalities & special features
Van der Knaap et al, Lancet Neurology 2019
Distribution of the white matter abnormalities
MLC
LBSL
AARS2
GLD
MLD
L-2-OH GA
Special features
MLC
VWM
mitochondrial
AGS
peroxisomal

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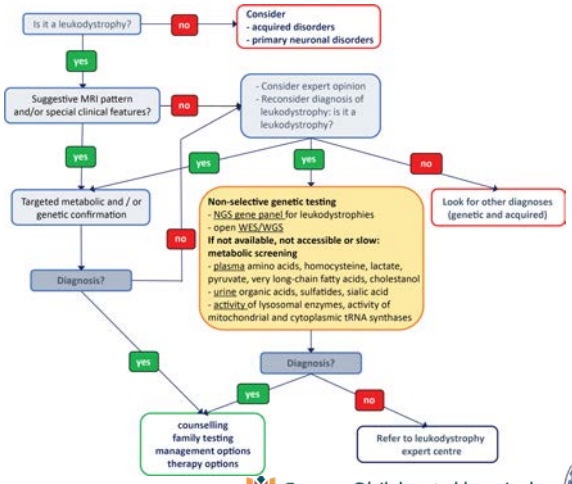
## Diagnostic flowchart for leukodystrophies




Van der Knaap et al, Lancet Neurology 2019

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## Treatment of leukodystrophies

**Disease-specific treatments**

- Treatment of the leukodystrophy (e.g. haematopoeietic stem cell transplantation for X-ALD or MLD, gene therapy for X-ALD or MLD)
- Treatment of disease-specific manifestations (e.g. Addison disease in X-ALD, premature ovarian failure in Vanishing White Matter, gallbladder involvement in MLD, Myopia in 4H leukodystrophy....)

**General management of leukodystrophy patients**

- Treatment of spasticity
- Scoliosis correction
- Guaranteeing adequate intake and growth

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## A recent case

**6 year-old boy**

- Normal pregnancy, perinatal period and development
- In the last 6 months increasing motor difficulties, falls easily and cannot step down from his bike any longer without (almost) falling
- At school, problems concentrating.

Neurological examination

- Friendly boy, cooperates well
- Mild ataxia and pyramidal syndrome (extensor plantar responses in the absence of elevated muscle tendon reflexes)



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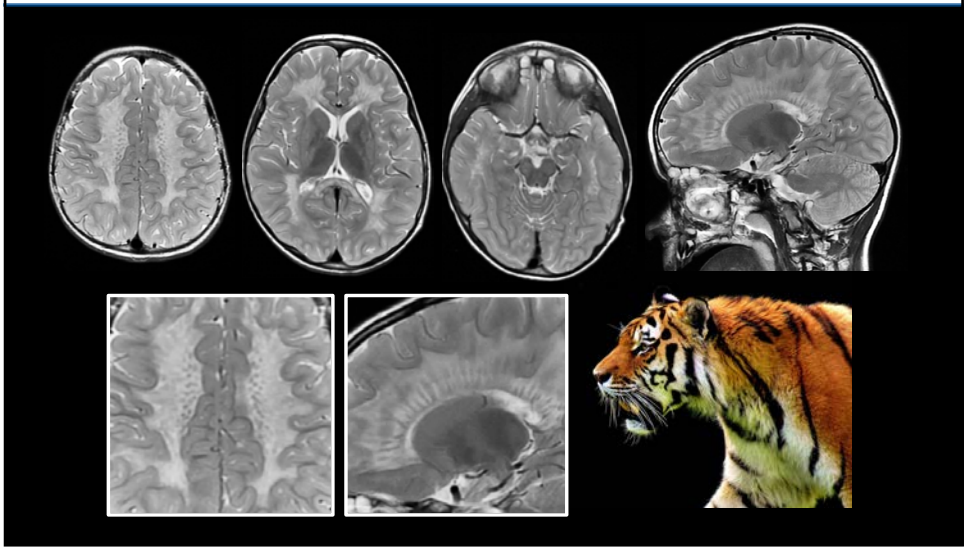
## A recent case – brain MRI



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## A recent case – what‘s next?

**4 year-old sister**

- Normal pregnancy, perinatal period and development
- No concerns regarding motor skills and cognition.

Neurological examination

- Friendly girl, cooperates well
- Absent tendon reflexes (arms)
- Otherwise normal
- Total IQ: 118



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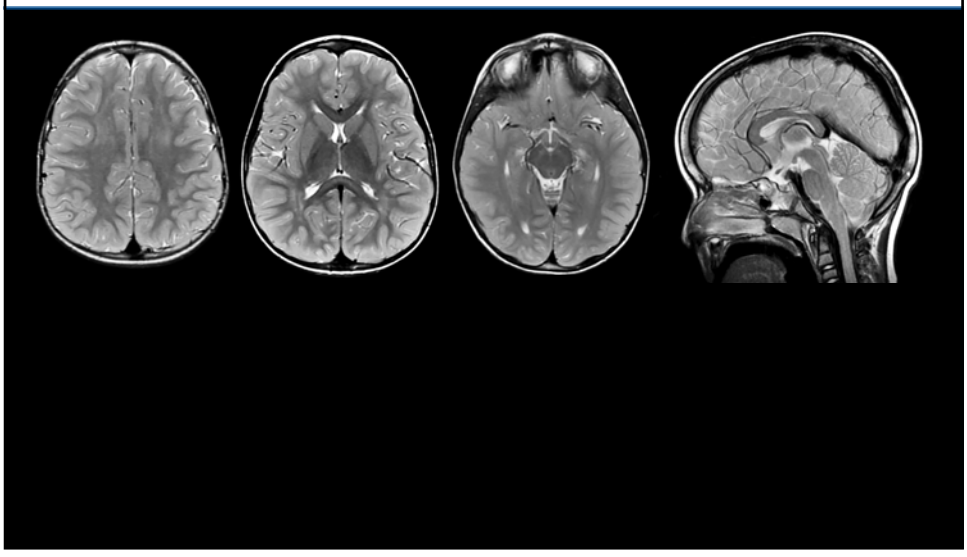
## A recent case – what‘s next?



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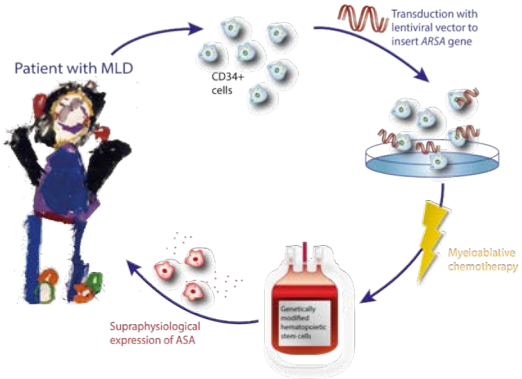
## A recent case: metachromatic leukodystrophy

**4 year-old sister**

- Referral for gene therapy

6 year-old brother

- Symptomatic treatment

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## Key points

- Leukodystrophies are heterogeneous genetic disorders primarily affecting brain white matter.
- Not all leukodystrophies are progressive.
- Brain MRI analysis very often helps to make a diagnosis („pattern recognition").
- Genetic diagnosis is possible in the large majority of cases.
- Treatment options are emerging, and timely diagnosis is essential!
- Active management of patients with a leukodystrophy is important, also when no causal treatment is existing.

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## Suggested reading

Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. *Neurology*. 2009;72(8):750–759. doi:10.1212/01.wnl.0000343049.00540.c8.

van der Knaap MS, Schiffmann R, Mochel F, Wolf NI. Diagnosis, prognosis, and treatment of leukodystrophies. *Lancet Neurol*. 2019;18(10):962–972. doi:10.1016/S1474-4422(19)30143-7.

van der Knaap MS, Bugiani M. Leukodystrophies: a proposed classification system based on pathological changes and pathogenetic mechanisms. *Acta Neuropathol*. 2017;134(3):351–382. doi:10.1007/s00401-017-1739-1.

Adang LA, Sherbini O, Ball L, et al. Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies. *Mol Genet Metab*. 2017;122(1-2):18–32. doi:10.1016/j.ymgme.2017.08.006.

Sessa M, Lorioli L, Fumagalli F, et al. Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. *Lancet*. 2016;388(10043):476–487. doi:10.1016/S0140-6736(16)30374-9.



## Q&A

1. Eye involvement in Leukodystrophy, clues - live answer
2. more about gene-therapy – this should be covered in separate sessions, e.g. on X-ALD and on MLD. We will organise this.
3. Are there adult onset leukodystrophies that can be treated with HSCT? - live answer
4. Is the MCT8 deficiency a typical leukodystrophy, too? No, this is delayed myelination, not hypomyelination.
5. How commonly you have seen ALD in females? Almost all females develop progressive spasticity in mid to late adulthood. Cerebral ALD is exceptional.
6. What about pre-symptomatic VLCFA screening in newborn males? You mean neonatal screening for X-ALD? This is done already in several states/countries/regions.
7. Skin involvement ? what clues to look for? hypopigmentation what else? E.g. chillblains in Aicardi-Goutières syndrome; photosensitivity in trichothiodystrophy, angiokeratoma in fucosidosis etc. for a full list, see the Lancet Neurology review (supplemental file).