Universitätsklinik für Kinder- und Jugendmedizin
Abt. Neuropädiatrie, Entwicklungsneurologie & Sozialpädiatrie

Co-financed by the Connecting Europe Facility of the European Union

European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

Update Metachromatic Leukodystrophy

Samuel Gröschel and Ingeborg Krägeloh-Mann

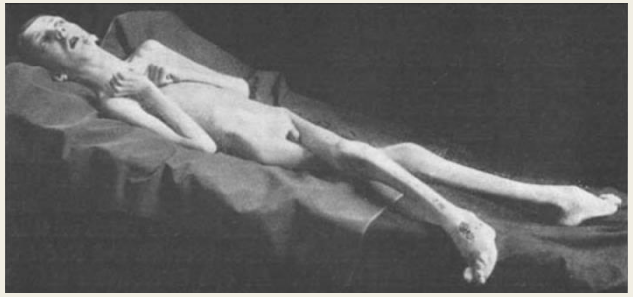
EBERHARD KARLS UNIVERSITÄT TÜBINGEN

Universitätsklinikum Tübingen

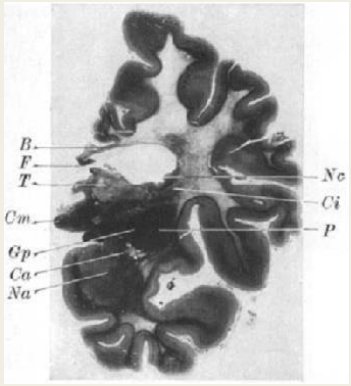
15.06.2021

Webinar outline

Almost 100 years ago (in Tübingen)…



Scholz 1925, Z.Gesamte Neurol.Psychiatr.



today…

Natural history, end points, disease burden

early diagnosis, early signs

Visualizing brain changes in vivo

New treatment options

Newborn Screening

Learning objectives

1. To understand the natural history of the disease with its different trajectories, their clinical characteristics and dynamics and the different needs
2. To understand the need to detect the early signs of MLD
3. To understand the possibilities of visualizing the brain changes with MR technologies
4. To get an overview about new treatment options and their indication
5. To learn about new developments concerning newborn screening, registries, networks, guidelines

MLD introduction

incidence ca. 1 : 100.000

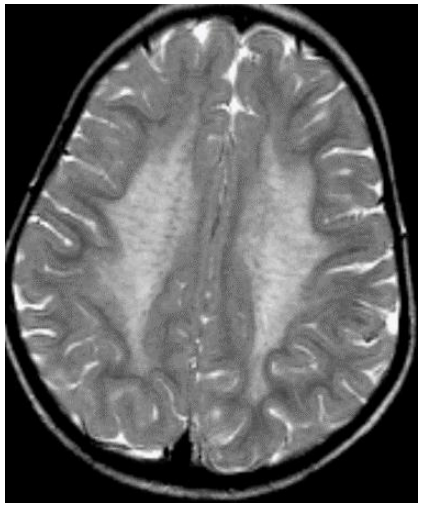
aut.rec., mutations ARSA gene (22q13)

enzyme deficiency (Arylsulfatase A) leads to lysosomal accumulation of sulfatides

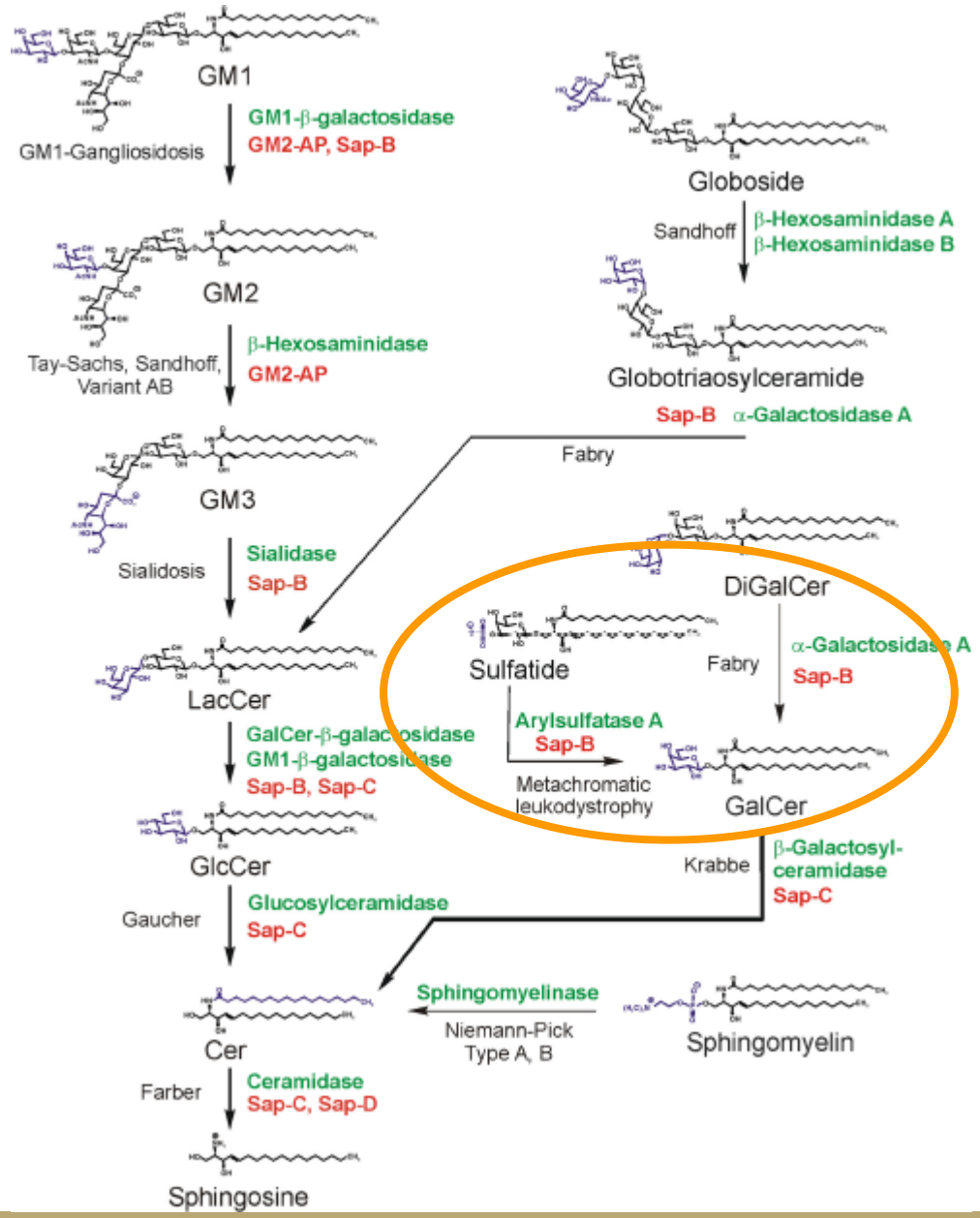
→ Demyelination

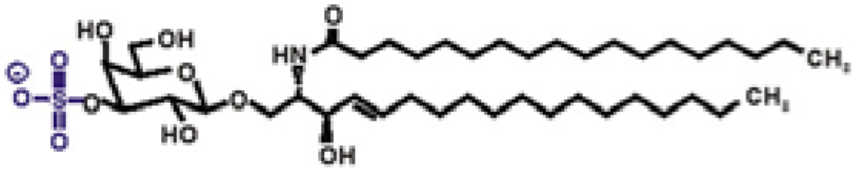
→ Severe neurologic dysfunction

Austin 1963, Kehrer et al. 2011



MLD: lysosomal storage disorder





Sulfatide

Arylsulfatase A

Sap-B

Metachromatic leukodystrophy

MLD clinical forms

Late infantile **< 2 ½ yrs.**	**spasticity, muscle weakness, motor decline,** followed by cognitive decline,
juvenile **2 ½ - 16 yrs.**	**cognitive and behavioural problems** **spasticity, ataxia, motor decline**
adult **> 16 yrs.**	**cognitive and behavioural problems** *neurologic signs only late*
characteristics	**Nerve conduction velocity reduced** **CSF protein elevated**

Gieselmann & Krägeloh-Mann, 2010 Neuropediatrics, 2014 OMMBID
Van Rappard, 2015 Best Pract Res Clin Endocrinol Metab
Fumagalli et al JIMD 2021

Different disease trajectories, their clinical characteristics and dynamics and the different needs

Hannah

- Family history, pregnancy, birth inconspicuous
- First motor and cognitive development normal

→ sits without support at age 7 months
→ crawls at age 8 months
→ walks with asstistance at age 10 months

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WHO Motor Development Study: Windows of achievement for six gross motor development milestones. Acta Paediatrica Supplement 2006;450:86-95

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  → sits without support at age 7 months (75% C.I.)
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  → walks with asstistance at age 10 months (75% C.I.)
- since 10 months: **gross motor development stagnating**
- At age 18 months: walks alone, but unstable
  (walking alone 50 and 75% C.I. 12, 13 months respec)
- At age 26 months diagnosis MLD - ARSA deficiency
- 27 months: infect with fever, then **gross motor decline**
  28 months: swallowing difficulties, loss of independent walking
  33 months: can no longer sit without support; speech dysarthric

Hannah 2 ½ years

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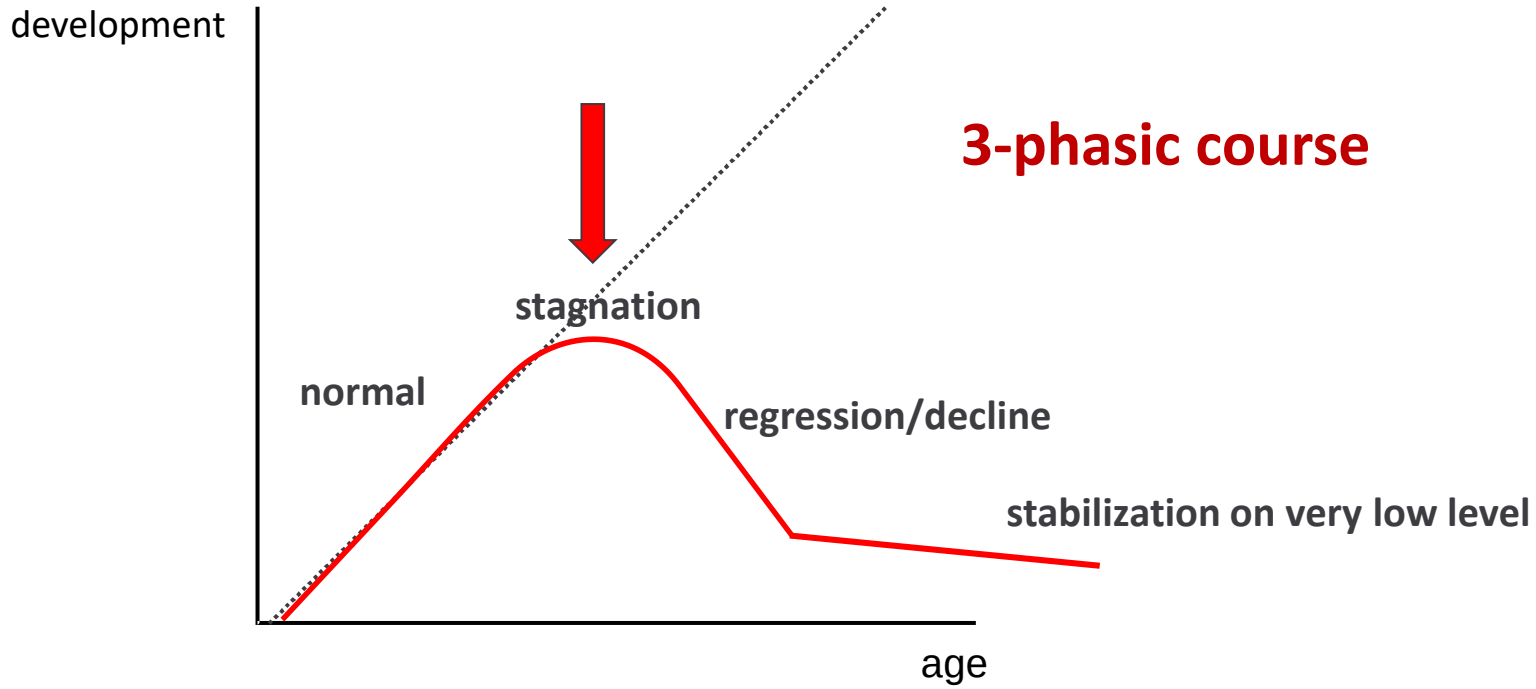
  35 months: can no longer grasp; does not speak any more
  36 months: looses head control, interest in environment reduced
  over several years severely disabled until death at 8 years

Hannah 3 ¼ years

Disease trajectory MLD



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Needs and management

Family support
periods with most heavy burden

Ammann-Schnell, Groeschel et al. Orphanet Rare Dis 2021

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Needs and management

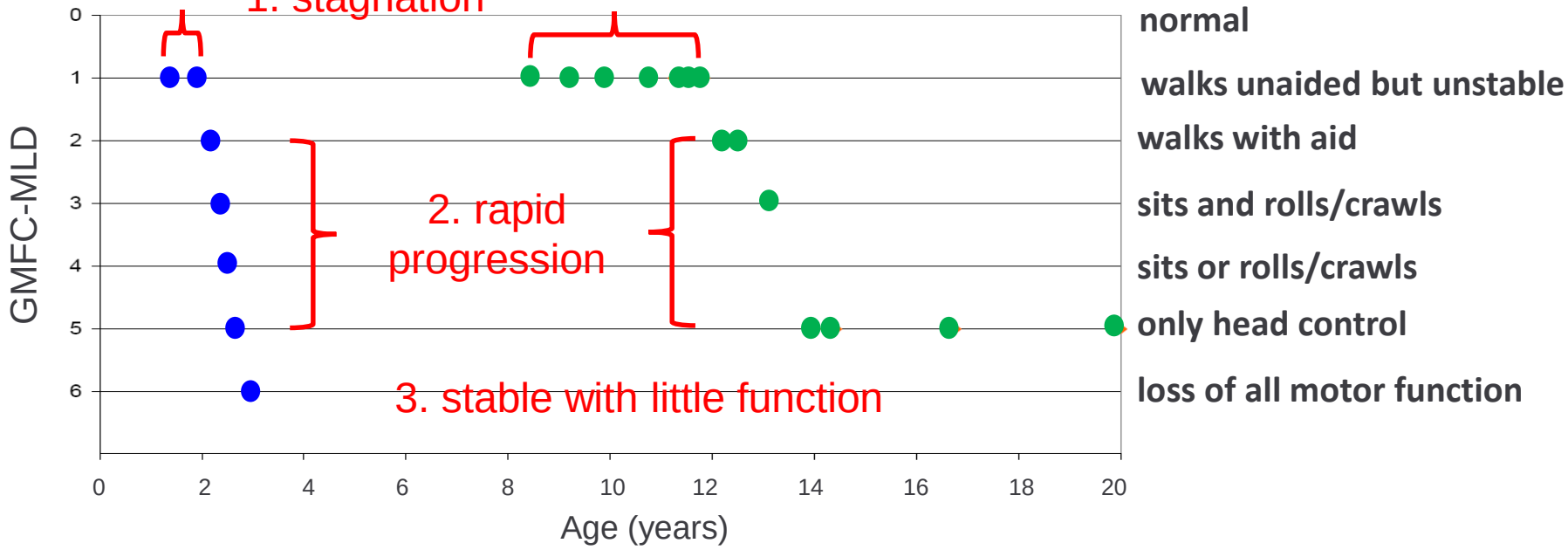
specific support for the child
- frustration due to motor-cognitive discrepancy
- spasticity may need medication (consider vigabatrin)
- gastrostomy
- needs for specific tools

Ammann-Schnell, Groeschel et al. Orphanet Rare Dis 2021

standardized description of gross motor trajectory:

Gross motor function classification for MLD – GMFC-MLD

late-infantile MLD **juvenile MLD**



LEUKONET

Kehrer C, Blumenstock G, Raabe C, Krägeloh-Mann I
Development and reliability of a classification system for gross motor function in children with metachromatic leucodystrophy
Dev Med Child Neurol 2011 Feb; 53(2):156-60

question

1. Gross motor decline in MLD

a. Is very variable and decline is slower the later the onset of the disease
b. Is invariably rapid independent of disease onset, once independent walking is lost
c. Is always a very early sign in MLD

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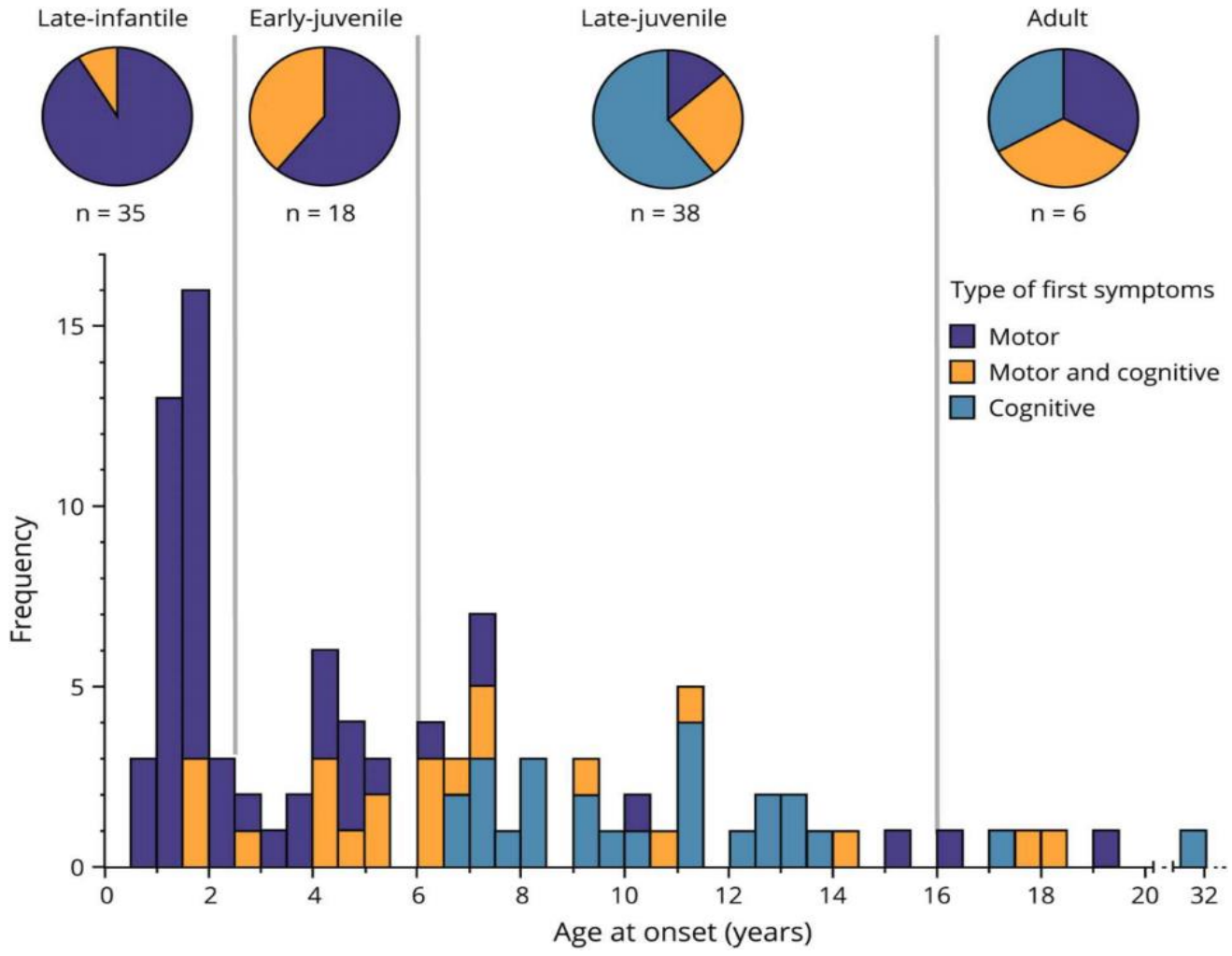
Does age at onset determine disease progression?
What is the role of type of symptoms at disease onset?

Gieselmann & Krägeloh-Mann, 2010 Neuropediatrics, 2014 OMMBID
Van Rappard, 2015 Best Pract Res Clin Endocrinol Metab
Fumagalli et al JIMD 2021

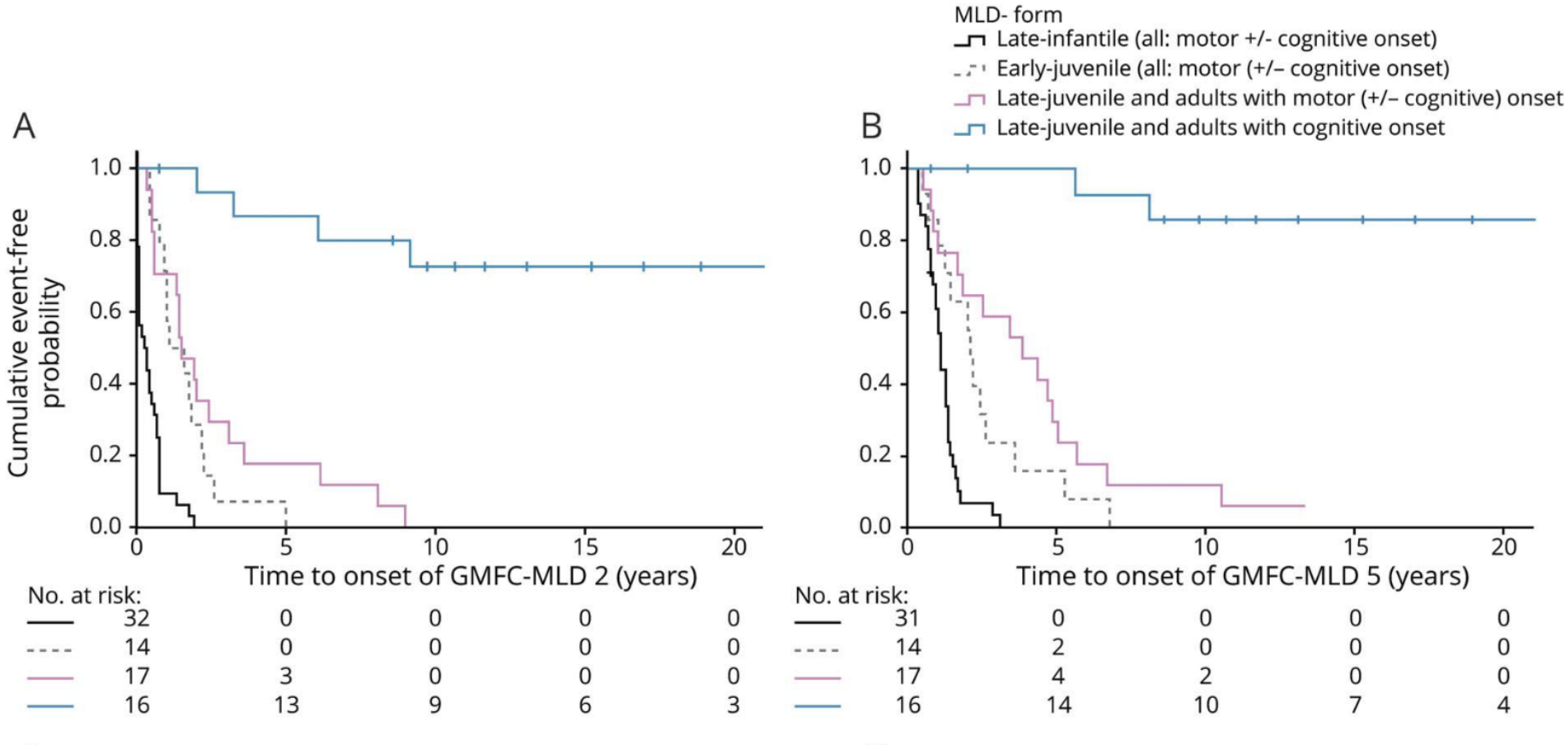
Type of first symptoms in different onset groups of MLD and their frequency



Kehrer, Elgün et al. Neurology 2021

Disease progression from onset to GMFC-MLD 5

(no gross motor function, but head control)
dependent on age and type of onset.



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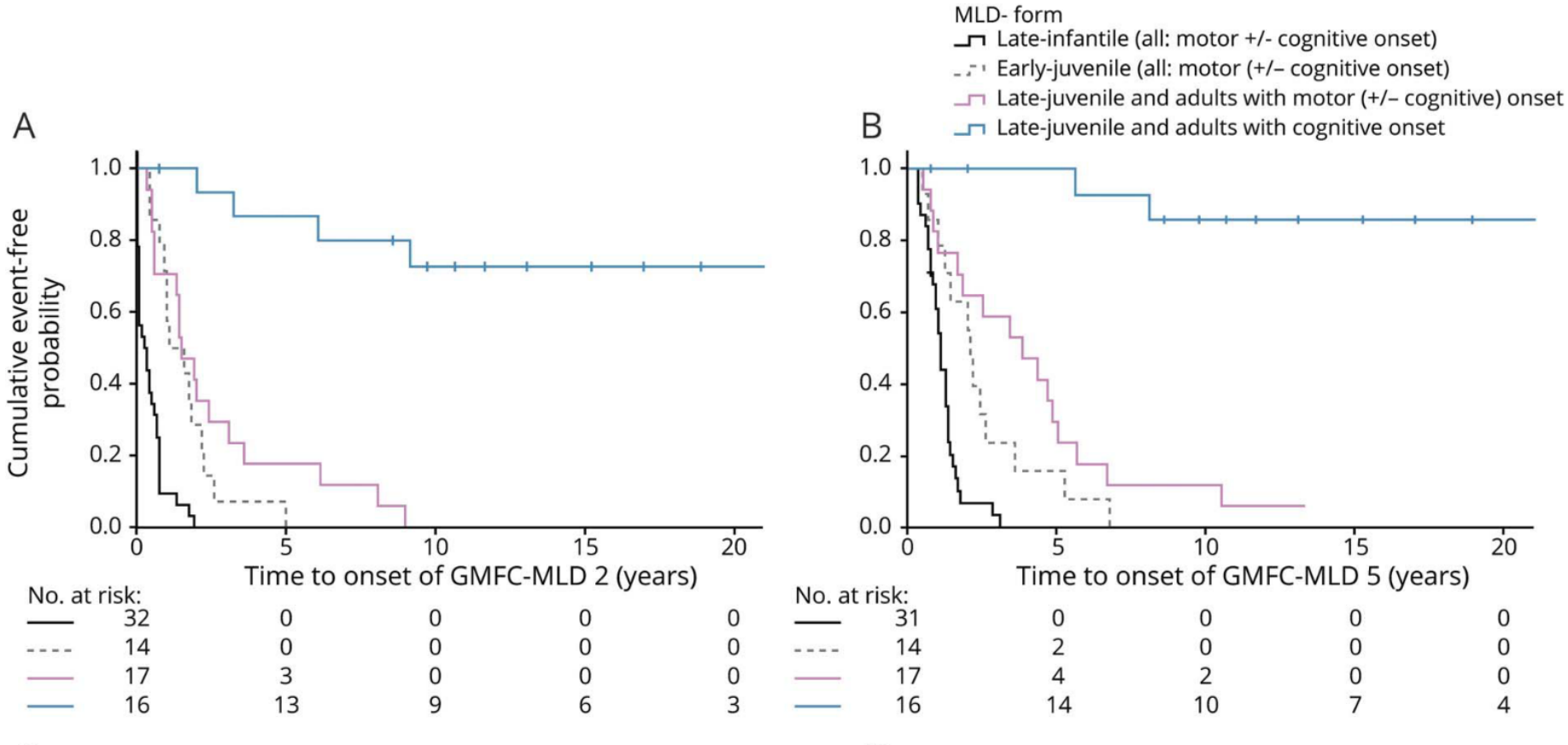


Kehrer, Elgün et al. Neurology 2021

Disease progression from onset to GMFC-MLD 5

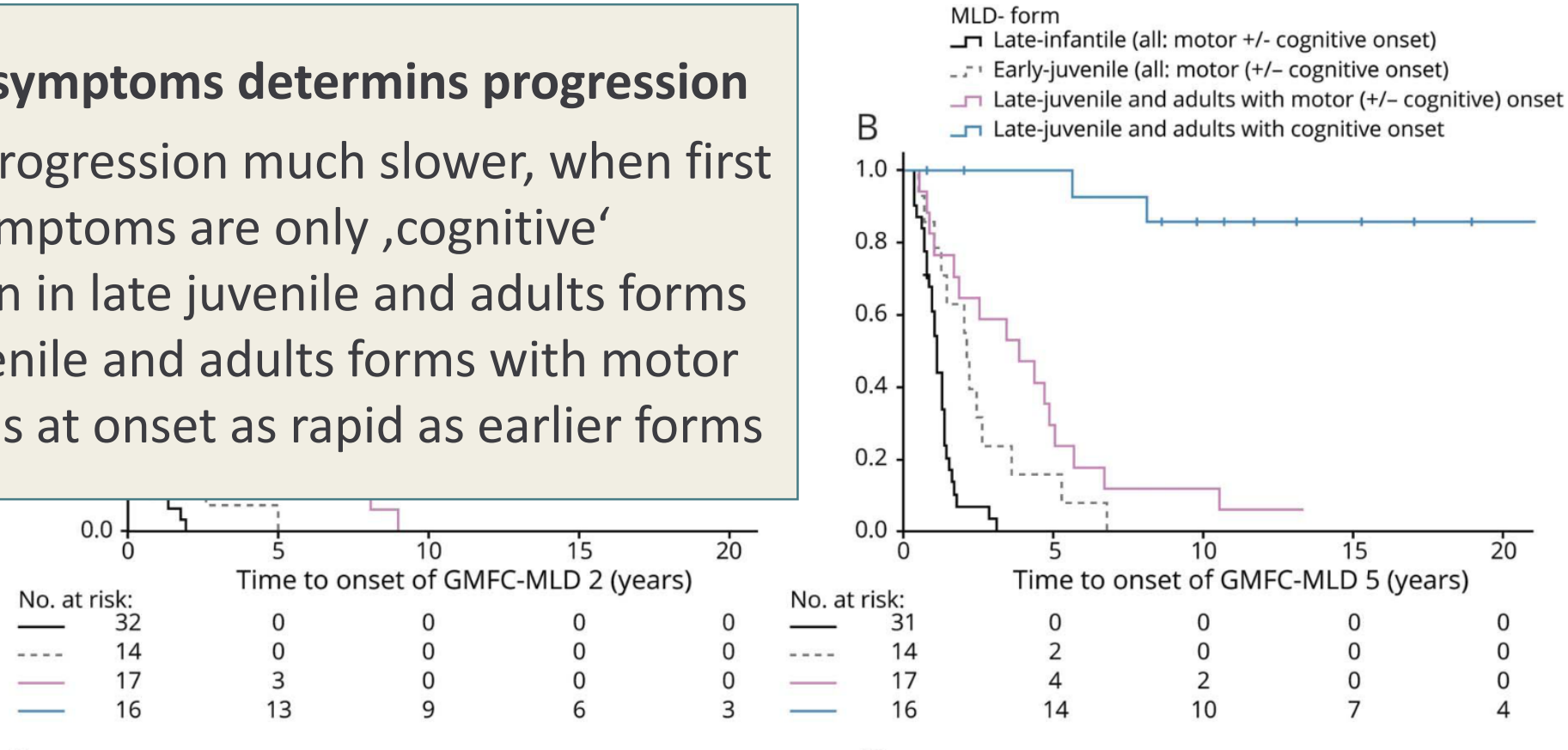
(no gross motor function, but head control) dependent on age and type of onset.

Type of symptoms determins progression

Disease progression much slower, when first symptoms are only ‚cognitive‘

only seen in late juvenile and adults forms

late juvenile and adults forms with motor symptoms at onset as rapid as earlier forms



Kehrer, Elgün et al. Neurology 2021

Possible misdiagnoses and pitfalls

Clumsy child with slow gross motor development – late-infantile MLD?

School difficulties – late-juvenile MLD?

check **developmental trajectory**

make a difference between always slow and stagnation

Possible misdiagnoses and pitfalls

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make a difference between always slow and stagnation

Guillain-Barré-Syndrome (progressive weakness, high CSF protein, contrast enhancement nerve roots)

check ARSA in a child with little improvement on i.v. immunoglobulines (especially when weakness subacute)

You thought of MLD but

ARSA normal – check for sulfatides in urine (activator deficiency)

Early Signs of MLD

- **Strabismus**

Acute-onset paralytic strabismus was an early sign in 22% of patients with late-infantile MLD
(preceding gross motor symptoms in ca 80%)

Beerepoot et al submitted

question

2. What are the most common early signs which should make you think of MLD?

a. A child with primary developmental delay shows signs of spasticity in childhood
b. A normally developed child then stagnates in gross motor development
c. A child with severe seizure disorder shows developmental decline

question

2. What are the most common early signs which should make you think of MLD?

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b. A normally developed child then stagnates in gross motor development
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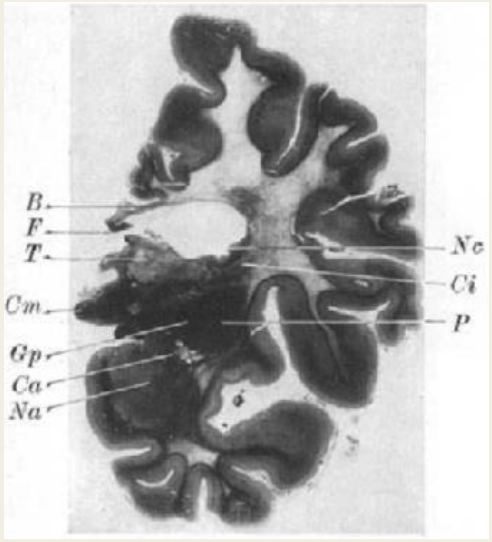
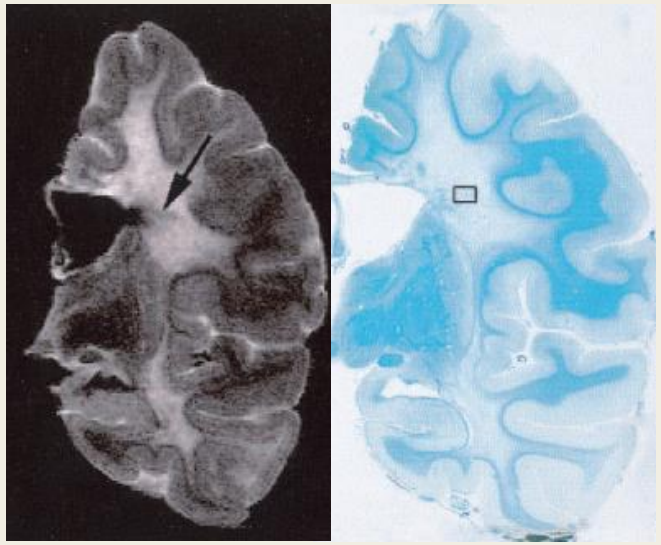
Visualizing brain changes

100 years ago…

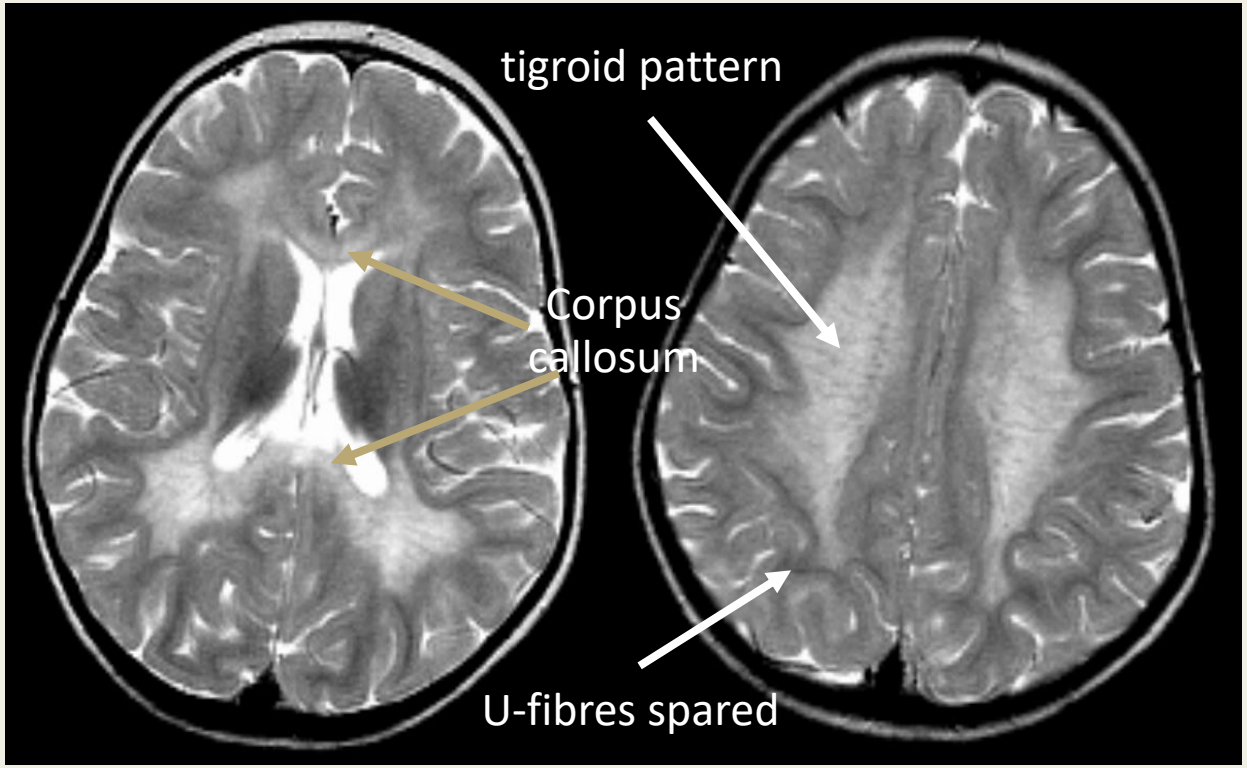


Scholz 1925, Z.Ges Neurol.Psychiatr.

Today…



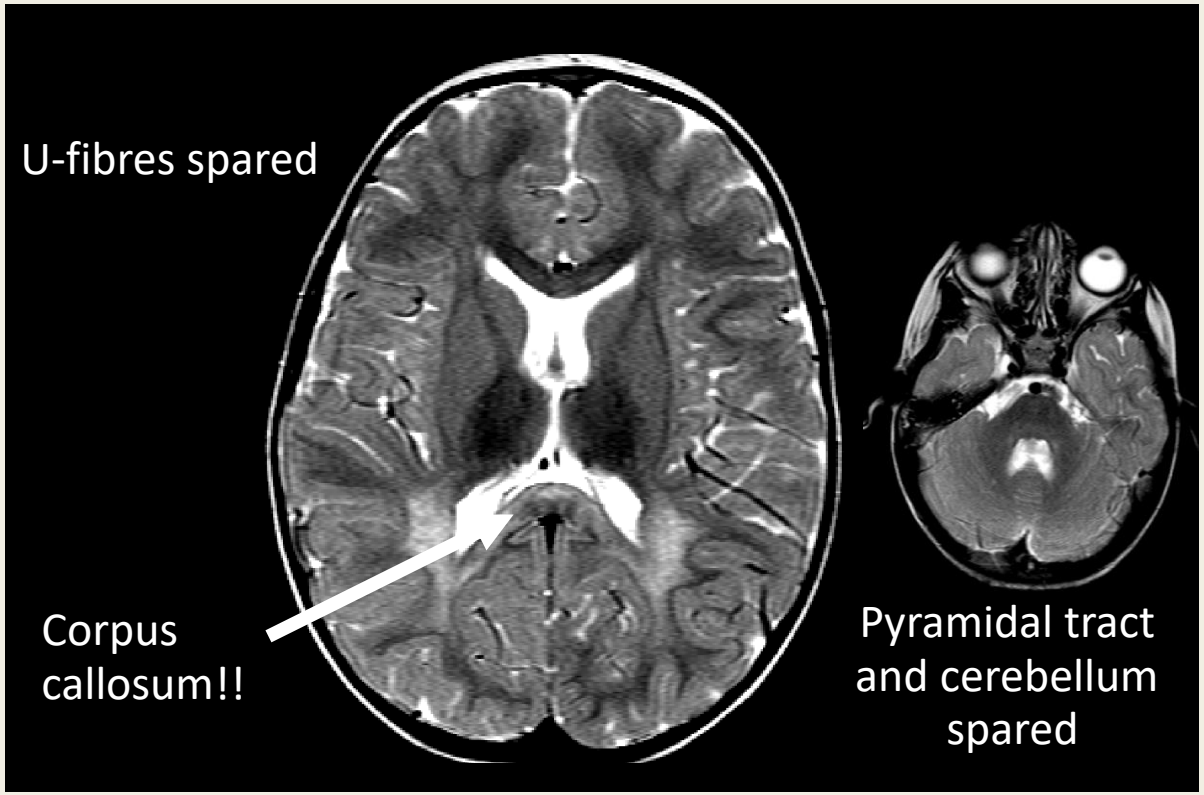
van der Voorn et al. 2005, AJNR



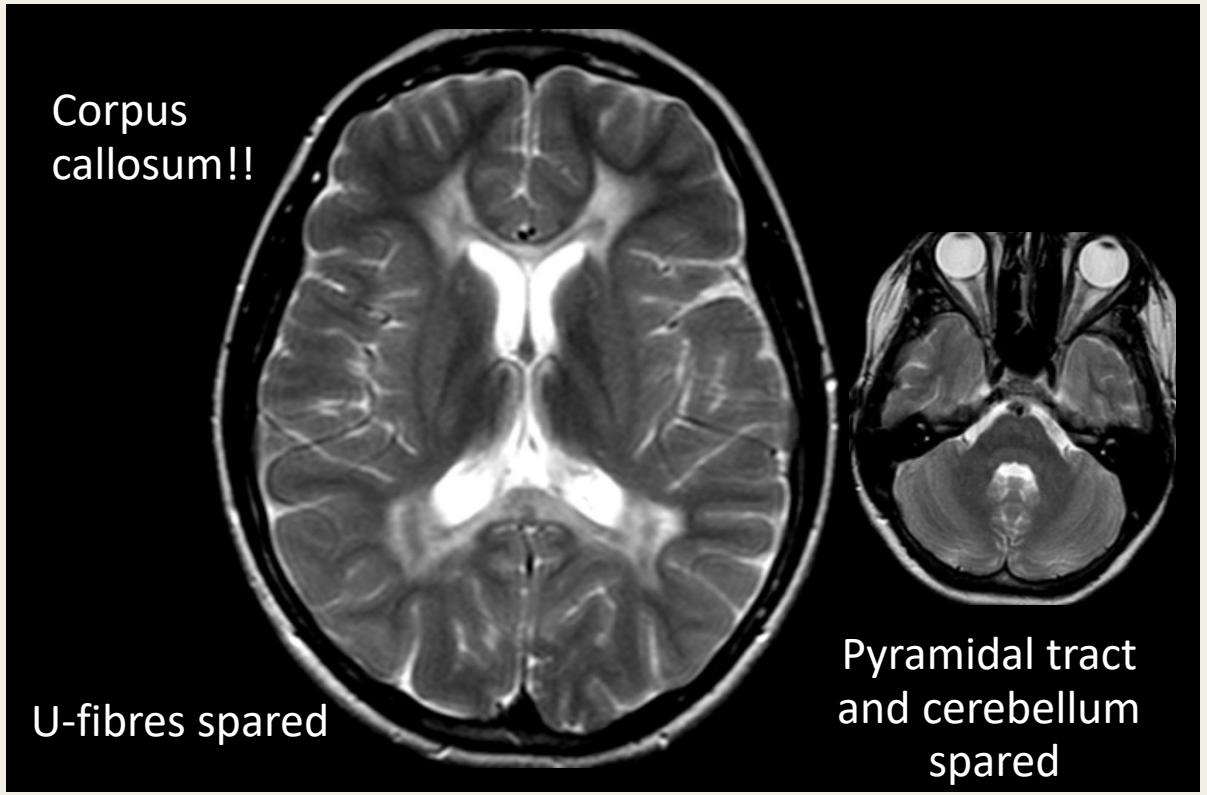
Groeschel et al. 2011, JIMD

Early MRI signs

late-infantile MLD



juvenile MLD



Groeschel et al. 2011, JIMD

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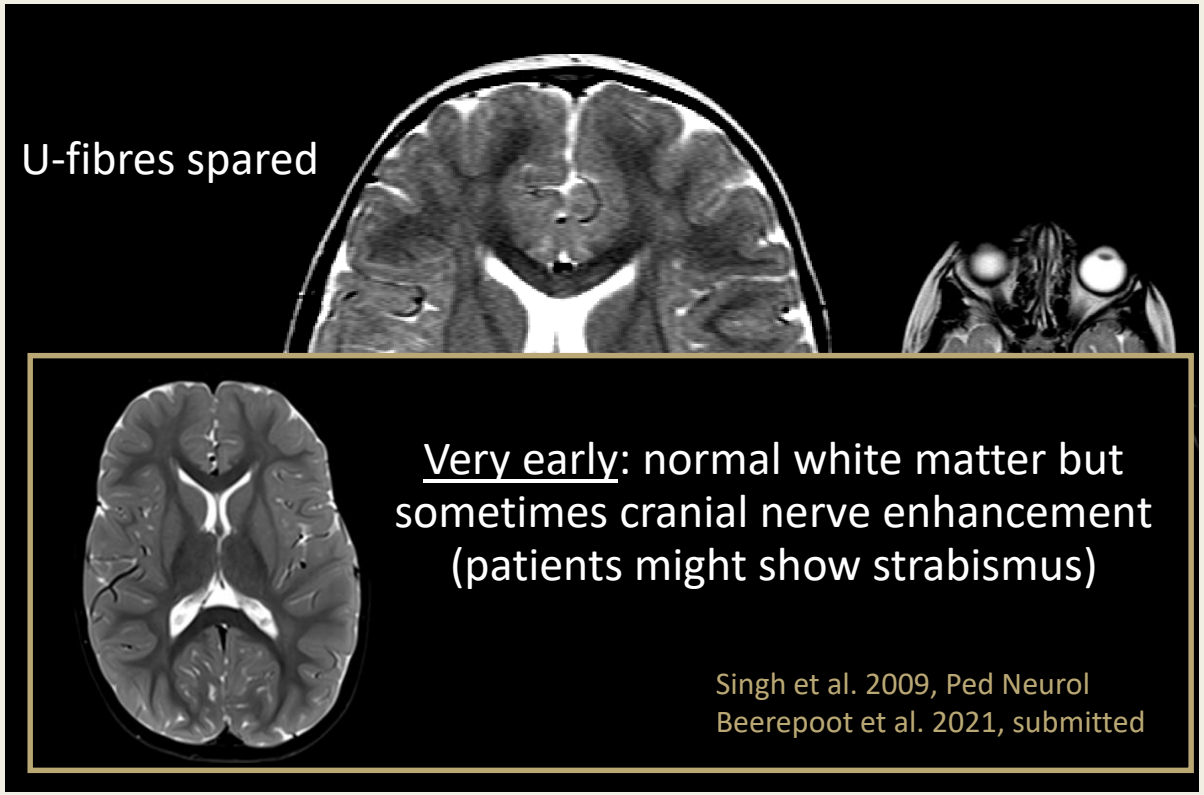
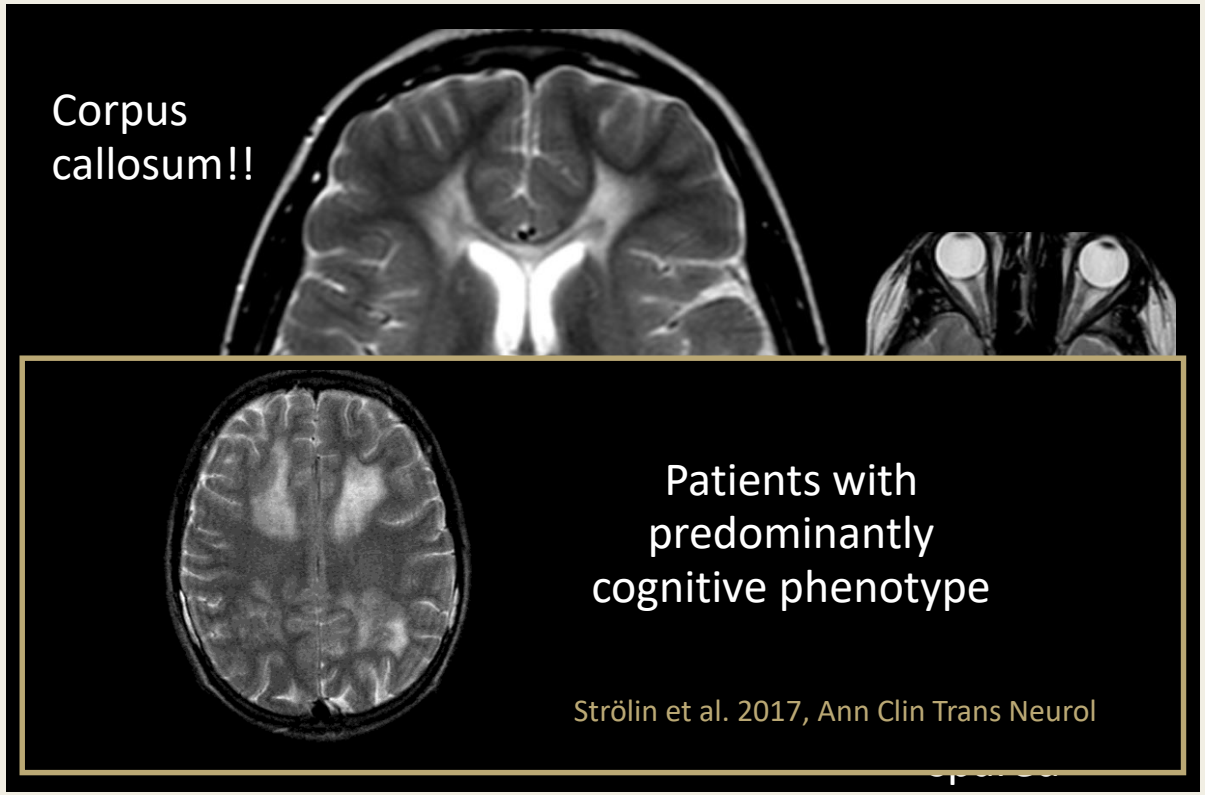


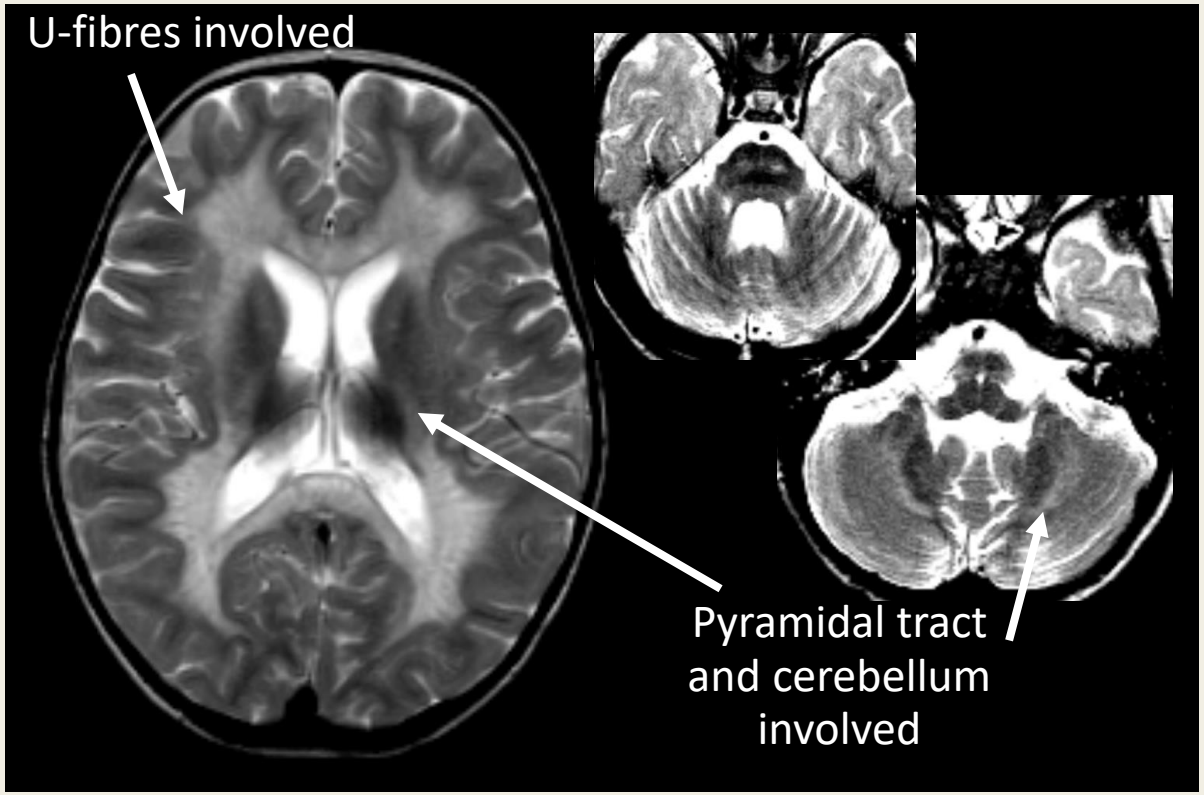
juvenile MLD



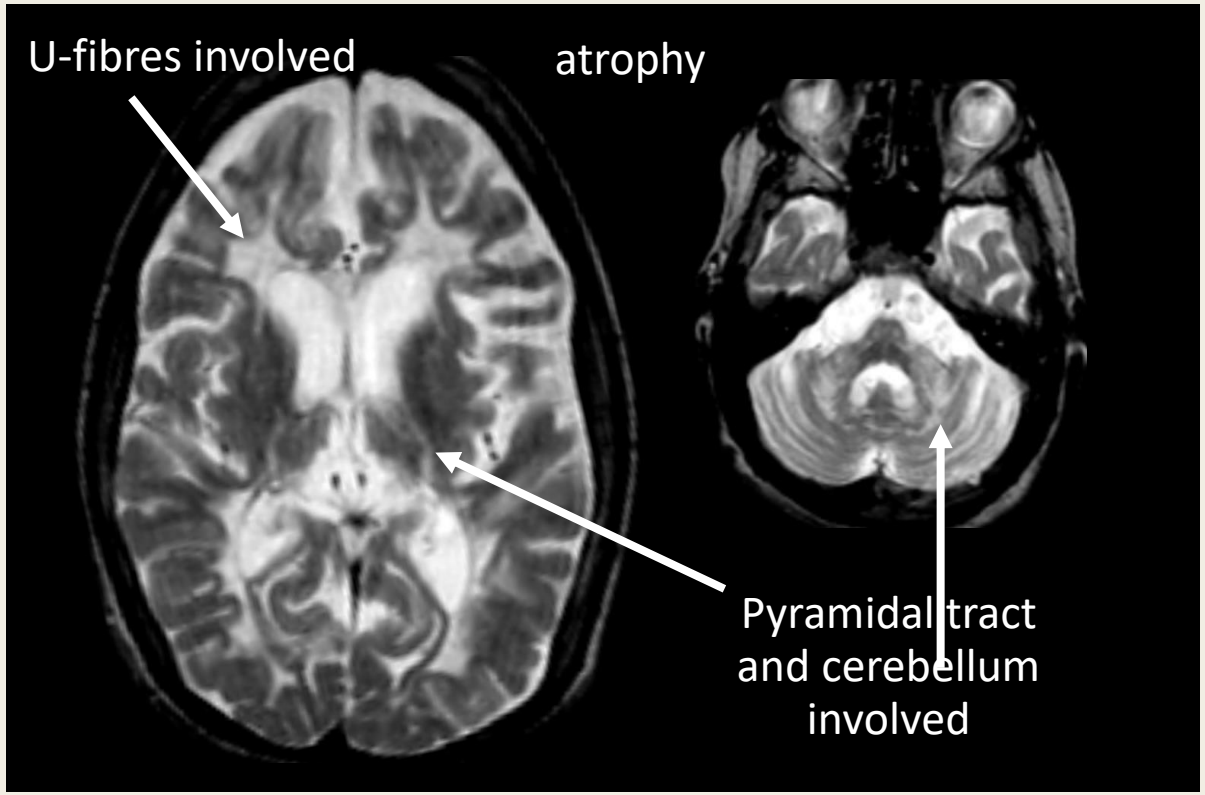
Groeschel et al. 2011, JIMD

Late MRI signs

late-infantile MLD



juvenile MLD



Groeschel et al. 2011, JIMD

question

3. MRI in late infantile MLD

a. Is abnormal when first clinical signs develop
b. Shows early cerebellar atrophy
c. May be judged normal at disease onset

question

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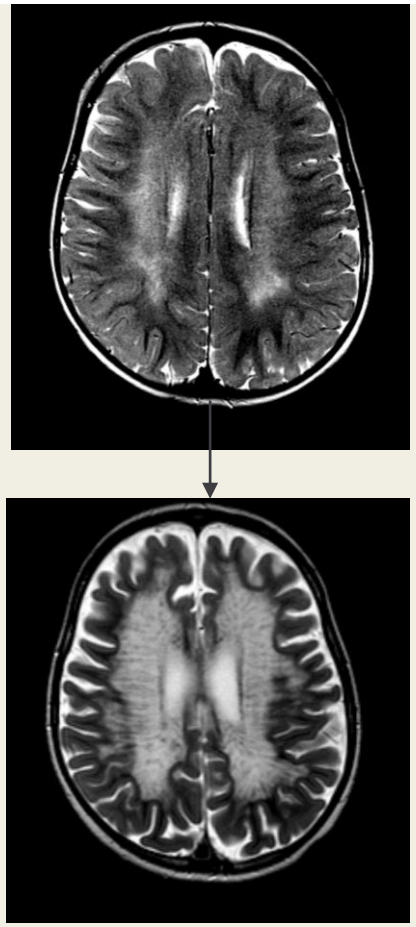
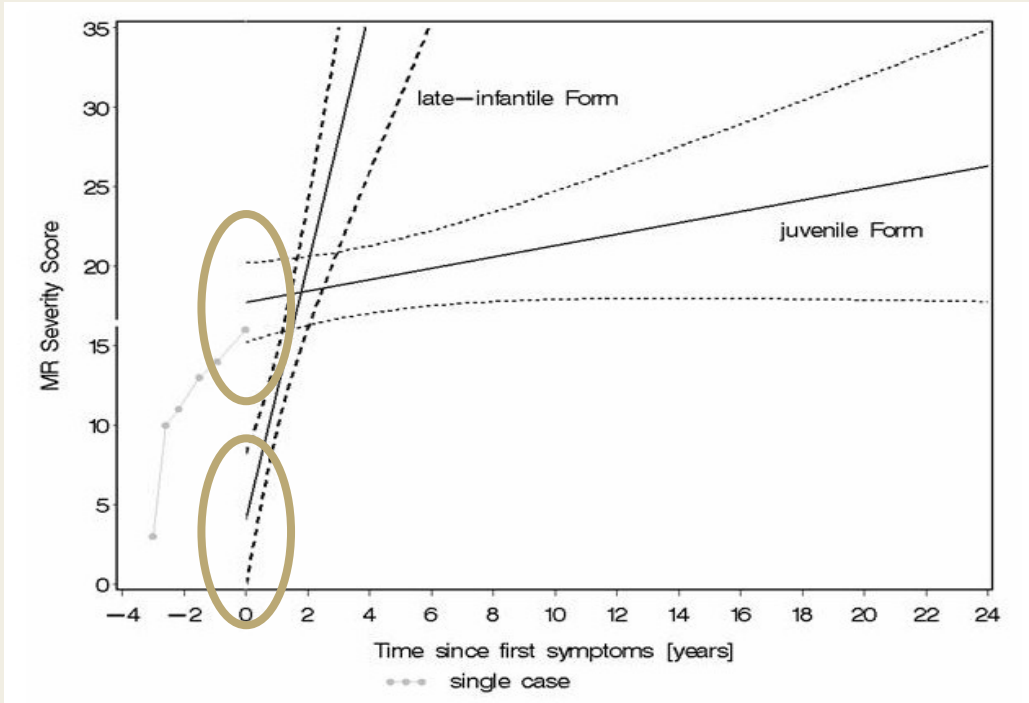
Quantification of brain changes in MLD – MR Score

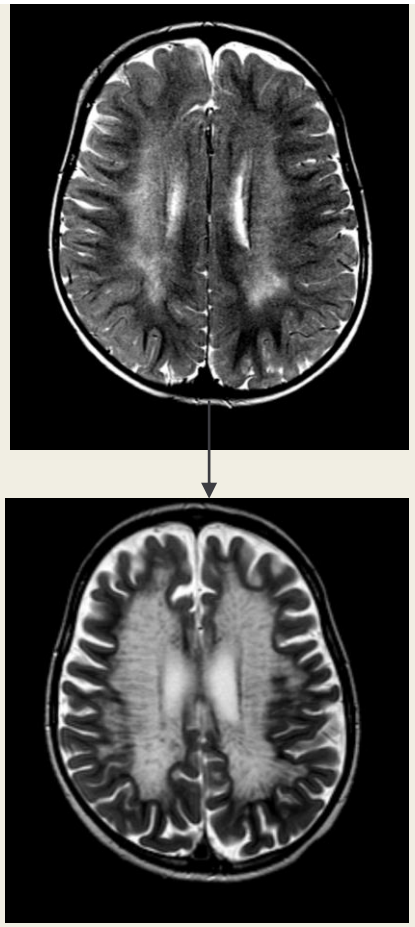


Brain Areas	Score	Maximum per Area
Frontal WM		**6**
Periventricular	0 1 2	
Central	0 1 2	
U-Fibers	0 1 2	
Parieto-occipital WM		**6**
Periventricular	0 1 2	
Central	0 1 2	
U-Fibers	0 1 2	
Temporal WM		**6**
Periventricular	0 1 2	
Central	0 1 2	
U-Fibers	0 1 2	
Corpus callosum		**4**
Genu	0 1 2	
Splenium	0 1 2	
Projection fibers		**6**
Internal capsule ant. limb	0 1 2	
Internal capsule post. limb	0 1 2	
midline pons	0 1 2	
Cerebral Atrophy	0 1 2	**2**
Thalamus	0 1	**1**
Basal ganglia	0 1	**1**
Cerebellum		**2**
White matter	0 1	
Atrophy	0 1	
Total		**34**



Eichler et al. 2009, AJNR
Groeschel et al. 2011, J Inh Met Dis

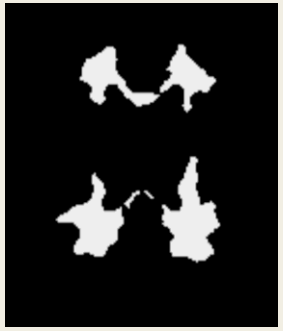
Quantification of brain changes in MLD – MR volumetry

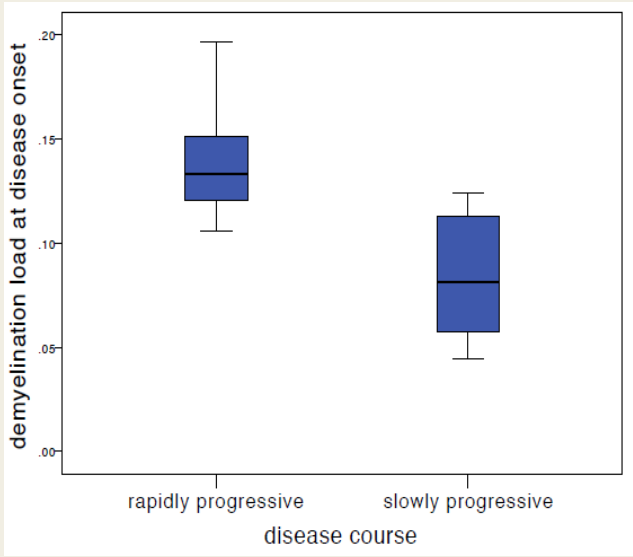


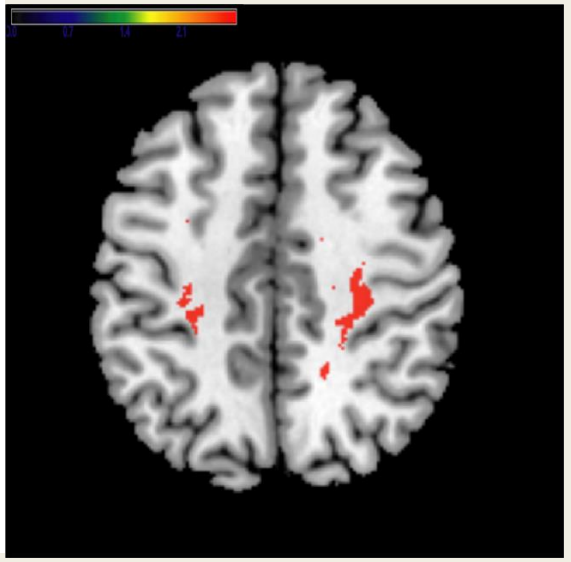
GM WM

early grey matter involvement in MLD

demyelination load





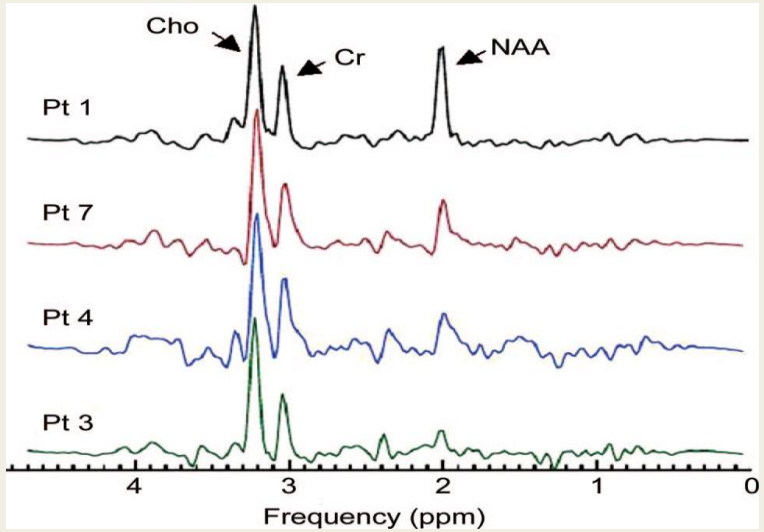


extent and spatial distribution of demyelination load relevant for prognosis in juvenile MLD

Groeschel et al. 2012, Neurology
Strölin et al. 2017, Ann Clin Transl Neurol

Advanced MRI methods in MLD: clinically meaningful biomarkers

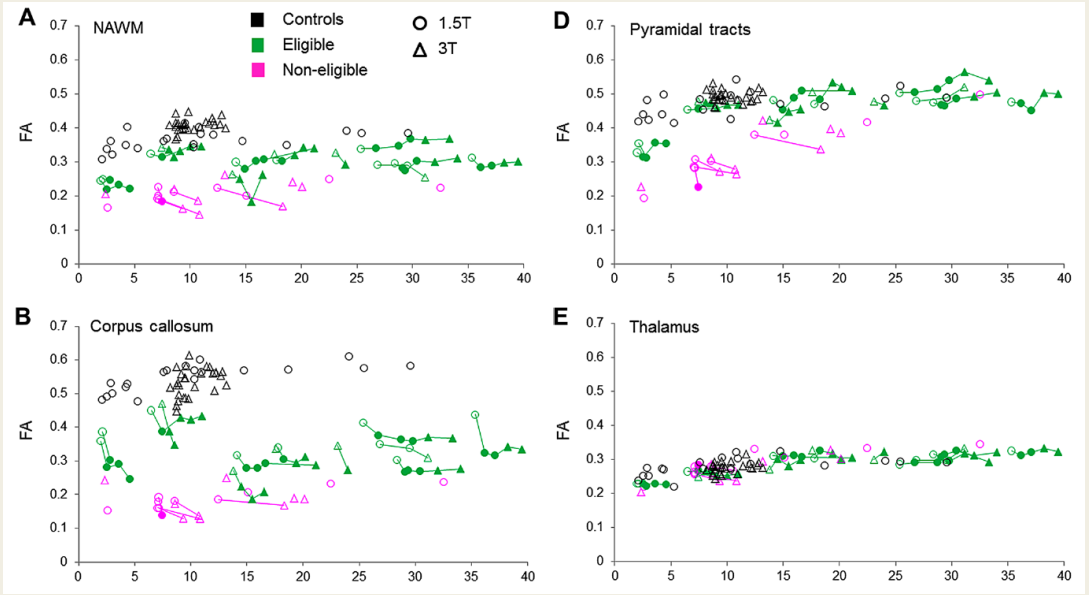
MR spectroscopy



NAA in white matter correlates with motor function

Dali et al. 2010, Neurol

MR diffusion tensor imaging



FA in pyramidal tract and corpus callosum distinguishes between mildy and severely affected patients

Rappard et al. 2018, J Neurol

New treatment options in MLD

hematopoietic stem cell transplantation (HSCT)

Krivit et al. 1999, Curr Opin Neurol
Page et al. 2019, Biol BMT
Wolf et al. 2020, Ann Clin Trans Neurol

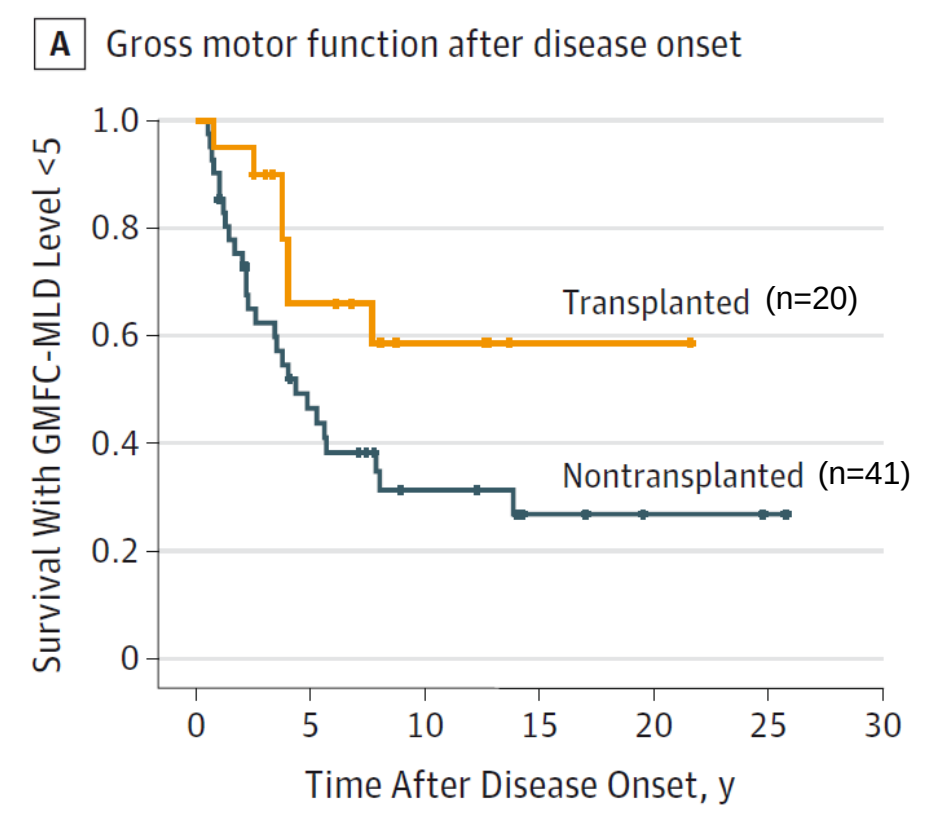
Lentiviral hematopoietic stem cell gene therapy (HSC-GT)

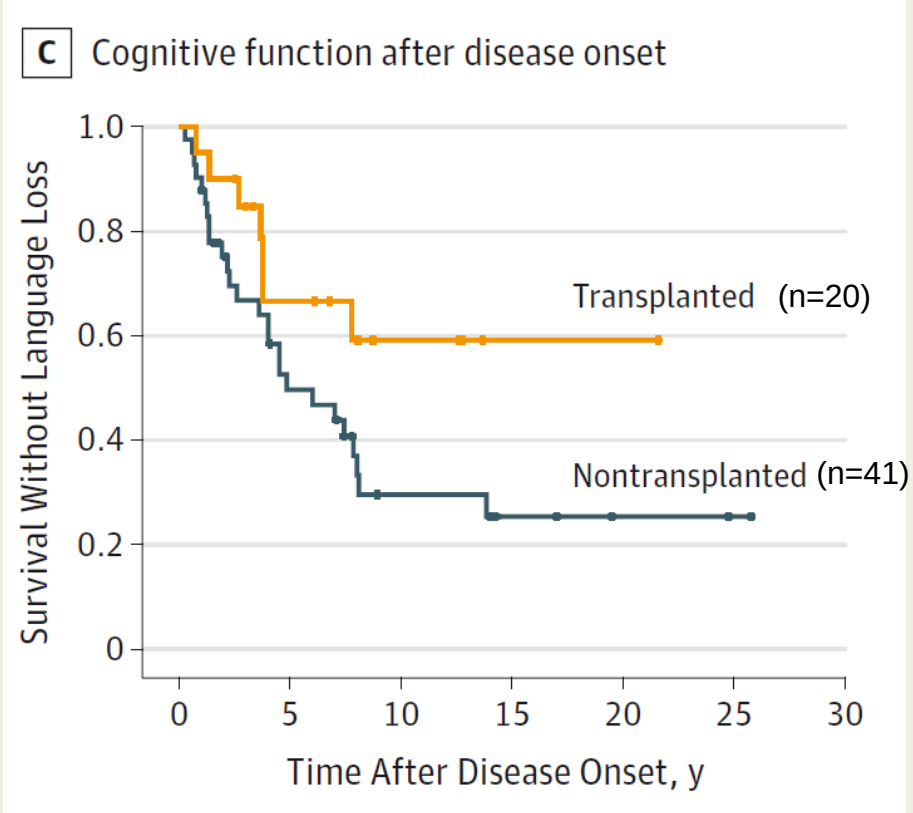
Biffi 2013, Science
Sessa 2005 Gene Therapy

Enzyme replacement therapy phase II trial

Dali et al.2020, Mol Ther

HSCT: an option in juvenile MLD





Groeschel, Kühl, Bley et al. 2016, JAMA Neurol

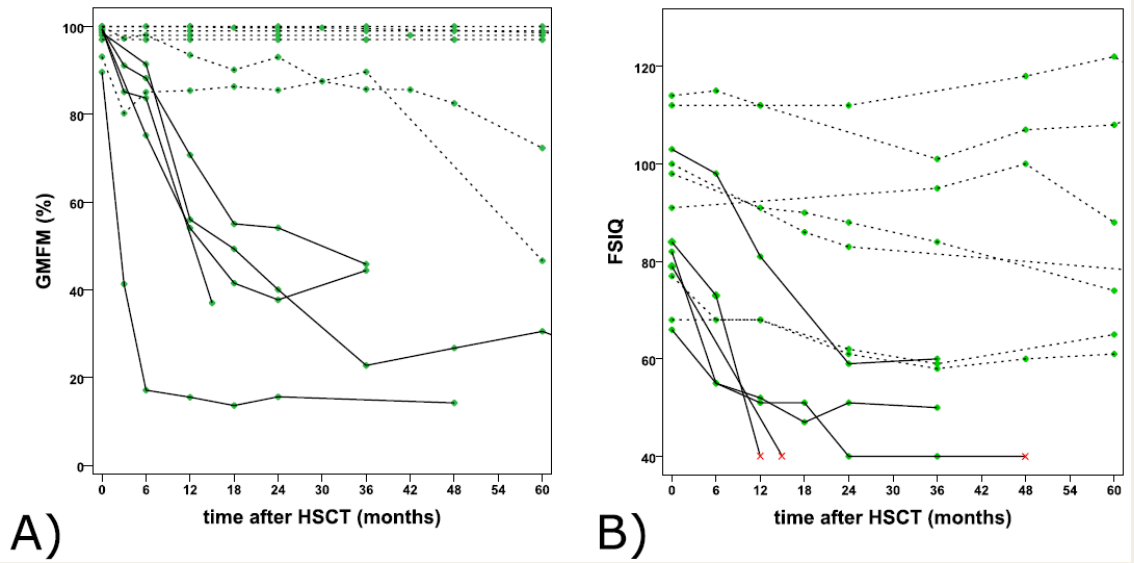
HSCT: early treatment!!!

Higher probability for good outcome when:

- GMFC-MLD 0 (or 1), or 1-2 years before anticipated loss of independent walking
- FSIQ (>70/>85)
- Higher Age at onset (> 4 years)
- Less MRI involvement
  - MRI score <18

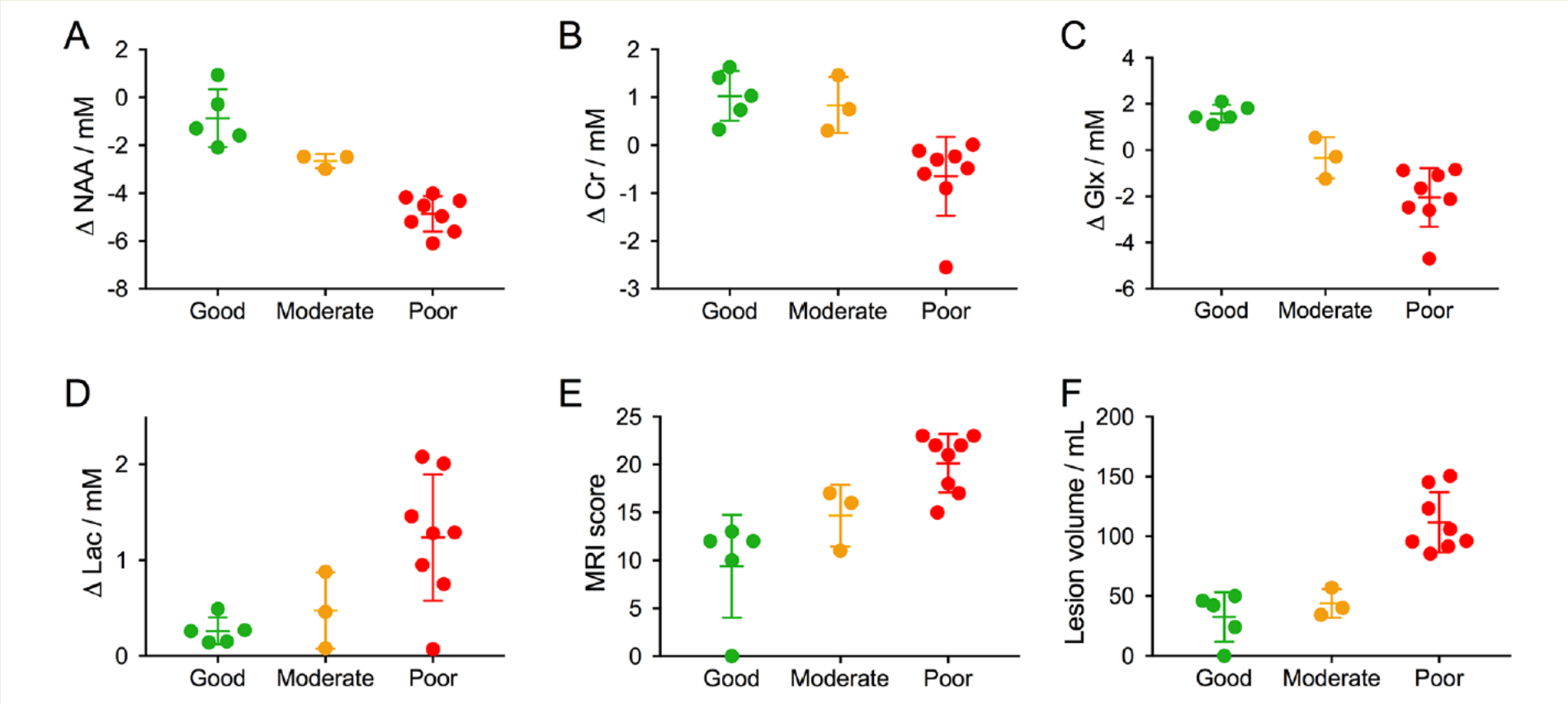
Rappard et al. 2016, 2017, 2018
Groeschel, Kühl, Bley et al. 2016

Cave:
HSCT has high mortality (TRM) rate (~20%, up to 37%)
HSCT can trigger rapid disease progression



Beschle et al. 2020, Mol Cell Ped

MRI surrogate parameter for HSCT outcome



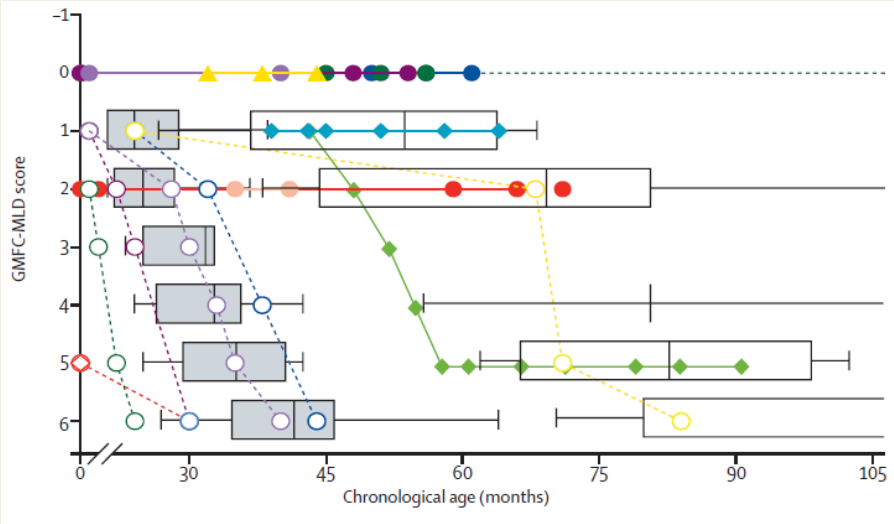
Rappard et al. 2017, J Neurol Neurosurg Psychiatry

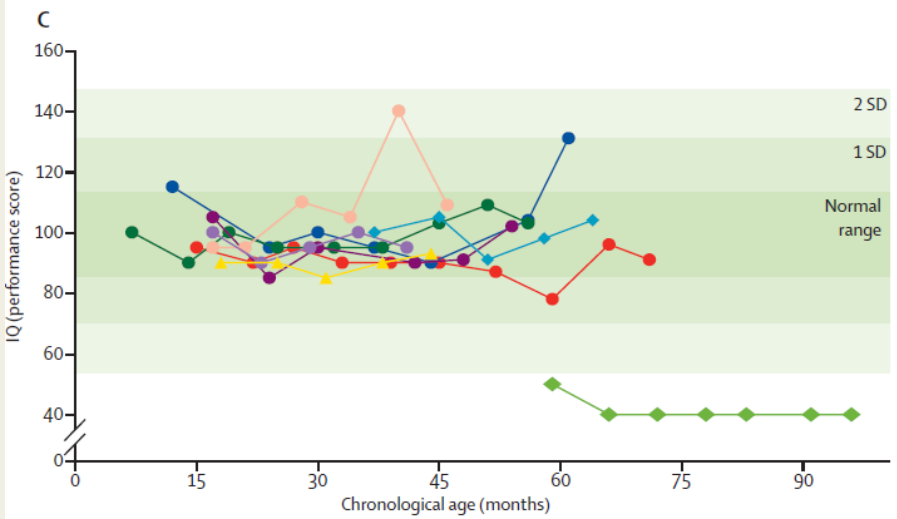
Lentiviral hematopoietic stem cell gene therapy

autologous stem cell transplantation, ex vivo transduced with lentiviral vector → overexpression of ARSA

Phase I/II study since 2010 with good safety and efficacy results
For presymptomatic late-infantile and early symptomatic early-juvenile

Biffi 2017, Mol Ther
Biffi et al. 2013, Science
Sessa et al. 2016, Lancet





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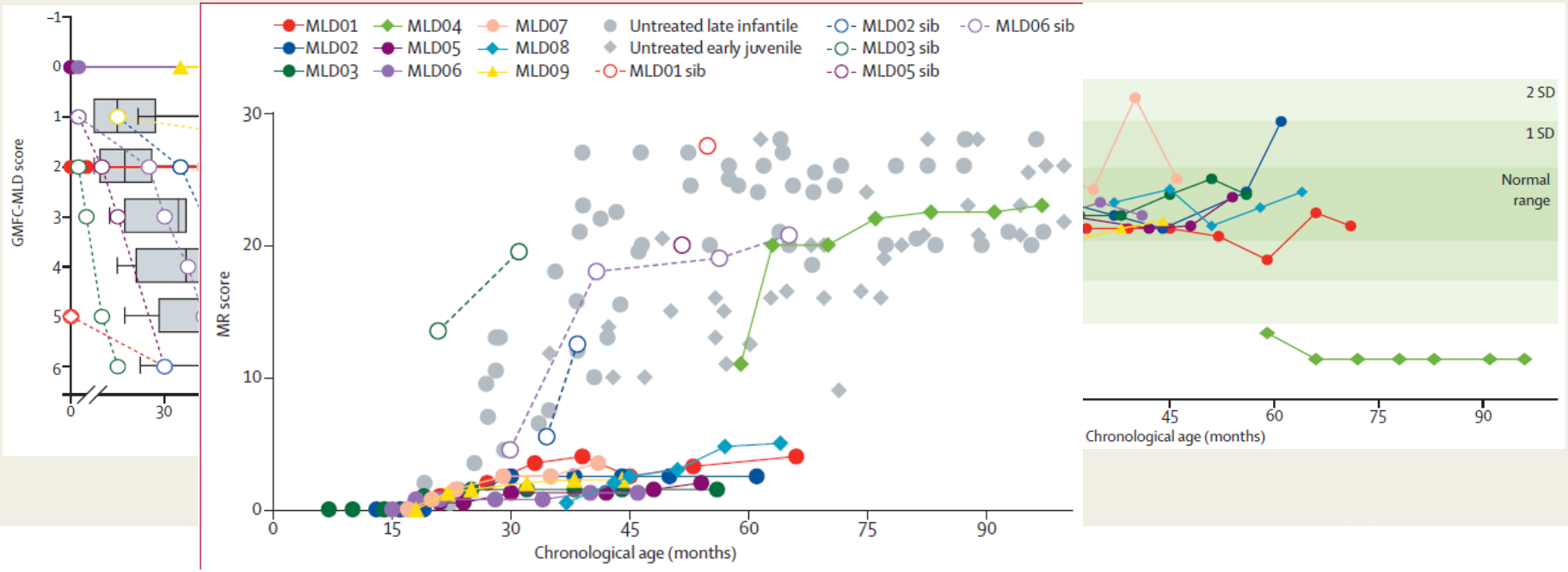

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Biffi et al. 2013, Science
Sessa et al. 2016, Lancet

EMA approved in Dec 2020

currently treatment centers in Europe (outside Milan) are being established (Tübingen ready summer 2021)

Enzyme replacement therapy

successful in MLD mice

Matzner et al. 2005, 2009
Stroobants et al. 2011, Hum.Mol.Genet

Intravenous phase I/II monocentric study: 2008-2010
→ no clinical benefit for symptomatic late-infantile form

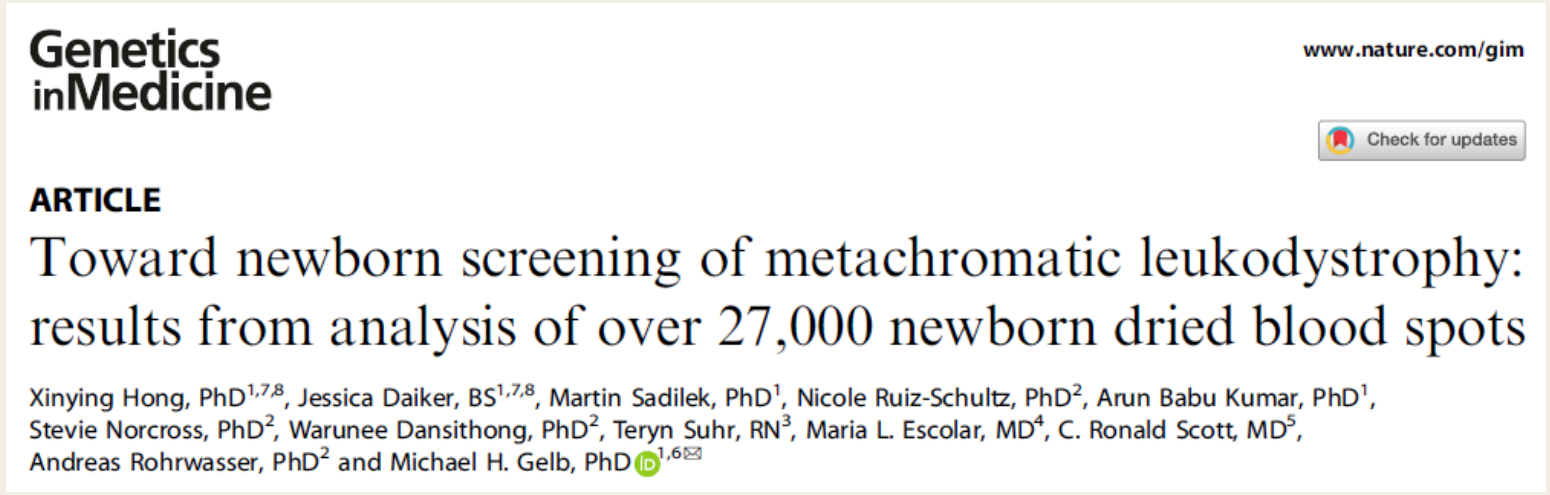
Dali et al. 2011, Eur J Paed Neurol

Intrathecal Pase I/II Studie (Shire plc): seit 2012-2016
- patients receiving highest dose (100mg EOW) with less severe decline

Dali et al. 2020, Mol Gen Metab

currently intrathecal multicenter phase II trial: recruiting 2019-2021 (now closed)
- 21 international study locations
- 150mg EW

Very early diagnosis: Newborn Screening



Genetics inMedicine

www.nature.com/gim

Check for updates

ARTICLE

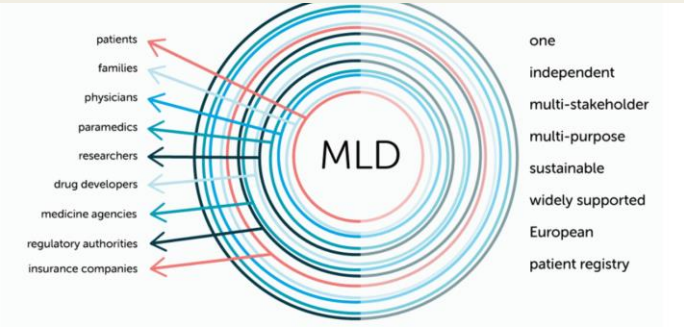
Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots

Xinying Hong, PhD[1,7,8], Jessica Daiker, BS[1,7,8], Martin Sadilek, PhD[1], Nicole Ruiz-Schultz, PhD[2], Arun Babu Kumar, PhD[1], Stevie Norcross, PhD[2], Warunee Dansithong, PhD[2], Teryn Suhr, RN[3], Maria L. Escolar, MD[4], C. Ronald Scott, MD[5], Andreas Rohrwasser, PhD[2] and Michael H. Gelb, PhD[1,6]✉

- Dried blood spot: ARSA activity + sulfatide + genetic confirmation
- Pilot studies in various countries/states

Working together in rare diseases…

the MLD initiative



MLD guideline

SSIEM ean european academy of neurology

European Reference Network

for rare or low prevalence complex diseases

Co-financed by the Connecting Europe Facility of the European Union

Network Neurological Diseases (ERN-RND)

ELA International - GEIE

MLD foundation We C.A.R.E.

GLOBAL LEUKODYSTROPHY INITIATIVE

A Rare Diseases Clinical Research Network Consortium

Summary – key conclusions

- **Natural history studies** are essential not only for counselling, but also as basis for therapy studies
- MLD usually has a **3-phasic course** with rapid decline once independent walking is lost; disease progression is **much slower, when first symptoms are only ‚cognitive‘** (only seen in late juvenile and adults forms)
- **Early signs**: deviation from developmental trajectory; late infantile strabism – think of MLD!
- **MRI** is helpful for diagnosis, prognosis and therapy evaluation
- **Conventional HSCT** can stabilize disease progression for juvenile MLD when done early
- **Lentiviral HSC-gene therapy** approved by EMA in 12/2020
- **Intrathecal ERT phase II still running** (recruitement closed)
- **Newborn screening** pending

Thank you for your attention and thanks to

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