Approach to the patient with suspected leukodystrophy

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Entry questions – Q1

Which statement regarding leukodystrophies is true:

a. Leukodystrophies are caused by primarily dysfunction of oligodendrocytes and the structure of myelin

b. Are always progressive disorders

c. Can be caused by disorders of astrocytes or microglia primarily

d. None of the above

Entry questions – Q2

Myelination of the brain is completed approximately at

a. Birth

b. 12 months

c. 24 months

d. Don’t know

Entry questions – Q3

The rate of diagnosis of leukodystrophies (in children) improved tremendously due to MRI pattern recognition and whole exome sequencing. On average the rate of diagnosis currently:

a. 25%

b. 50%

c. 85%

d. Don’t know

Outline of this presentation

- The concept of leukodystrophy
- MRI pattern recognition as the basis for diagnosis
- Whole exome sequencing: changing phenotypes
- Emerging treatments and newborn screening
- Putting it all together: diagnostic approach
- MRI patterns: most common leukodystrophies
- Current research and challenges for the future

What is a leukodystrophy?

Genetically determined progressive disorders selectively involving the central nervous system white matter

In the 20th century considered to always directly affect myelin directly or oligodendrocytes

Observation of the past decades challenge this narrow definition

van der Knaap et al, Acta Neuropathol, 2017

Should the definition of leukodystrophy be adapted?

- Some disorders are not progressive and can even improve
- Myelin or oligodendrocyten not always primarily affected

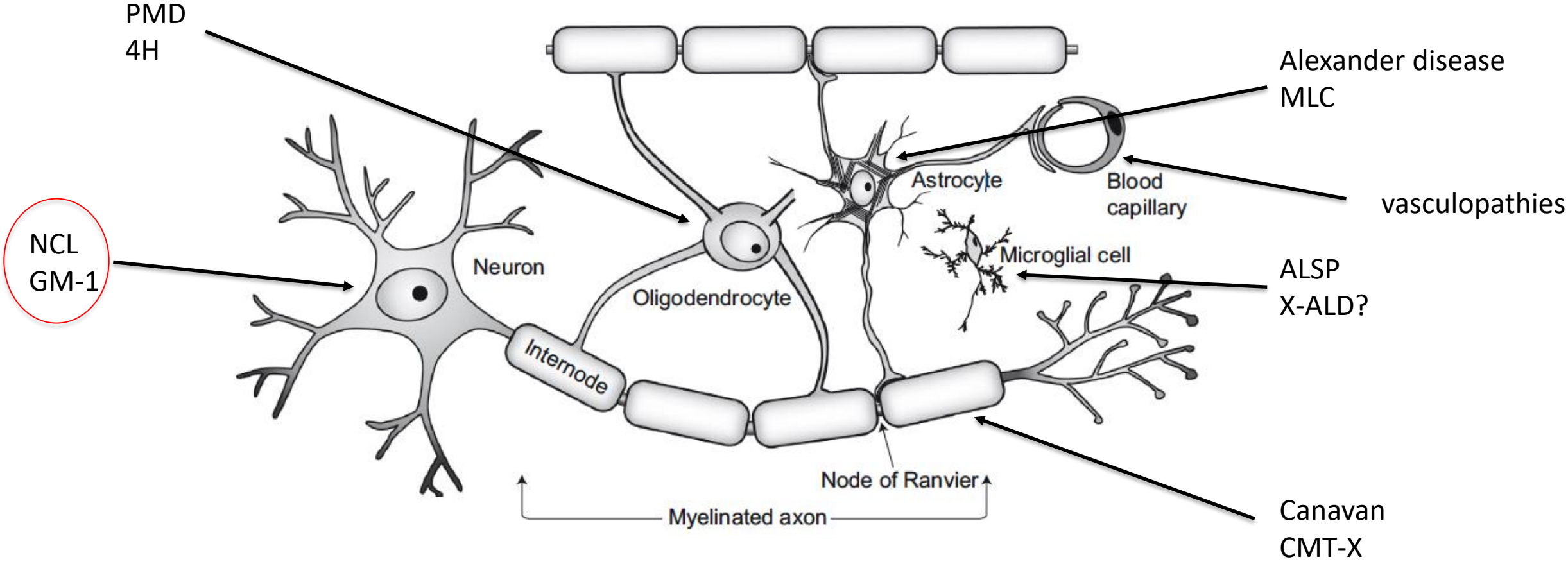
Leukodystrophies are genetically determined disorders primarily affecting CNS white matter (irrespective of the specific component involved) and with a variable the disease course

For many leukodystrophies the pathophysiology is poorly understood (for instance X-ALD)

van der Knaap et al, Acta Neuropathol, 2017

How to classify leukodystrophies

Half of brain mass is CNS white matter



van der Knaap et al, Acta Neuropathol, 2007
Diffusion MRI, 2nd edition

A proposed classification based on pathophysiology

Table 1 A new classification of genetic white matter disorders

Myelin disorders	Leuko-axonopathies
Hypomyelination	a. Hypomyelination with atrophy of the basal ganglia and cerebellum [80]
a. Pelizaeus-Merzbacher disease [224]	b. Hypomyelination with congenital cataract [66]
b. Peripheral neuropathy, central hypomyelination, Waardenburg-Hirschsprung [36]	c. Early-onset neuronal degenerative disorders
c. Cx47-related Pelizaeus-Merzbacher-like disease [36]	1. Gangliosidosis GM1 and GM2 [75, 250]
d. Hypomyelination of early myelinated structures [104]	2. Infantile neuronal ceroid lipofuscinosis [79]
Demyelination	3. *AGC1*-related disease [265, 268]
a. Metachromatic leukodystrophy [214]	4. *AIMP1*-related diseases [58]
b. Multiple sulfatase deficiency [214]	5. *HSPD1*-related disease [134]
c. Globoid cell leukodystrophy (Krabbe disease) [214]	d. Pol III-related leukodystrophies [269]
d. X-linked adrenoleukodystrophy, cerebral from [173]	e. Leukoencephalopathy with brainstem and spinal cord involvement and high lactate [231]
Myelin vacuolization	f. Hypomyelination with brainstem and spinal cord involvement and leg spasticity [216]
a. Mitochondrial diseases with leukoencephalopathy [159]	g. Giant axonal neuropathy [135]
b. Phenylketonuria [94]	Microgliopathies
c. Canavan disease [91]	a. *CSF1R*-related disorders [153, 179]
d. Other selected disorders of amino acid metabolism [2]	1. Hereditary diffuse leukoencephalopathy with spheroids
e. Cx32-related (X-linked) Charcot-Marie-Tooth disease [45]	2. Pigmentary ortochromatic leukodystrophy
Astrocytopathies	b. Nasu-Hakola disease [193]
a. Alexander disease [25]	Leuko-vasculopathies
b. Megalencephalic leukoencephalopathy with subcortical cysts [23]	a. Cerebral AD arteriopathy with subcortical infarcts and leukoencephalopathy [162]
c. ClC-2-related disease [45]	b. Cerebral AR arteriopathy with subcortical infarcts and leukoencephalopathy [162]
d. Vanishing white matter [48]	c. Cathepsin A-related arteriopathy with strokes and leukoencephalopathy [31]
e. Aicardi-Goutières syndrome and variants [255]	d. Cerebral amyloid angiopathy [162]
f. Oculodentodigital dysplasia (Cx43) [1]	e. Leukoencephalopathy with calcifications and cysts [98]
g. Giant axonal neuropathy [135]	

van der Knaap et al, Acta Neuropathol, 2017

Approach to diagnosis

- A (neuropathologic/pathophysiologic) classification is important, but does not directly guide the clinician
- Symptoms are both aspecific (CNS symptoms like spasticity and ataxia) and specific (hypodontia for 4H, adrenal failure for X-ALD, etc)
- Signs and symptoms alone do not reliably diagnose leukodystrophies (especially in the early stage)
- Specific MRI patterns defined the field from the late 1980s

MRI pattern recognition

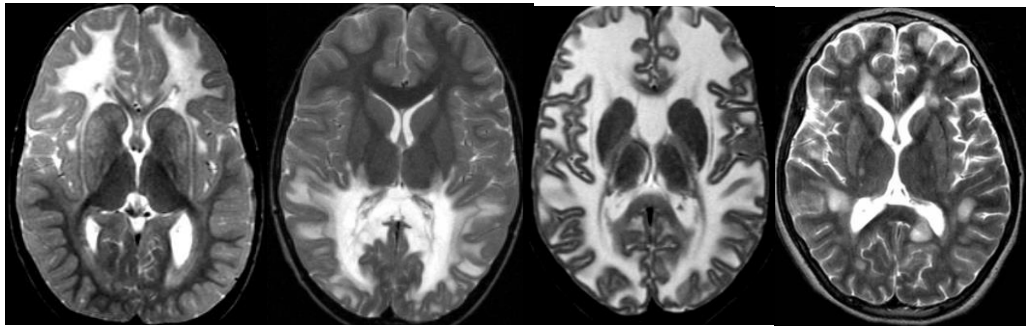
- Revolutionised the field of leukodystrophy diagnosis and research from the 1980s onward
- Classification by clinical features and MRI pattern identified new disorders (LBSL, MLC)
- Made accurate diagnosis and gene discovery possible (linkage analysis)

van der Knaap et al, Ann Neurol, 2003

MRI pattern recognition in leukodystrophies

- Systematic analysis of many different white & gray matter structures and lesion characteristics
- Items with the highest differentiating value are:
    1. confluent and symmetrical versus multifocal and asymmetrical
    2. predominant localisation of the abnormalities
    3. nature of the white matter abnormalities
    4. presence of special features
- Integration of the MRI data into patterns with high diagnostic specificity
- Combination with clinical information
- Short differential diagnosis

N.B. There are always exceptions!



van der Knaap et al, Neuroradiology, 1991
van der Knaap et al, Radiology, 1999
van der Knaap et al, Neurology, 2008

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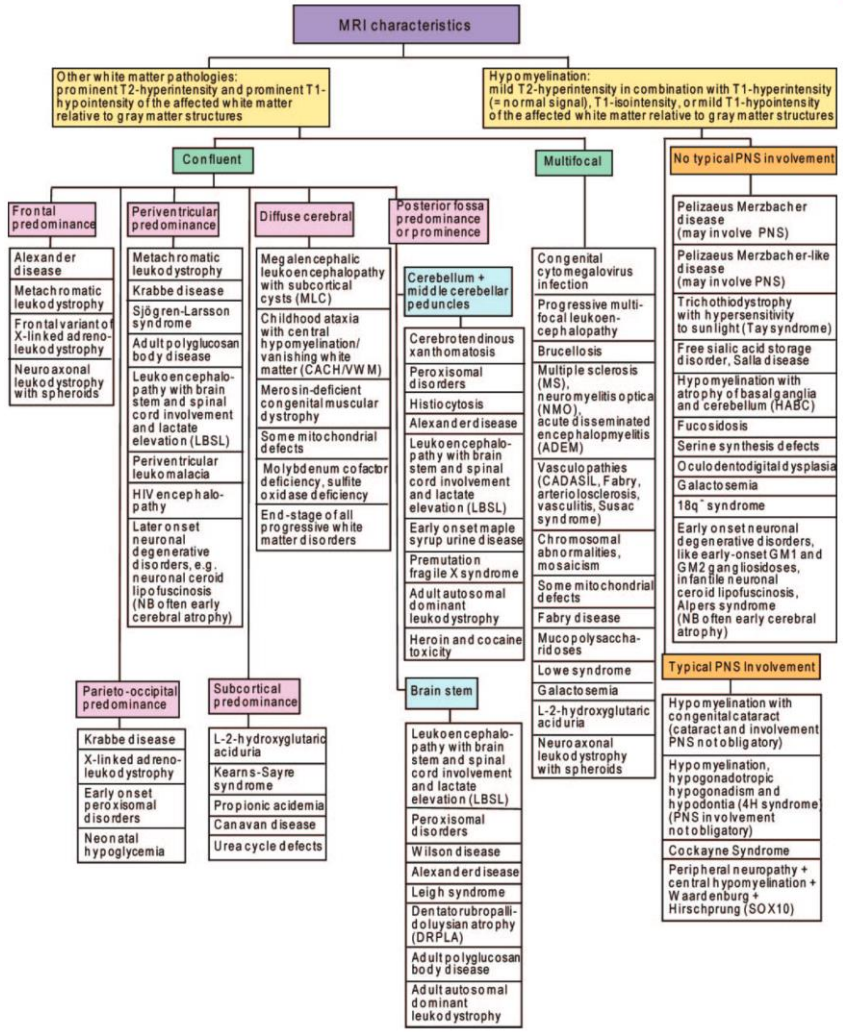
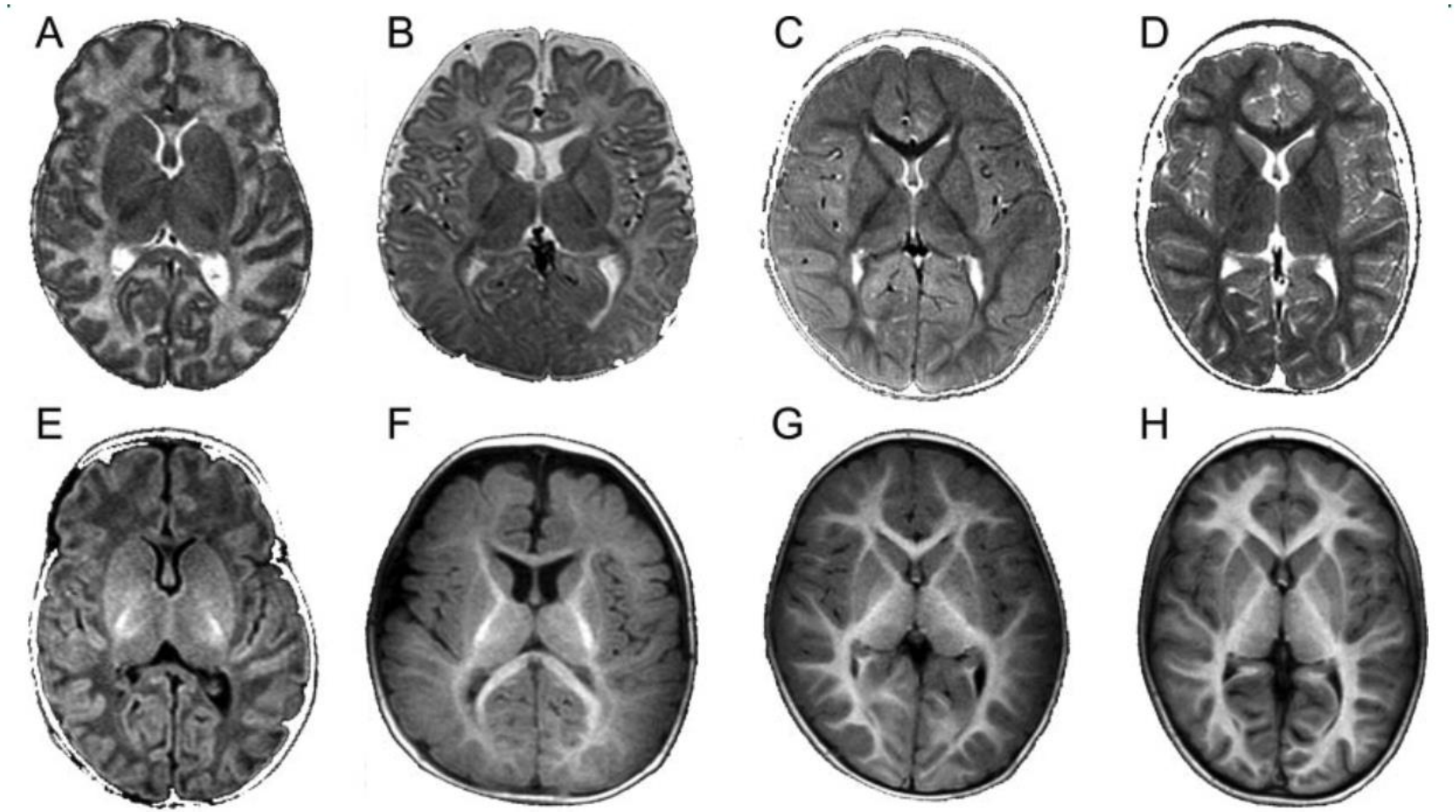
MRI pattern recognition in leukodystrophies



van der Knaap et al, Neurology, 2008

Myelination is not complete at birth



Birth | 6 months | 1 year | 5 years

van der Knaap et al, Neurology, 2008

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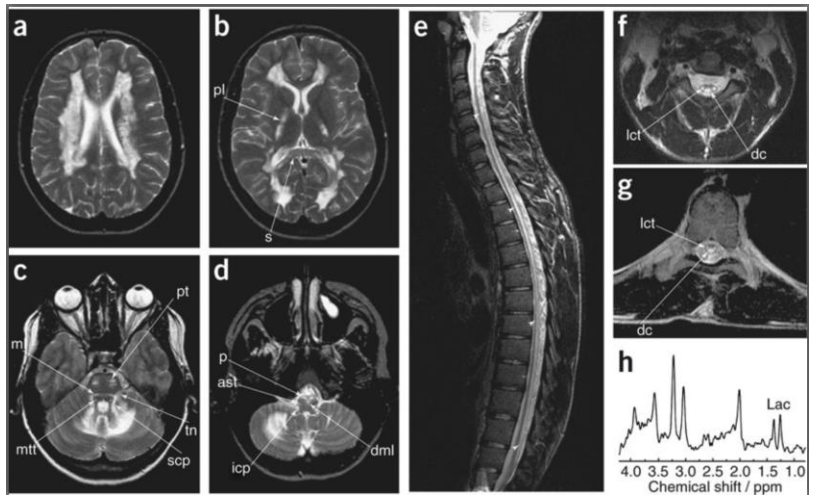
Trio whole exome sequencing: a game changer

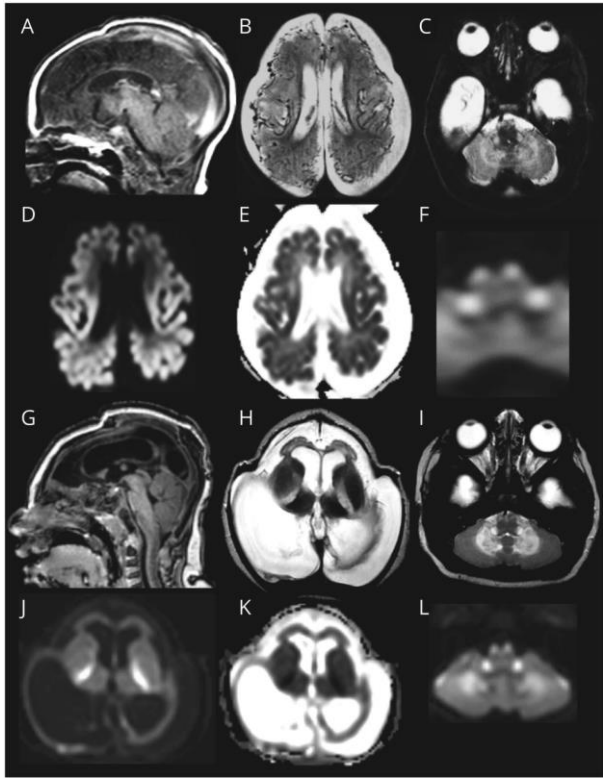
- For many leukodsytrophies a causative gene has been identified
- Open WES / panels make it possible to screen large numbers of genes in a short period of time
- Diagnosis rate has greatly increased (up to 85%)
- Still: accurate clinical and MRI description remains very important to interpret results (both in case genetic results are “negative” and “positive”)
- Phenotypes are expanding: mostly at the extreme ends of the spectrum

Helman et al, Ann clin Transl Neurol, 2020

A phenotypic spectrum for all leukodystrophies



"classic LBSL" 2003



"severe LBSL" 2021

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van der Knaap et al, Ann Neurol, 2003
Stellingwerff et al, Neurol Genet, 2021

Some leukodystrophies are treatable

Allogeneic hematopoietic cell transplant (HCT) is an option for some leukodystrophies

X-linked adrenoleukodystrophy (ALD): early stage disease (Loes score < 9)

Metachromatic leukodystrophy (MLD): some later onset forms and early stage disease

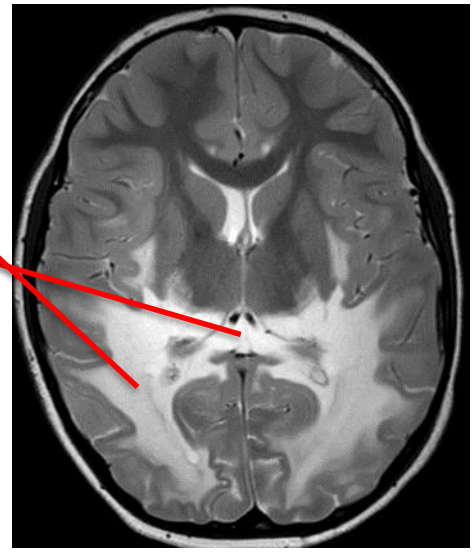
Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP): early stage disease

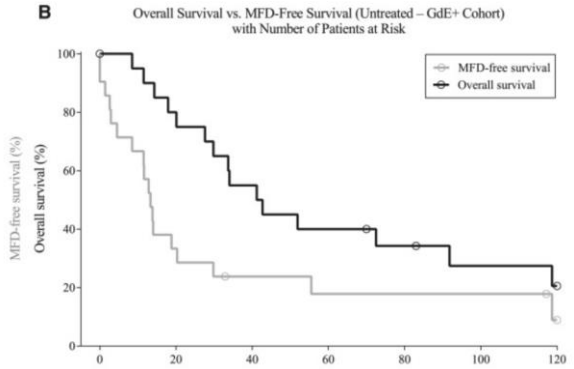
Example: the leukodystrophy of ALD

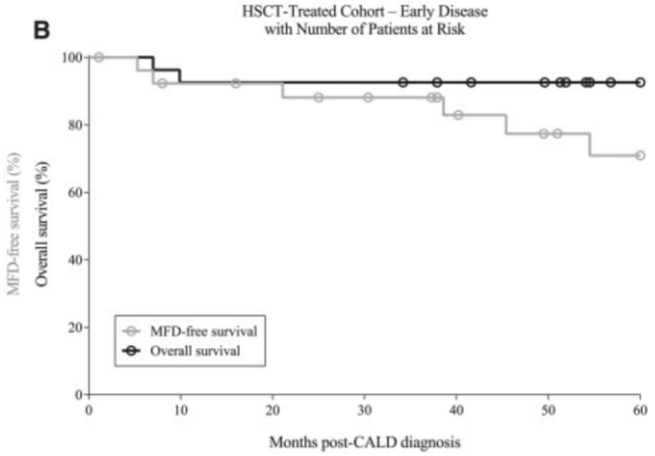
Table MRI Severity Scale

- Parieto-occipital WM (maximum 4)
- Anterior temporal WM (maximum 4)
- Frontal WM (maximum 4)
  - Periventricular
  - Central
  - Subcortical
  - Local atrophy
- Corpus callosum (maximum 5)
  - Splenium
  - Body
  - Genu
  - Splenium atrophy
  - Genu atrophy
- Visual pathway (maximum 4)
  - Optic radiations
  - Meyer's loop
  - Lateral geniculate body
  - Optic tract
- Auditory pathway (maximum 4)
  - Medial geniculate body
  - Brachium to inferior colliculus
  - Lateral lemniscus
  - Pons
- Projection fibers (maximum 2)
  - Internal capsule
  - Brainstem
- Cerebellum (maximum 2)
  - White matter
  - Atrophy
- Basal ganglia (maximum 1)
- Global atrophy (maximum 4)
  - Mild
  - Moderate
  - Severe
  - Brainstem

Loes score (0 – 34)







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Loes et al, AJNR, 1994

Raymond et al, Biol Blood Marrow Transplant, 2019

Emerging treatments

Lentiviral gene therapy for autologous transplant voor ALD (elivaldogene autotemcel) and MLD (atidarsagene autotemcel).

Several small compounds (like guanabenz for VWM, leriglitazone for ALD)

ASO (anti-sense oligonucleotide) therapy for Alexander disease

AAV-9 gene therapy for ALD, Krabbe disease, MLD

(Emerging) treatments mean considering newborn screening (NBS)

- NBS for ALD implemented in (parts of) the USA and the Netherlands
- Possibility for follow-up and optimal timing of treatment
- Opportunities for research: accurate knowledge of natural history and phenotypic spectrum

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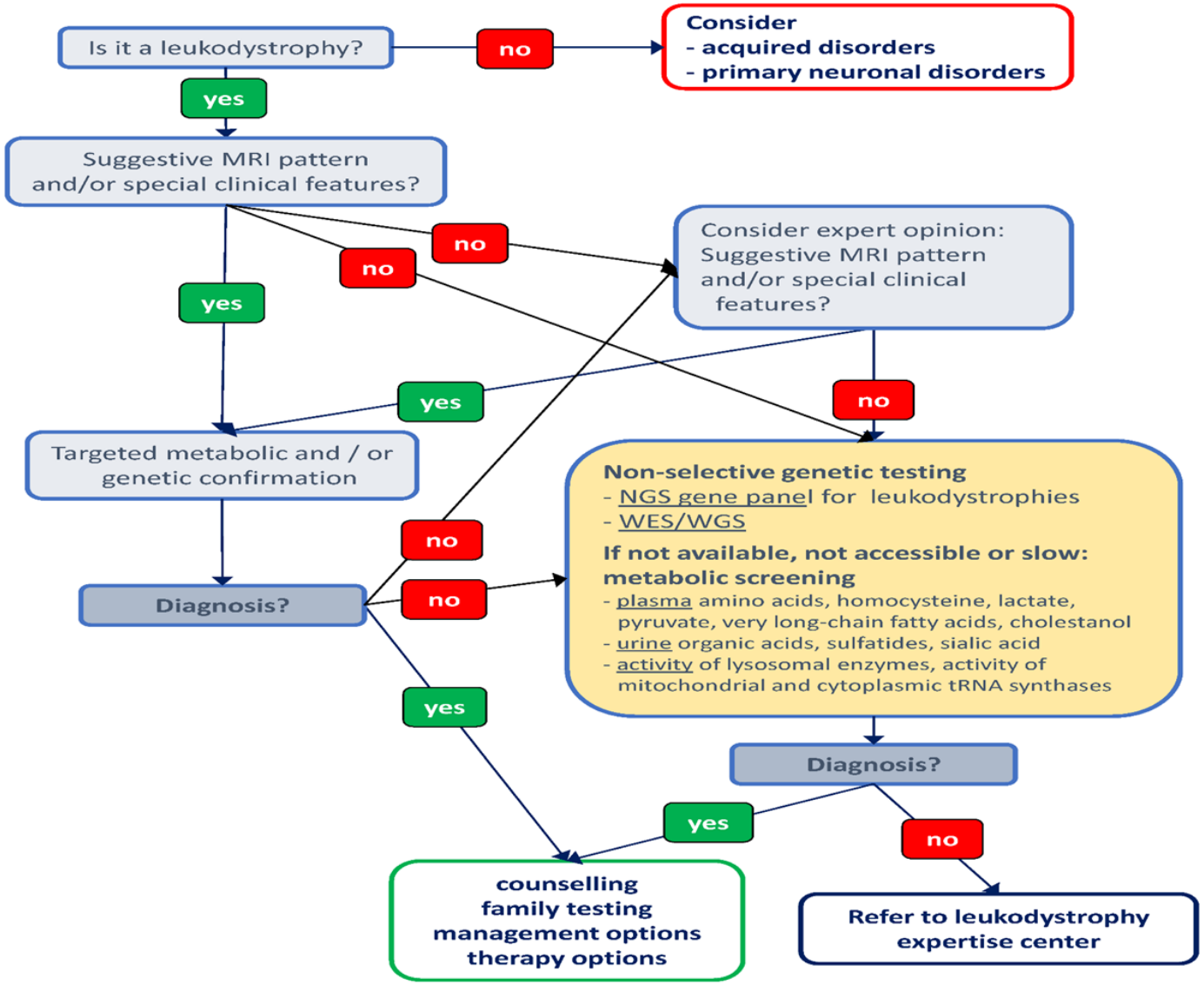
Barendsen et al, Front Cell Dev Biol, 2020

Approach to the patient with a suspected leukodystrophy



van der Knaap et al, Lancet Neurology, 2019

Now some classic MRI patterns

- Use the algorythm to describe the pattern
- Describe additional features

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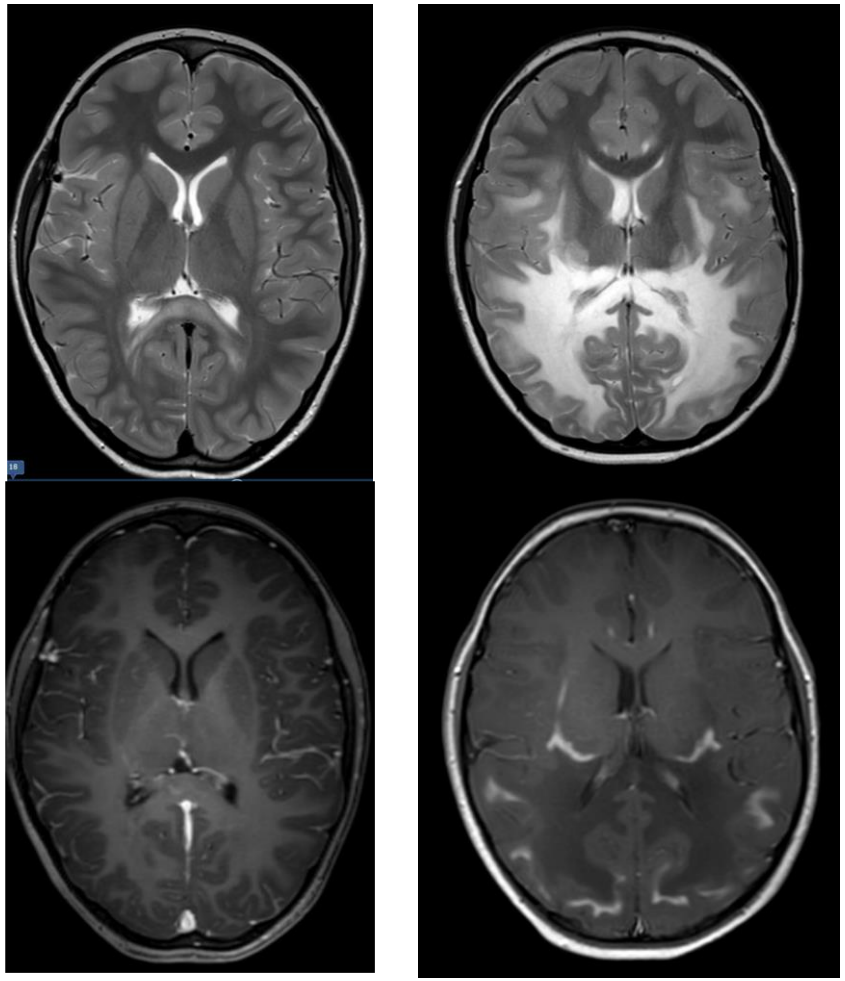
Pattern 1

Early disease

Late disease



Confluent, symmetrical,
parieto-occipital predominance

Gd+ beyond the leading edge of the lesion

ALD

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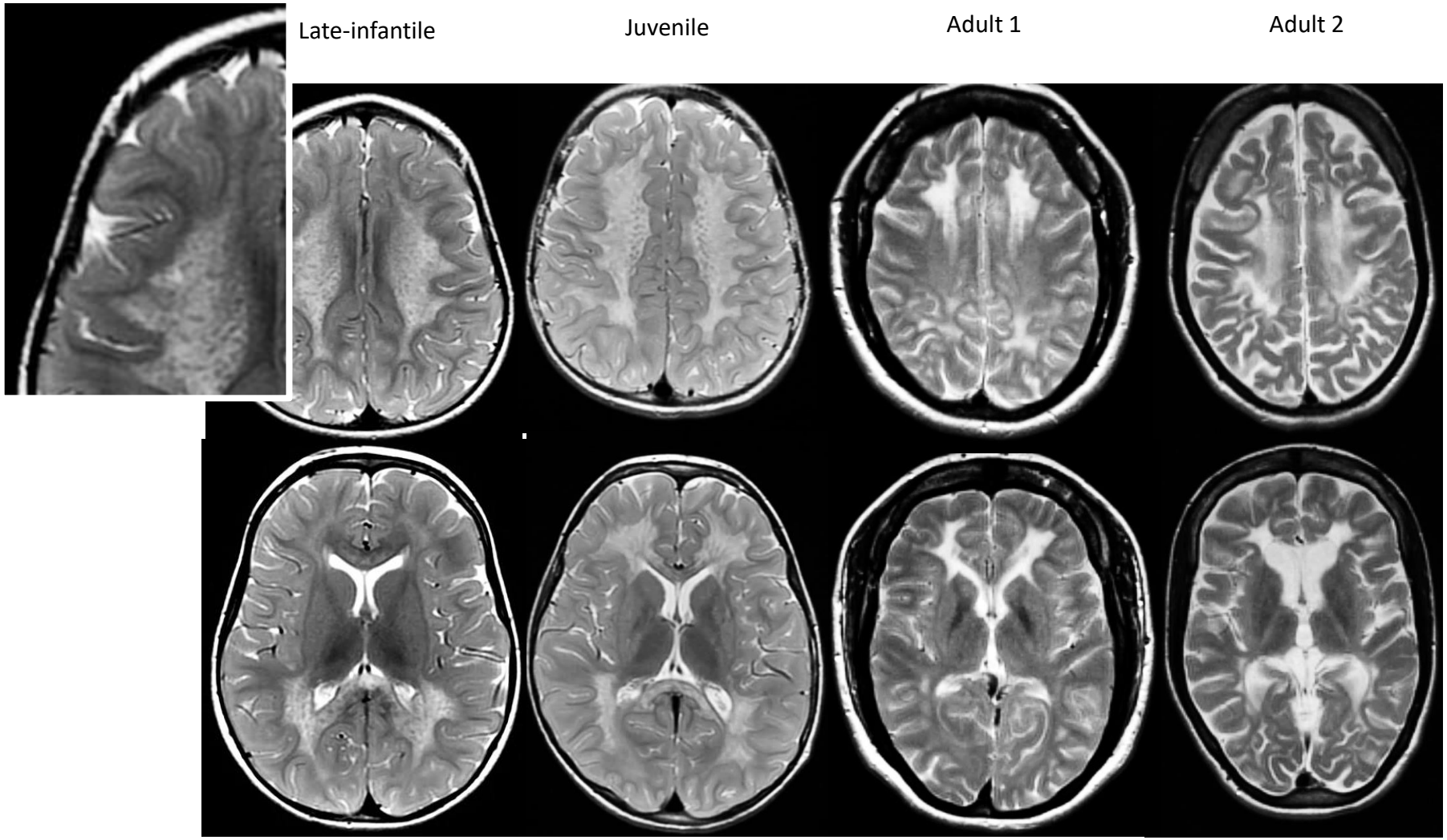
Pattern 2



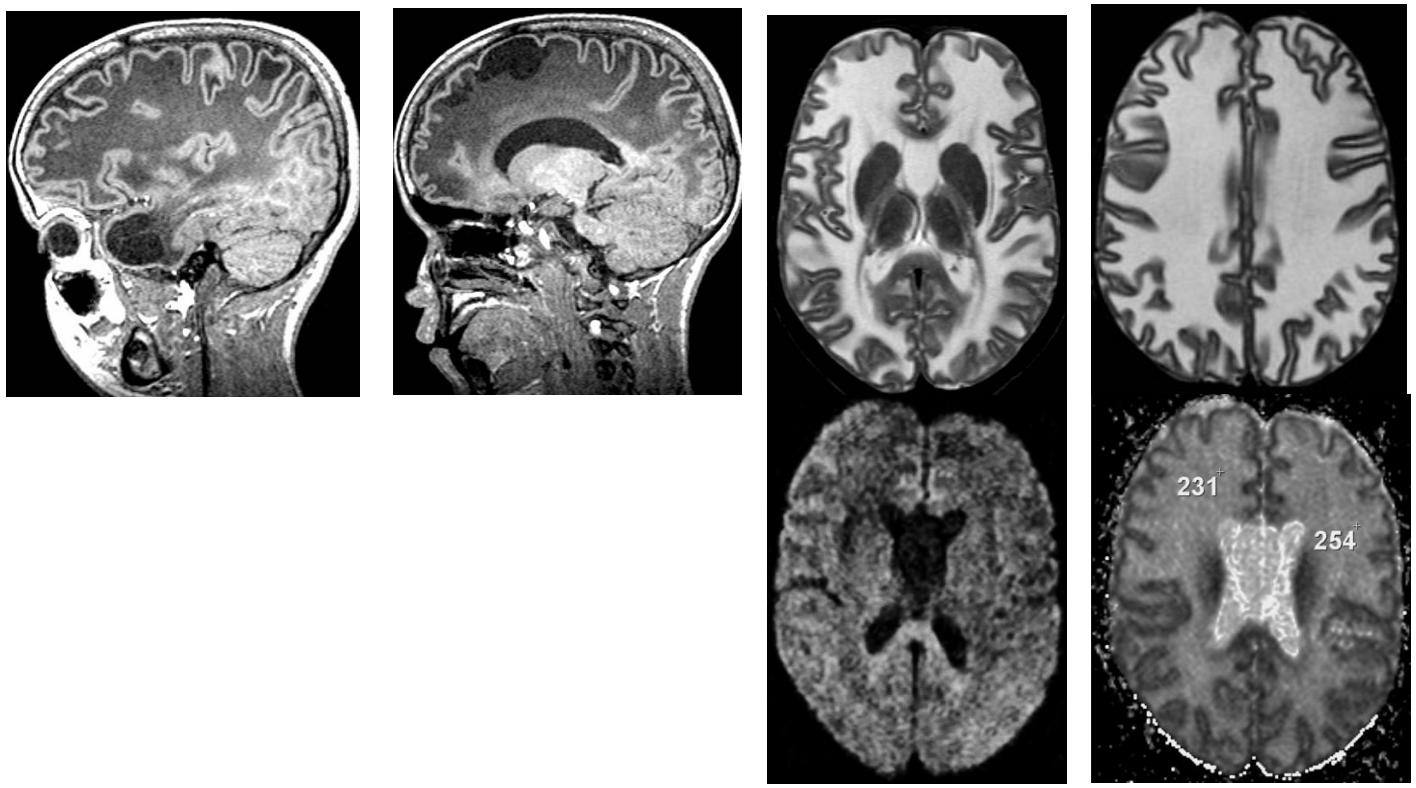
Confluent, symmetrical periventricular predominance

Leopard skin sign/tigroid pattern

MLD

Courtesy of Prof. N. Wolf

Pattern 3



Confluent, symmetrical, diffuse cerebral

Subcortical cysts

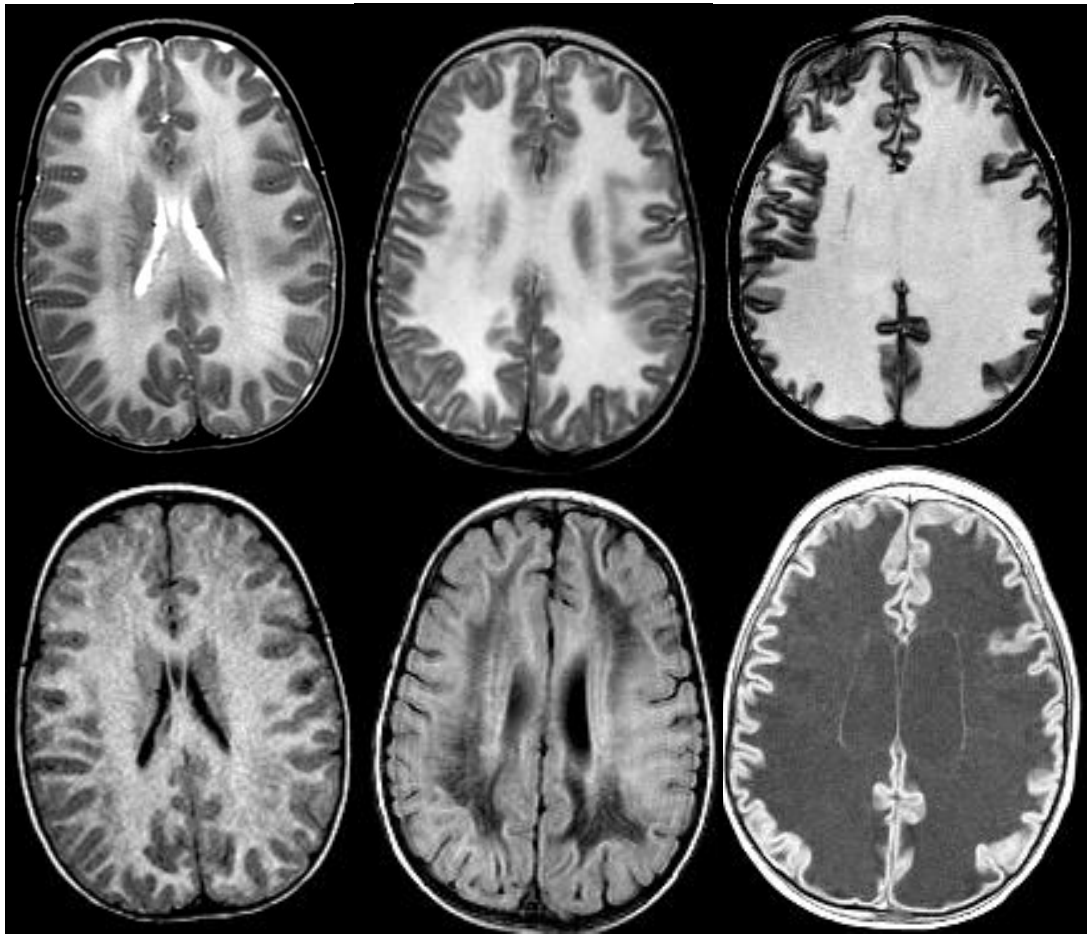
qMRI indicate increased white matter water content and large water spaces

MLC

Courtesy of Prof. v.d. Knaap

Pattern 4

early stage → end stage



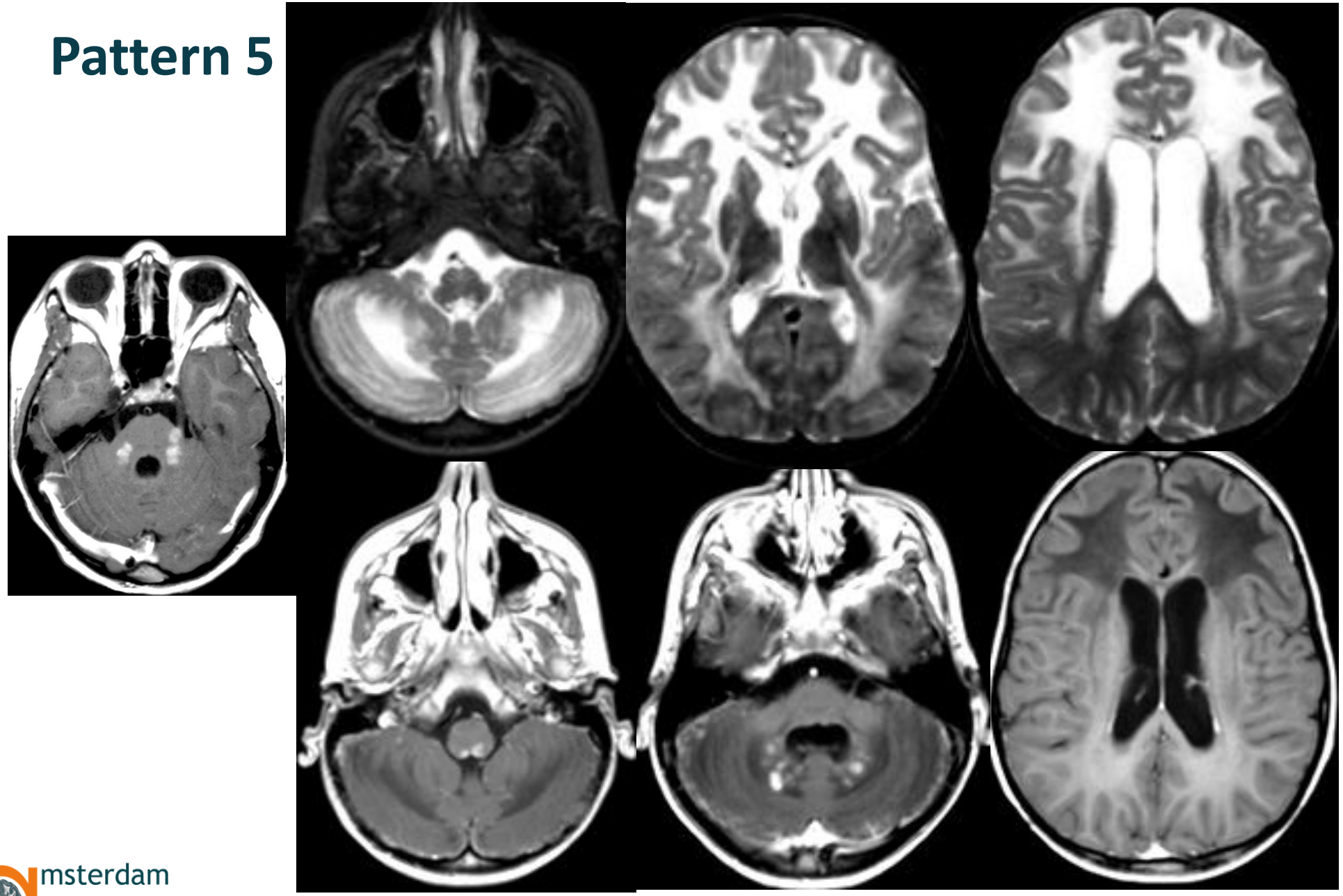
Confluent, symmetrical
Diffuse cerebral

Rarefaction of the white matter

VWM

Courtesy of Prof. v.d. Knaap

Pattern 5



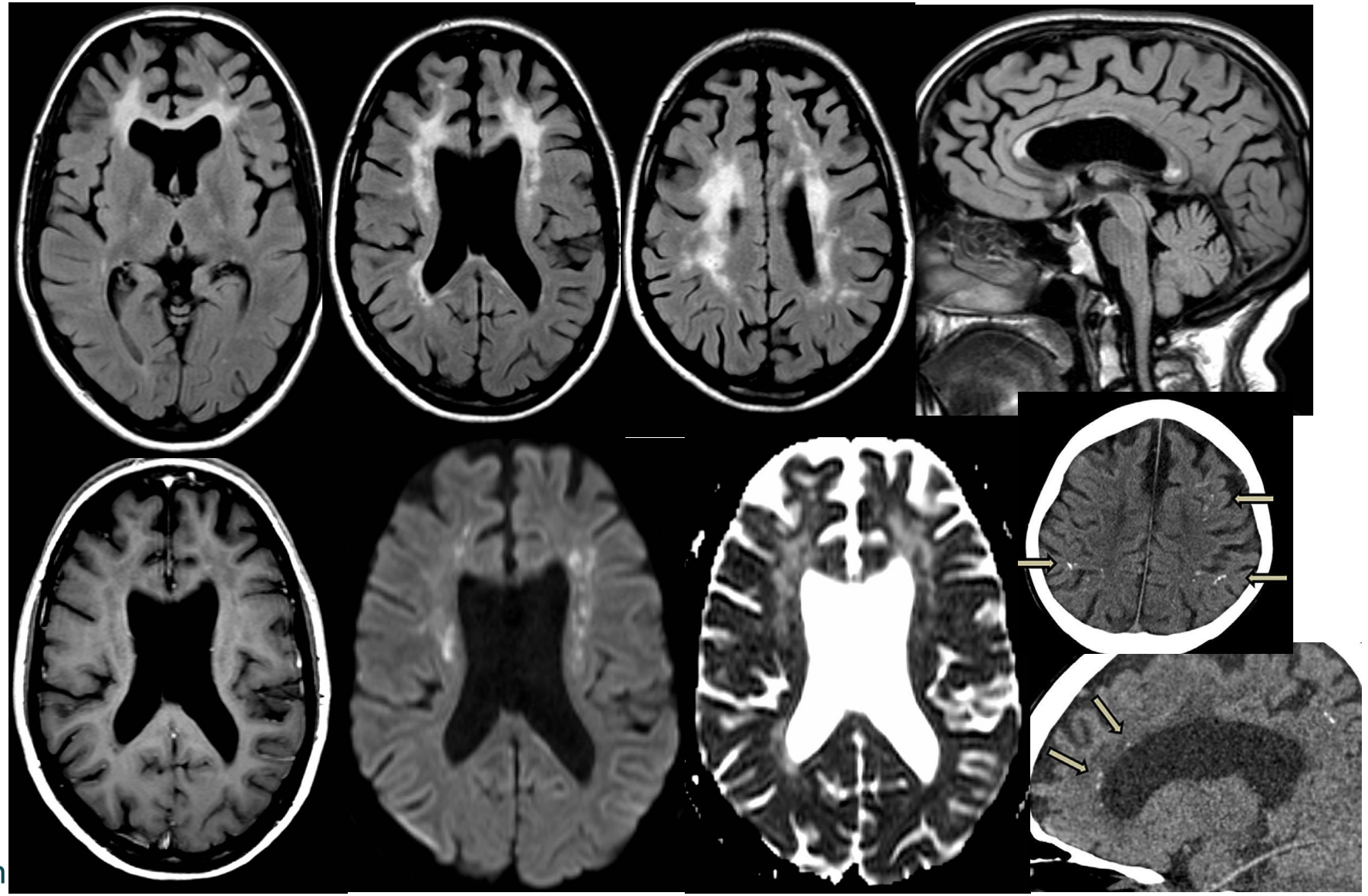
Confluent, symmetrical
Frontal and posterior fossa predominance

Gd+

Alexander disease

Courtesy of Prof. v.d. Knaap

Pattern 6



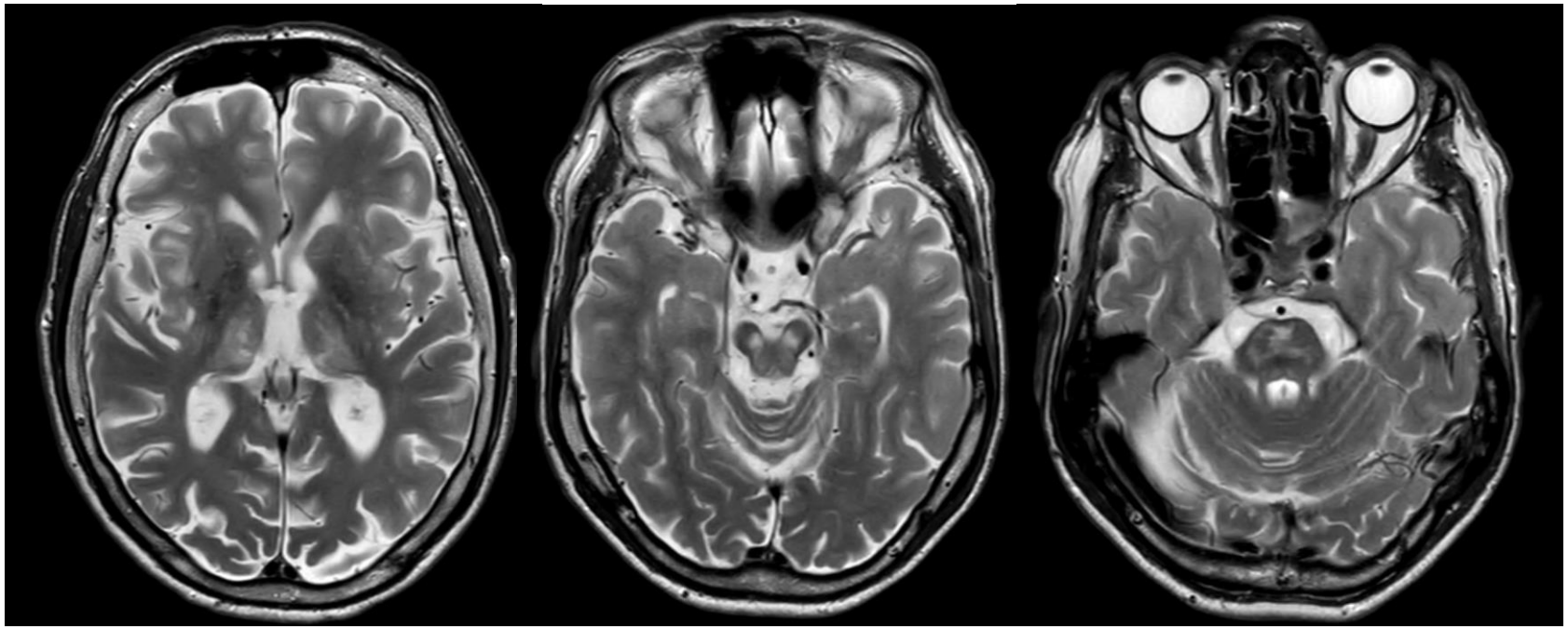
Patchy, multifocal, asymmetric

Calcifications

ALSP

Courtesy of Prof. v.d. Knaap

Pattern 7



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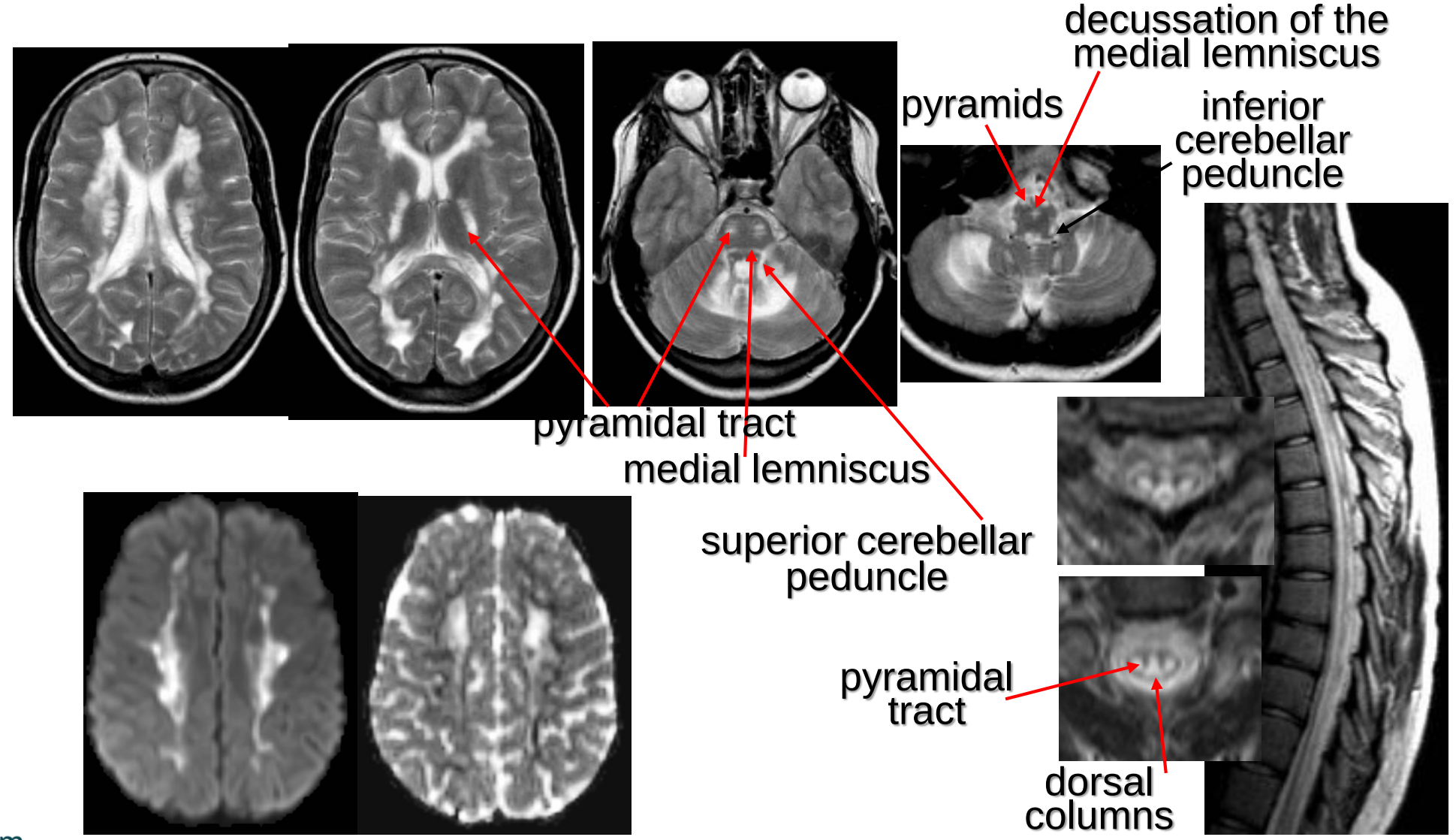
Pattern 8



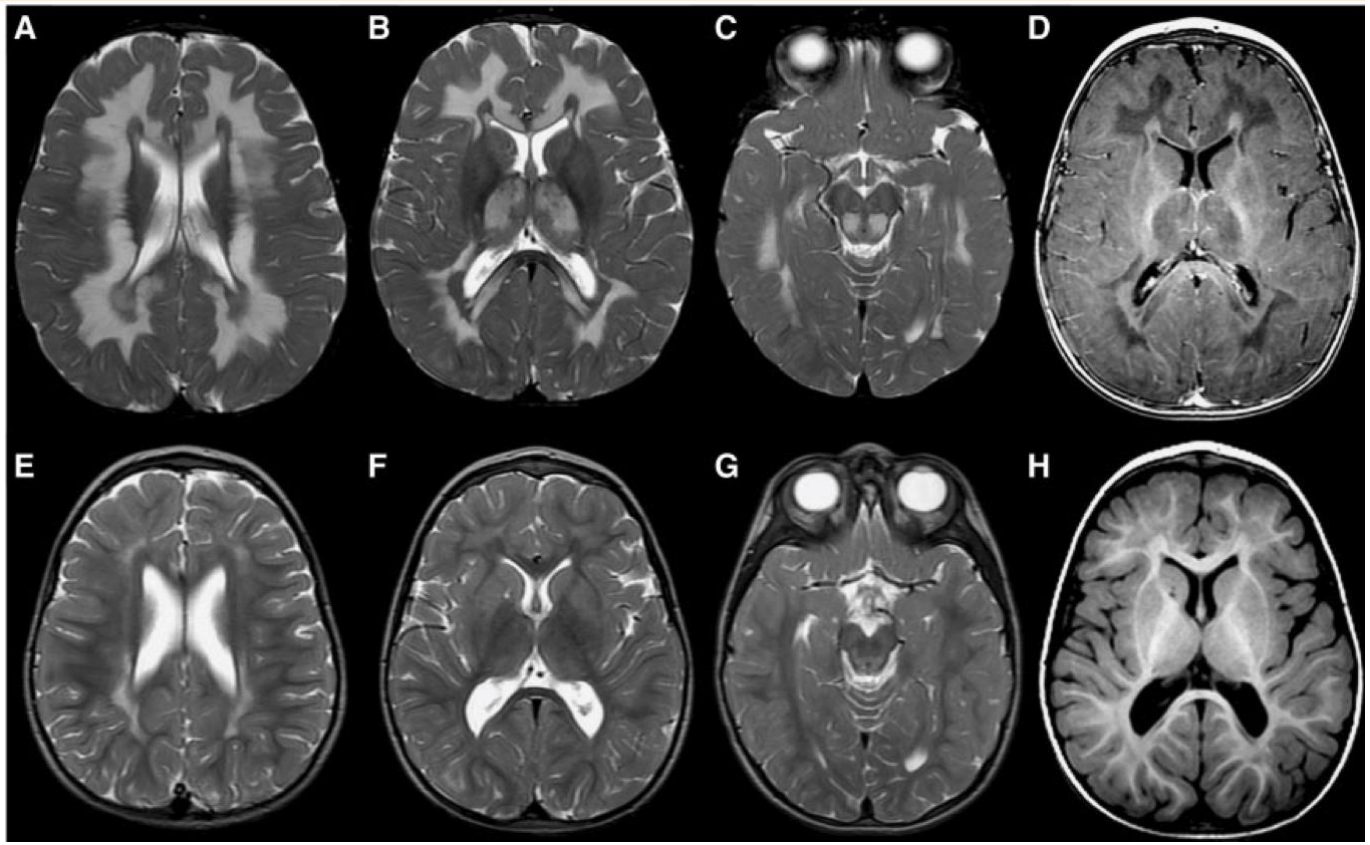
LBSL (*DARS2*)

van der Knaap et al, Ann Neurol, 2003

Pattern 9

11 months

3 years



LTBL
(*EARS2*)

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Current research and challenges for the future

- Newborn screening for ALD, MLD, Krabbe
- Many emerging treatments
- Clinical trials remain very challenging
  - Current clinimetric tools have many limitations
  - Especially problematic in rare diseases
- Better clinical trials (less patients, shorter follow-up) would greatly accelerate therapy development

Guidelines are emerging: but also highlight many knowledge gaps

CONTEMPORARY ISSUES IN PRACTICE, EDUCATION, & RESEARCH OPEN ACCESS

International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy

A Consensus-Based Approach

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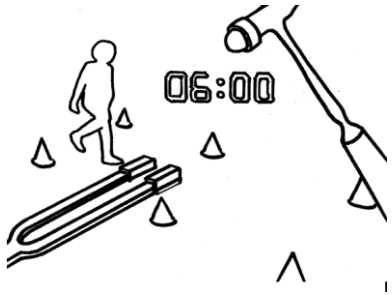
Example: clinical trials in ALD

- Determining the presence of spinal cord disease is easy
- Quantifying disease severity is not
- Current outcome measures are not specific and not sensitive to small change, have “floor- and ceiling effect”

- Example: 6 minute walk test (226 patients per group for a trial with a duration of 1 year to detect a change of 50% in progression of spinal cord disease)



Huffnagel et al, Brain, 2019

New outcome measures are needed

- Directly measure the underlying pathology
- Are sensitive to small changes in severity of spinal cord disease
- No “floor” and “ceiling” effect: more patients eligible (men in wheelchair and women)

- Predictors to stratify patients (risk of cerebral ALD, rate of progression) also needed

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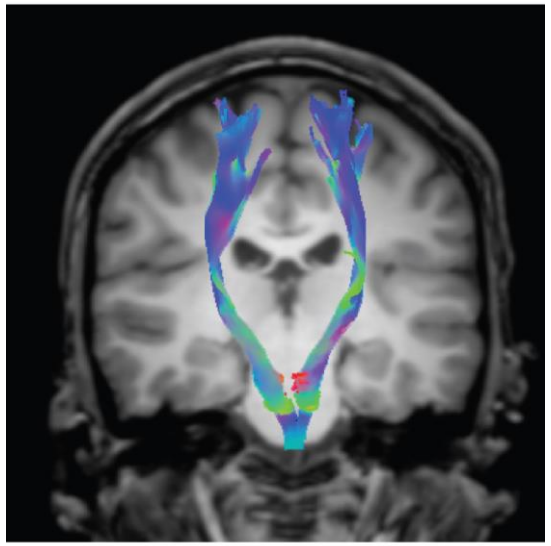
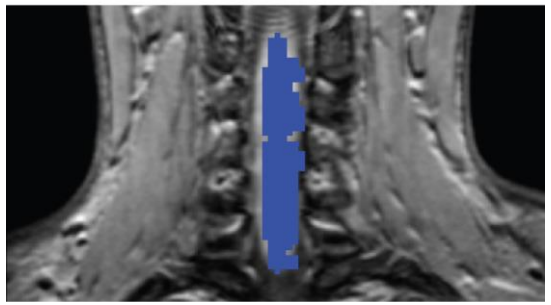
Towards objective outcome measures and predictors

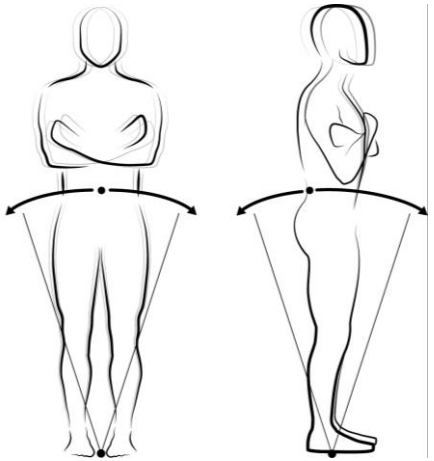
qMRI
(like DTI and CSA)



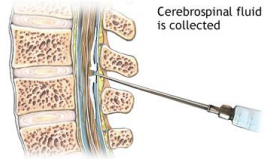


Optical coherence tomography

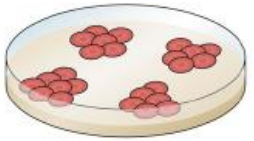
Sway and dynamometry



Plasma, CSF



iPSC derived neuronal cells



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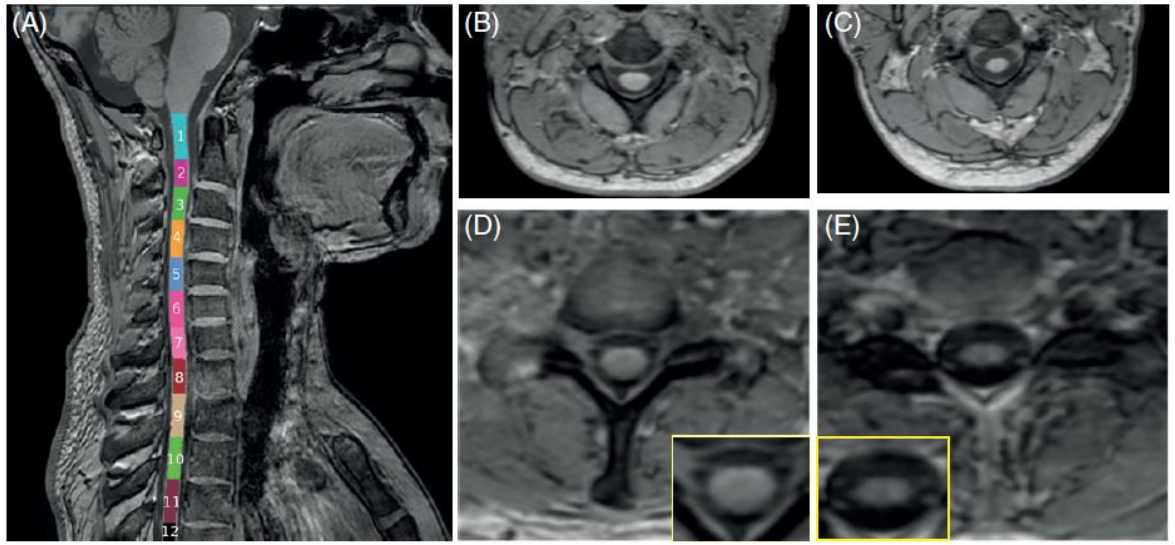
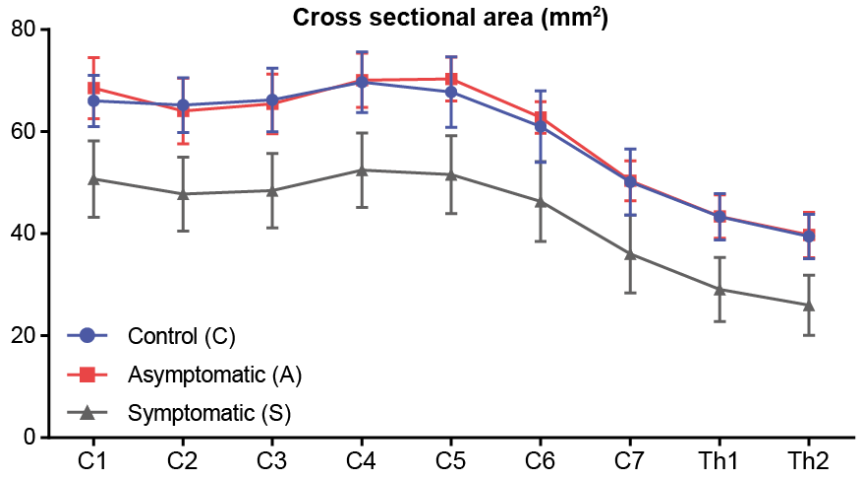
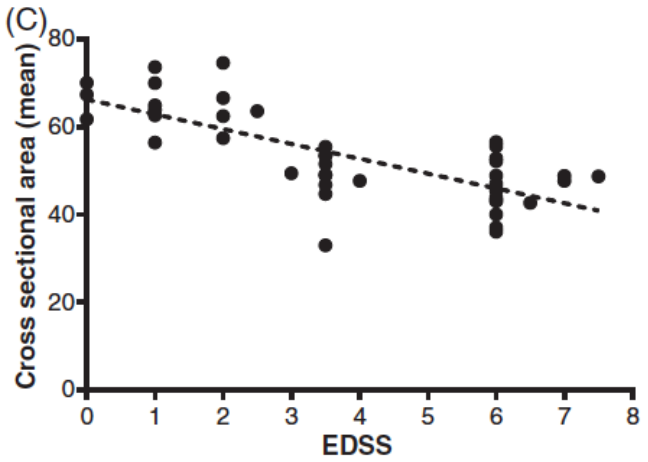
qMRI: cross sectional area of spinal cord







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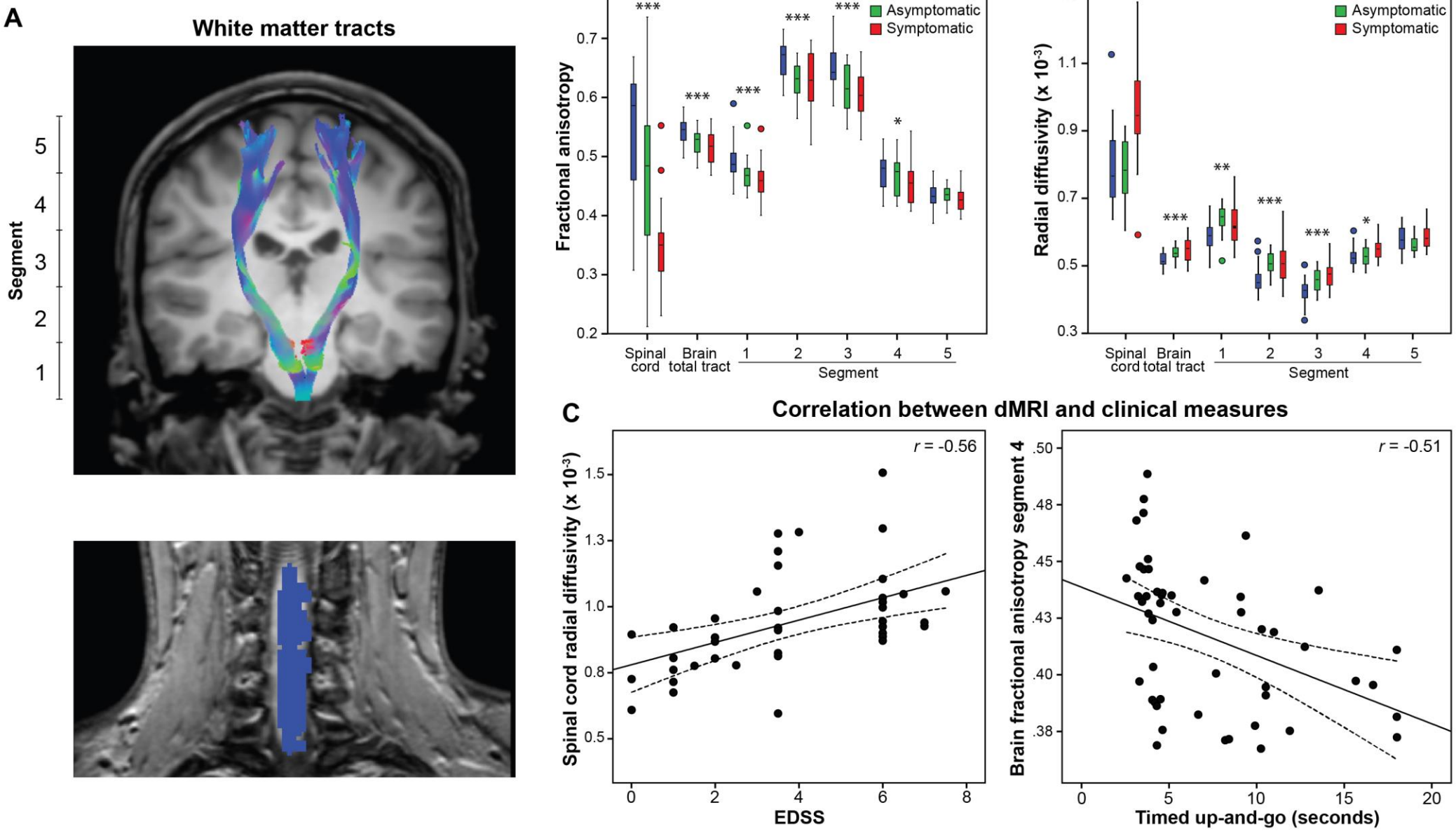
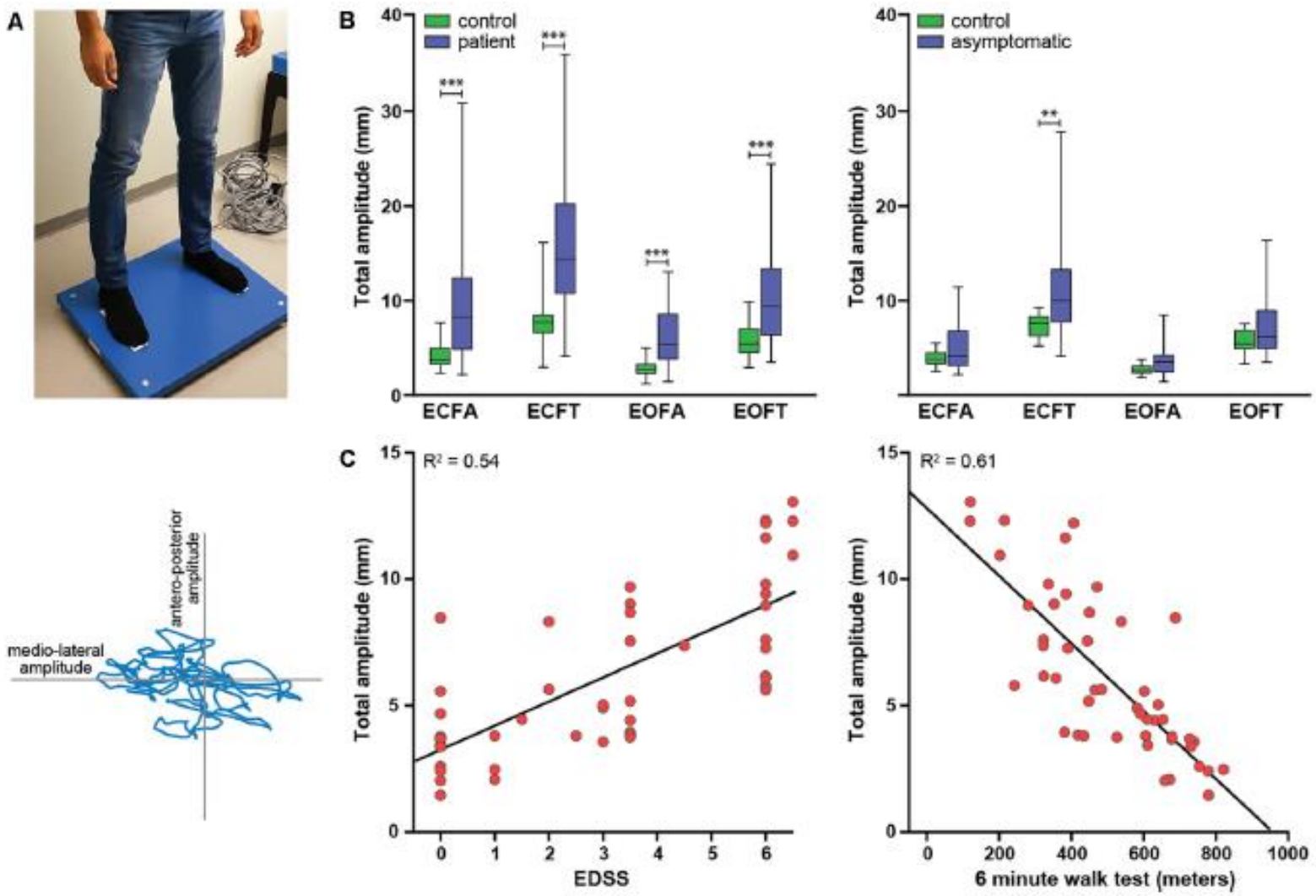
Dubey et al, 2005
Castellano et al, 2016
Huffnagel et al, Neurology, 2019
Van der Stadt, JIMD, 2020

qMRI: DTI of motor tracts in brain and spinal cord area

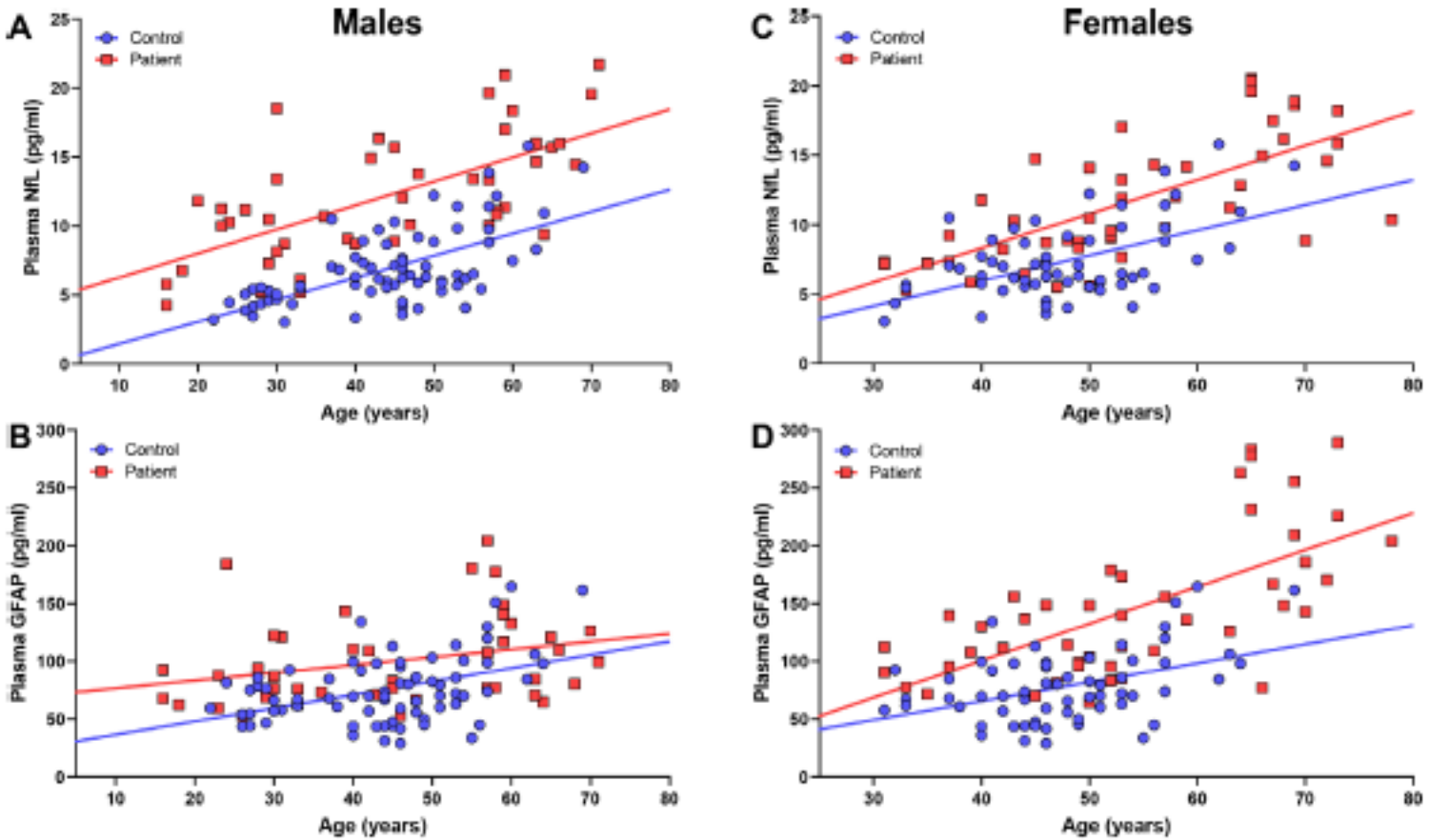


Force plate analysis / body sway



van Ballegoij et al, Frontiers Physiol, 2021

Neurofilament light and GFAP



Males	Patient (n=45)	Control (n=74)	p-value	Effect size
Age, years	44.0 ± 16.7	44.1 ± 10.8	0.978	
NfL, pg/ml	11.2 (9.0-15.7)	6.2 (5.2-8.4)	<0.001	0.49
GFAP, pg/ml	87.0 (71.0-120.7)	70.1 (55.6-93.1)	<0.001	0.13

Females	Patient (n=47)	Control (n=61)	p-value	Effect size
Age, years	54.0 ± 12.4	47.7 ± 8.1	0.002	
NfL, pg/ml	10.4 (8.2-14.7)	6.5 (5.6-8.9)	<0.001	0.19
GFAP, pg/ml	136.0 (95.3-173.4)	71.9 (57.4-98.2)	<0.001	0.27

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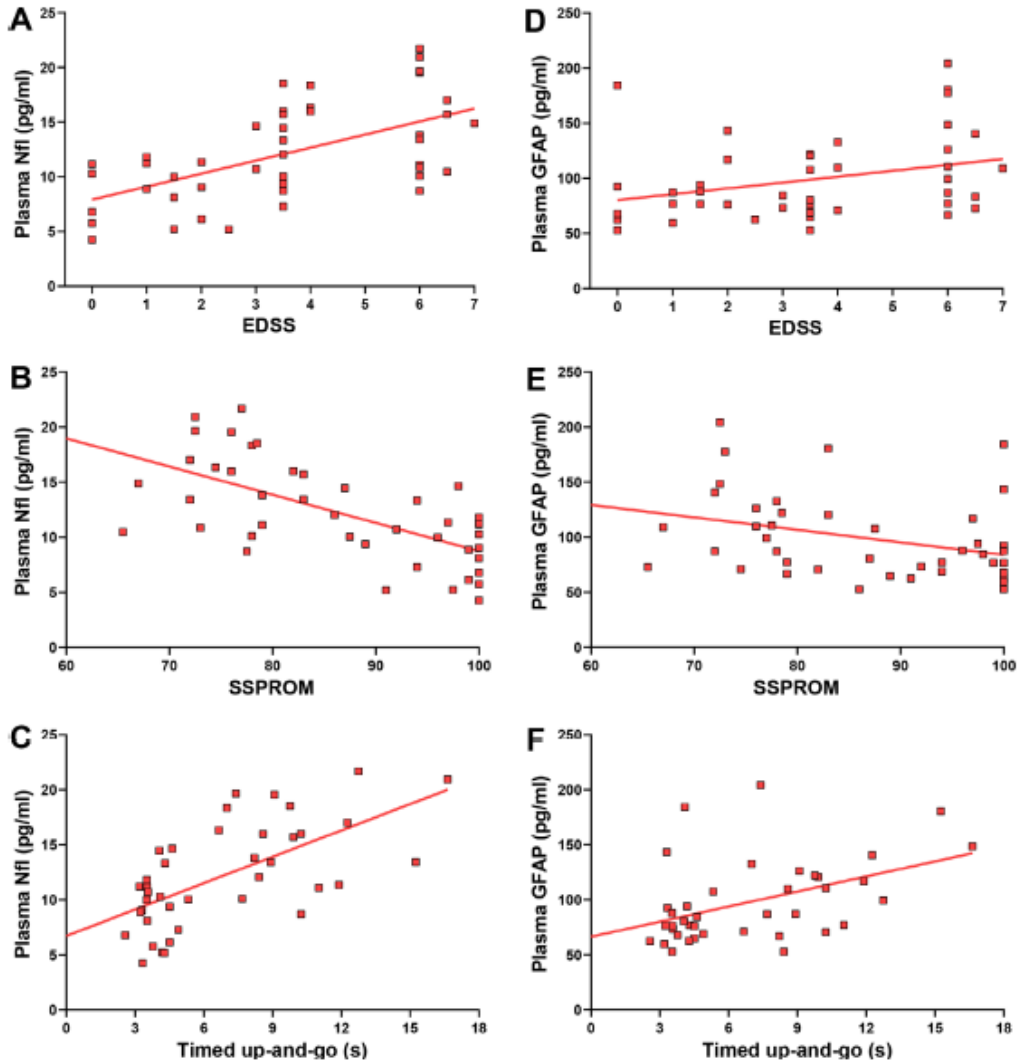
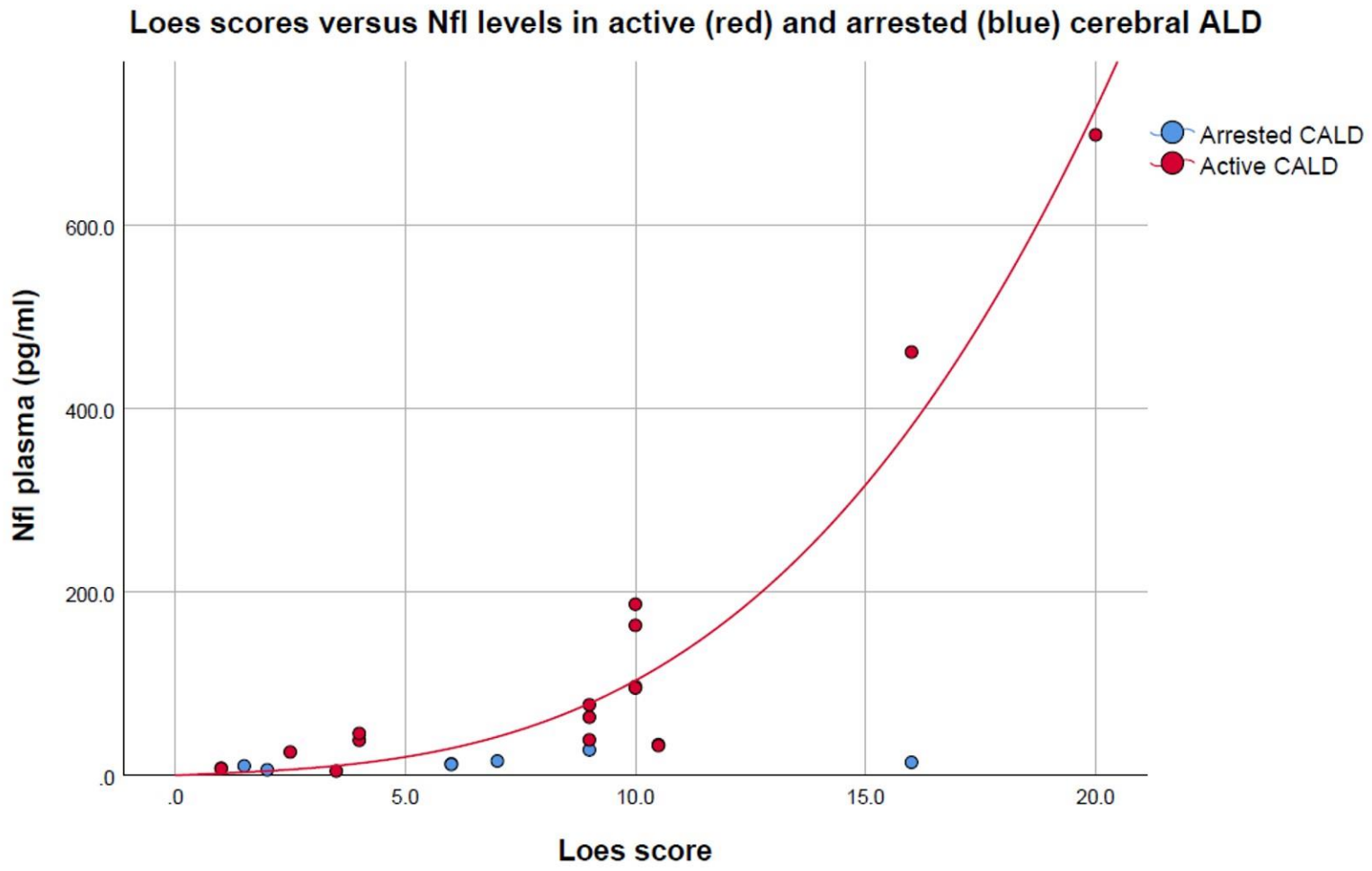
van Ballegoij et al, ACTN, 2021

Neurofilament light and GFAP



van Ballegoij et al, ACTN, 2021

Neurofilament light and GFAP



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Unpublished data

Summary

- Clinical features in combination with MRI pattern recognition allowed the description of clinico-radiological syndromes
- WES improves rate of diagnosis and futher delineation of the disease spectrum
- Standard MRI protocols (T1, T2, FLAIR, DWI) are adequate for diagnosis and follow-up in clinical practice
- Emerging treatments means better outcome measures for clinical trials are needed, qMRI techniques are being developed to use as surrogate outcome measures

Exit questions – Q1

Which statement regarding leukodystrophies is true:

a. Leukodystrophies are caused by primarily dysfunction of oligodendrocytes and the structure of myelin

b. Are always progressive disorders

c. Can be caused by disorders of astrocytes or microglia primarily

d. None of the above

Exit questions – Q2

Myelination of the brain is completed approximately at

a. Birth

b. 12 months

c. 24 months

d. Don’t know

Exit questions – Q3

The rate of diagnosis of leukodystrophies (in children) improved tremendously due to MRI pattern recognition and whole exome sequencing. On average the rate of diagnosis currently:

a. 25%

b. 50%

c. 85%

d. Don’t know

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