European Reference Network
for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

european academy of neurology

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Network Neuromuscular Diseases (ERN EURO-NMD)

Webinar

‘Measuring disease severity in chronic progressive myelopathy’

by Marc Engelen

Amsterdam University medical Center, the Netherlands

15. March 2022

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Learning objectives

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

- **describe the natural history of the myelopathy of X-ALD**
- **discuss the most common clinimetric tools used for chronic progressive myelopathy**
- **know about ongoing research to improve clinimeteric tools and outcome measures for clinical trials**

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Webinar outline

- **Introduction on X-linked adrenoleukodystrophy (ALD)**
- **Natural history of ALD**
- **Current clinimetric tools**
- **Developing new clinimetric tools**

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Key conclusions

Current clinimetric tools to quantift severity and progression of myelopathy have important limitations

Clinical trials in X-ALD (and similar disorders) are difficult because of slow disease progression

New outcome measures are needed and are in development

From Schilder’s disease to adrenoleukodystrophy

Aus dem pathol.-anatom. Universitätsinstitute (Vorstand: Hofr. Prof. Weichselbaum) und dem Karolinen-Kinderspitale (dirig. Primararzt: Doz. Dr. Knöpfelmacher) in Wien.

Zur diffusen Hirn-Rückenmarksklerose im Kindesalter.

Von

Dr. Walther Haberfeld und **Dr. Fritz Spieler.**

(Mit 3 Abbildungen.)

Die Encephalitis periaxialis diffusa

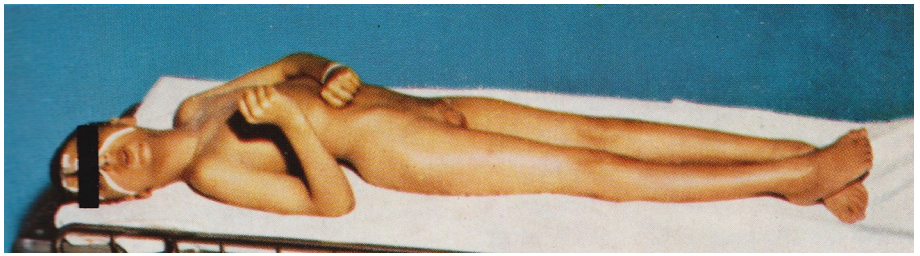
(nebst Bemerkungen über die Apraxie des Lidschlusses).

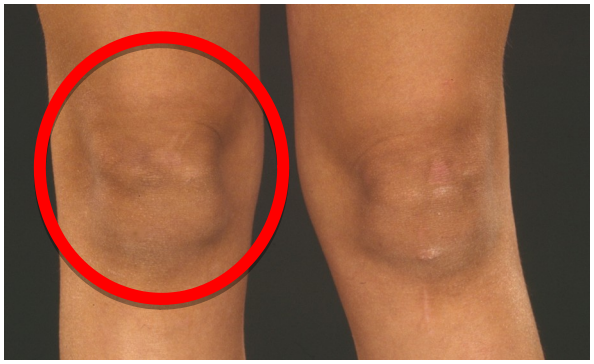
Von

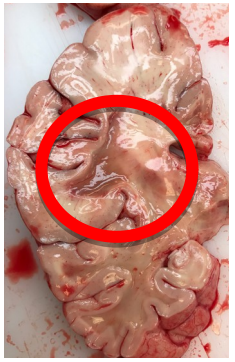
Paul Schilder.

Mit 11 Textabbildungen.

(Eingegangen am 19. März 1924.)





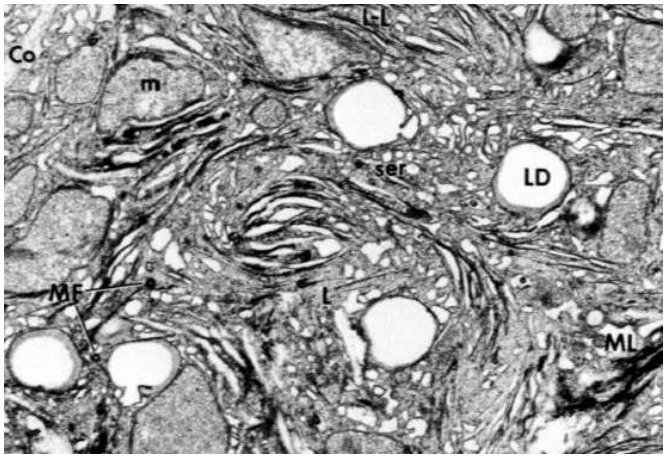


Haberfeld et al, 1910

Schilder, 1924

Blaw, 1972

To a metabolic disorder with a much wider clinical spectrum



1972: inclusions in adrenal glands

1976: accumulation of VLCFA

A plasma biomarker for diagnosis was established!

Adrenomyeloneuropathy:
A probable variant of adrenoleukodystrophy

II. General pathologic, neuropathologic, and biochemical aspects

HERBERT H. SCHAUMBURG, M.D., JAMES M. POWERS, M.D., CEDRIC S. RAINE, Ph.D., PETER S. SPENCER, Ph.D., JOHN W. GRIFFIN, M.D., JOHN W. PRINEAS, M.D., and DIETHELM M. BOEHME, M.D.

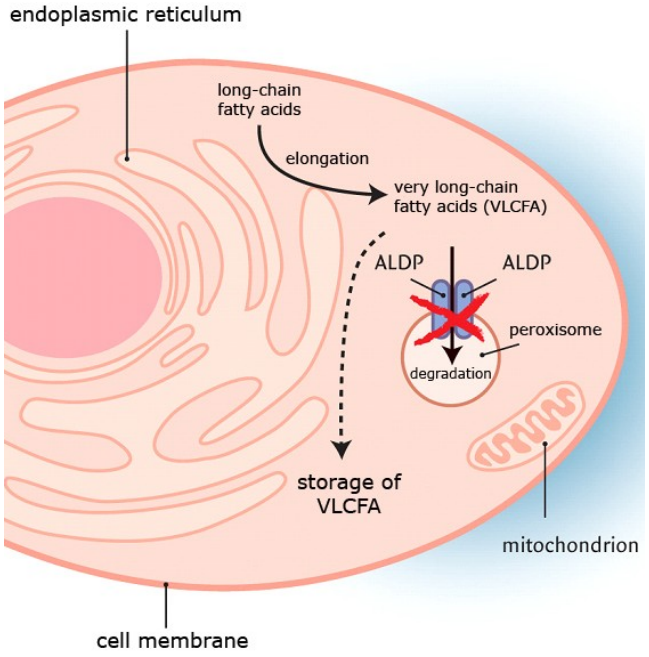
Spastic Paraplegia Associated with Addison's Disease: Adult Variant of Adreno-Leukodystrophy

H. Budka, E. Sluga, and W.-D. Heiss
Neurological Institute and Neurological Clinic, University of Vienna

Received May 13, 1976

Budka et al, J Neurol, 1976
Schaumburg et al, Neurology, 1977
Moser et al, Neurology, 1981
Schaumburg et al, 1972
Igarashi et al, 1976

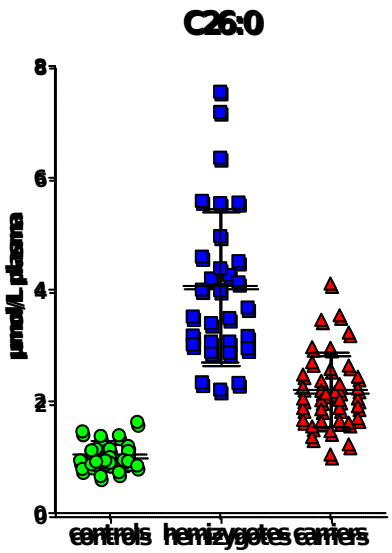
Biochemistry and genetics

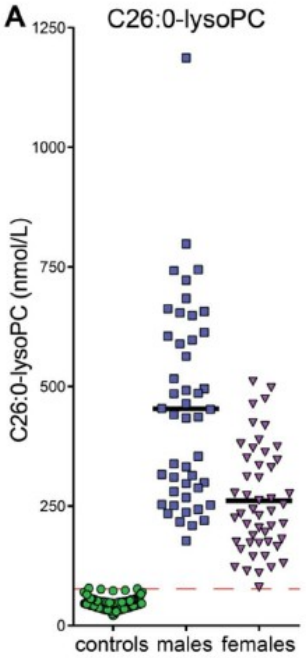


- Peroxisomal metabolic disease
- Mutation in *ABCD1* gene (X-linked)
- Accumulation of C26:0
- >10.000 patients in Europe

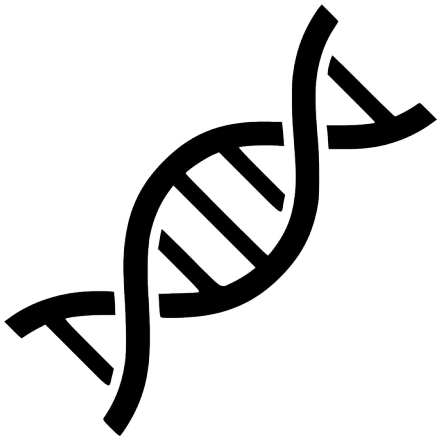
Kemp et al, Nature Reviews Endo, 2016

Diagnosis



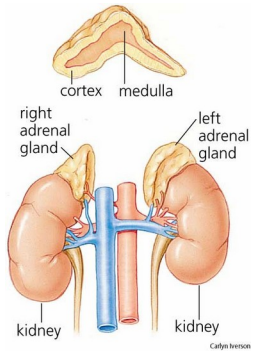


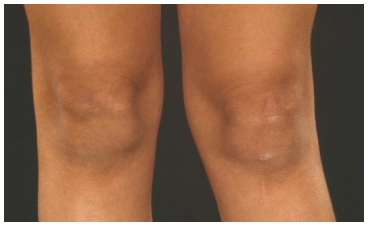
ABCD1 mutation analysis

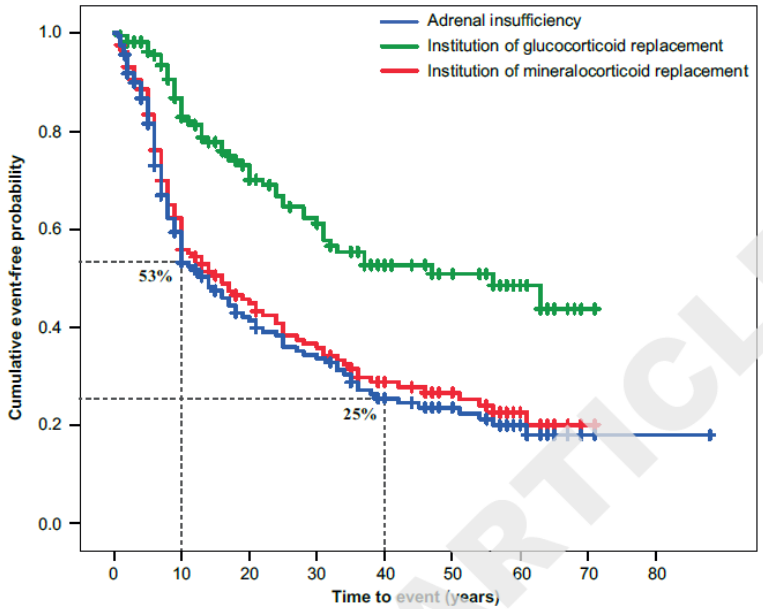


Kemp et al, Nature Reviews Endo, 2016
Huffnagel et al, Mol Genet Metab, 2017

Clinical features: adrenal failure





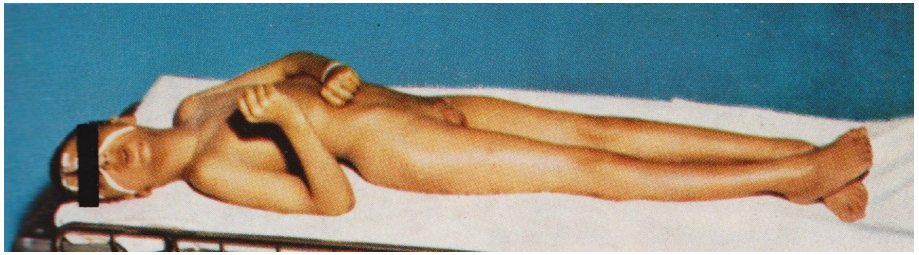


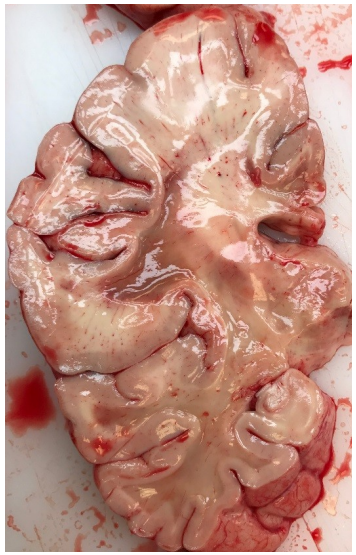
Huffnagel et al, JCEM, 2019

Clinical features: cerebral ALD

- rapidly progressive leukodystrophy – months to years
- occurs after 3 years of age, peak before 10 years, lifetime prevalence 60%
- onset unpredicatable!

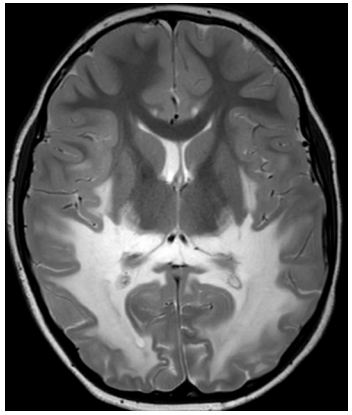
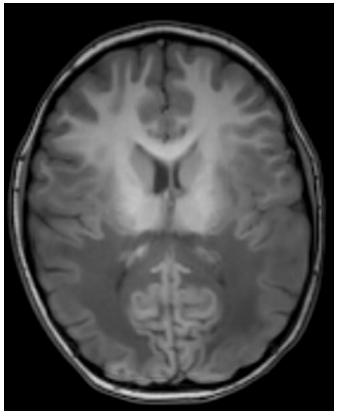
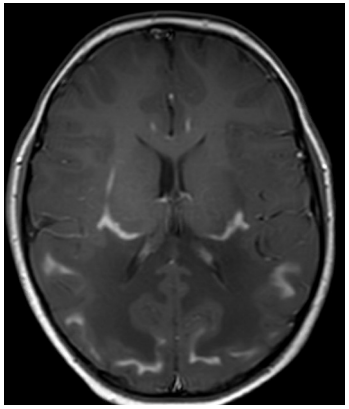
- neuropsychological and psychiatric deficits
- focal neurological deficits
- seizures
- untreated usually progressive





Engelen et al, OJRD, 2012
Powers et al, Clin Neuropathol, 1985

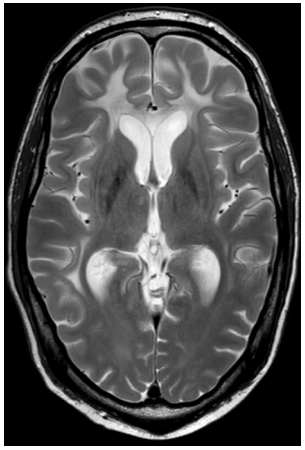
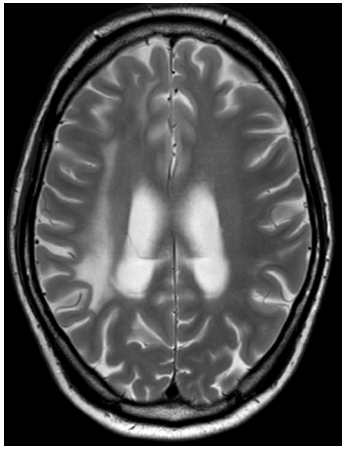
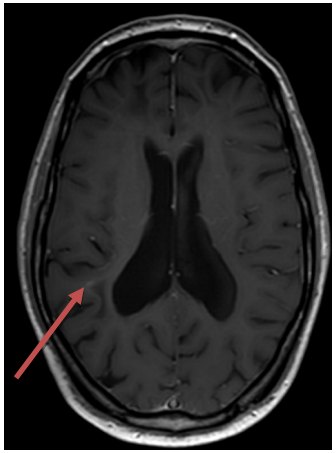
Clinical features

80% start in splenium and extends into occipital, parietal and frontal white matter

gadolinium enhancement in the lesion (just beyond the leading edge)

Clinical features

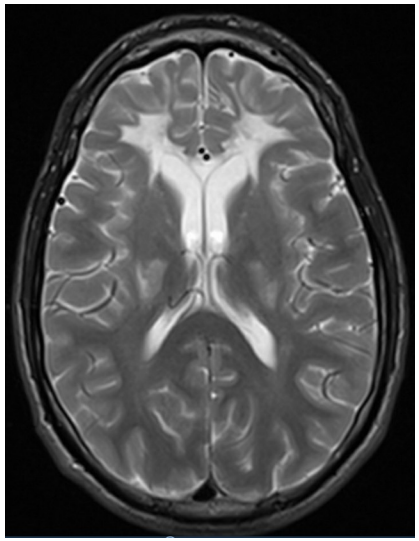




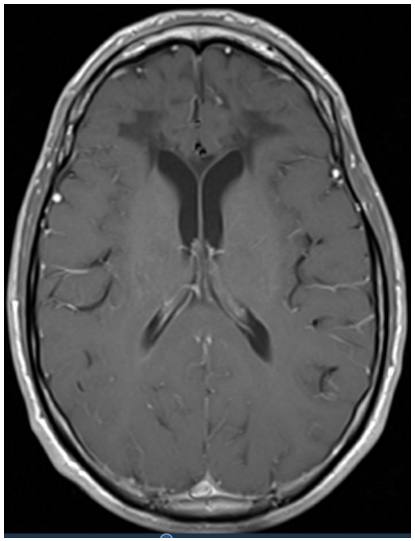
20% start in genu and extend into frontal white matter

Enhancement can be subtle (wait 5 – 10 min after contrast administration!)

Rarely in posterior fossa initially

Clinical features





Lesions can arrest spontaneously, but sometimes also “re-activate” later

Probably not so rare

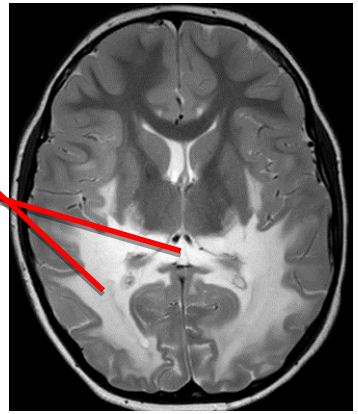
Eichler et al, Arch Neurol, 2007
Carlson et al, J Neurol, 2021

Disease severity in cerebral ALD: lesion load on MRI of the brain

Quantify by Loes score (0 – 34)

***Table** MRI Severity Scale*

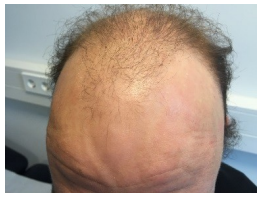
Parieto-occipital WM (maximum 4)
Anterior temporal WM (maximum 4)
Frontal WM (maximum 4)
Periventricular
Central
Subcortical
Local atrophy
Corpus callosum (maximum 5)
Splenium
Body
Genu
Splenium atrophy
Genu atrophy
Visual pathway (maximum 4)
Optic radiations
Meyer's loop
Lateral geniculate body
Optic 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

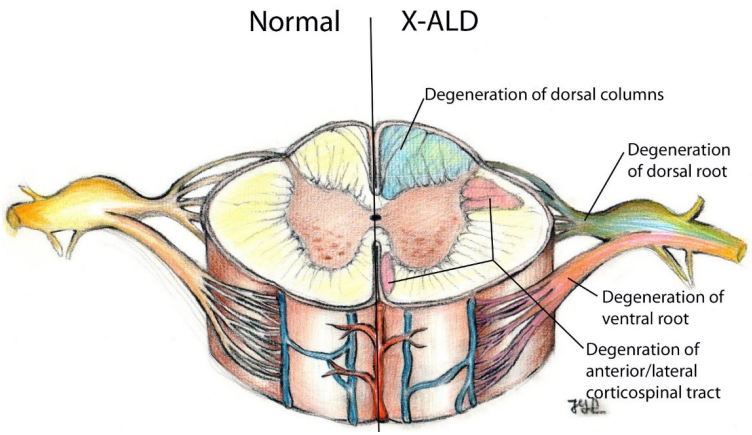


Loes et al, AJNR, 1994

Clinical features: spinal cord disease of ALD ("adrenomyeloneuropathy")

- Axonal degeneration in spinal cord and peripheral nerves
- All men and about 90% of women develop spinal cord disease
- "Core phenoype" in adulthood





Sensory ataxia

Spasticity

Gait disorder

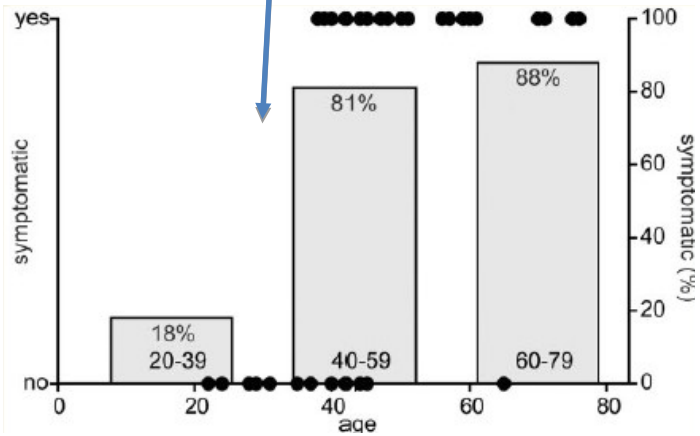
Huffnagel et al, Brain, 2019

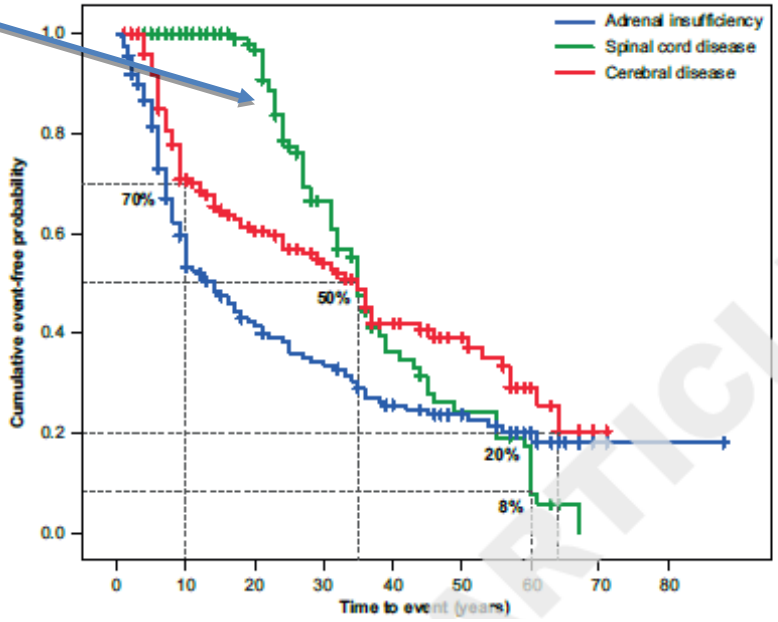
Clinical features

Age of onset of spinal cord disease highly variable

Progression is slow in men (years), very slow in women (decades)

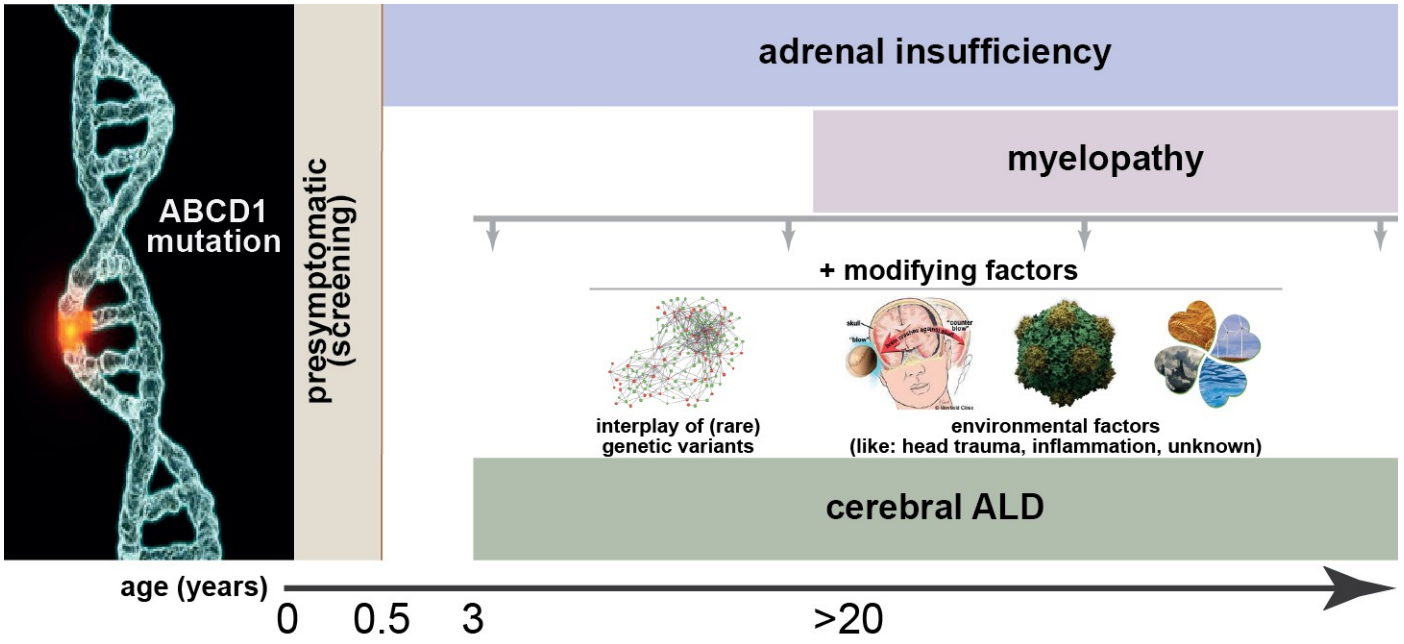
No treatment





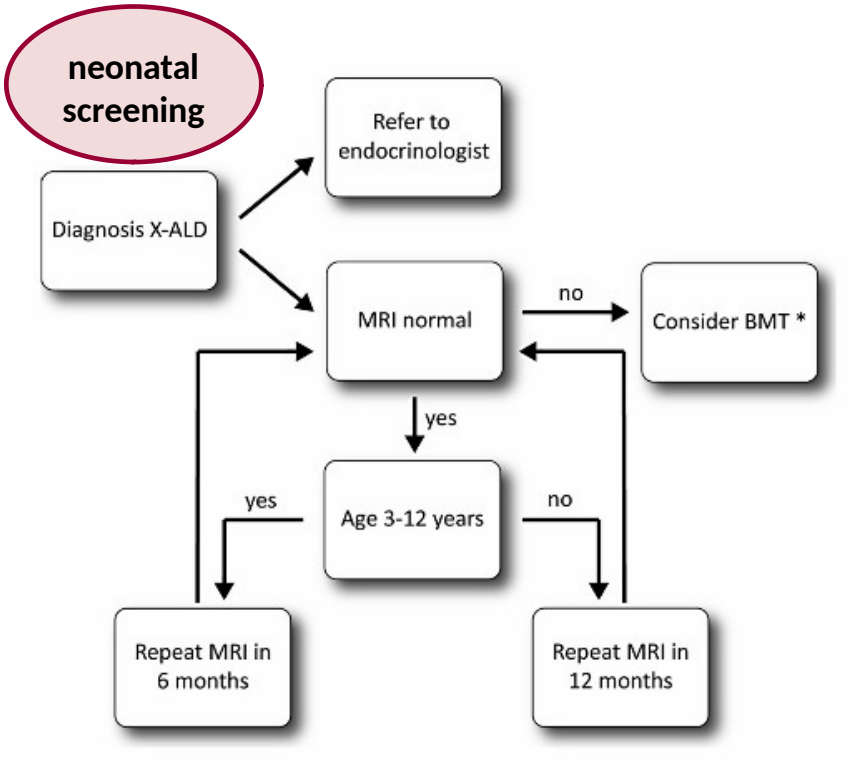
Huffnagel et al, 2018
Huffnagel et al, 2019

Clinical features: summary



Kemp et al, Nature Reviews Endo, 2016

Follow-up and treatment



Engelen et al, OJRD, 2012

Follow-up and treatment

Table 1 Summary of clinical characteristics of the five patients

Transplantation					VLCFA pre-Tx		VLCFA post-Tx		Examination			
Patient	Age Tx	Donor	Chimerism	GvH	C26:0	C26/C22	C26:0	C26/C22	Age	AI	myelopathy	Mutation
A	4	sib	100 %	No	2.26	0.06	2.48	0.05	23	+	+	p.Ile657del
B	6	MUD	n.a.	No	2.56	0.08	1.6	0.08	18	+	−	not known
C1	9	MUD	100 %	No	n.a.	n.a.	0.77	0.02	25	+	+	p.Pro543Leu
C2	7	MUD	100 %	No	5.17	0.07	1.7	0.03	22	+	+	p.Pro543Leu
D	6	sib	100 %	No	1.75	0.06	2.73	0.05	23	+	−	p.Leu220Pro

So no HCT if no cerebral ALD!

Geel van et al, JIMD, 2015

The natural history of spinal cord disease in men

Outcome measure	Baseline	Follow-up	Change	*P*-value	*n*	Test statistic	Effect size
EDSS	6.0 (0–7.0)	6.0 (2.0–7.0)	0.34 (0.03 to 0.65)	0.034*	25	2.12	0.30
SSPROM	79.12 ± 10.67	76.34 ± 12.49	−2.78 (−4.93 to −0.63)	0.013*	25	2.67	0.53
Timed up-and-go, s	7.99 ± 3.09	8.80 ± 3.50	0.82 (0.08 to 1.55)	0.032*	19	2.32	0.53
6-minute walk test, m	429.0 (202.0–695.0)	400.5 (260.5–676.0)	−19.67 (−35.4 to −3.9)	0.019*	24	2.34	0.34
mJOA	13.00 (12–18)	14.00 (10–18)	−0.24 (−0.69 to 0.21)	0.260	25	NA	NA
ALDS	88.65 (49.70–89.47)	88.65 (39.58–89.47)	0.48 (−2.09 to 3.06)	1.000	24	NA	NA
ICIQ-MLUTS	17.04 ± 8.87	17.17 ± 9.31	0.13 (−1.71 to 1.97)	0.885	23	NA	NA
SF-36 physical component	−1.43 (−4.95–0.47)	−1.65 (−5.29–0.71)	0.00 (−0.34 to 0.34)	0.775	24	NA	NA

Changes are detectable over a period of 2 years with EDSS, SSPROM and GUGO and 1 year with 6 MWT

PRO and QoL measures do not register change

Huffnagel et al, 2019

The natural history of spinal cord disease in women

Cohort study with 65 women (34 follow-up assessments)

Table 5 Progression rates

	N	Clinical progression	Stable score	Improvement score	Baseline (range)	Follow-up (range)	Progression rates per year		
							All women	Symptomatic at baseline ($N = 19$)	Asymptomatic at baseline ($N = 15$)
EDSS	32	21	11	0	2.75 (0–6)	3.5 (1.5–6)	0.08	0.06	0.17
ALDS	34	10	17	7	89.47 (71.92–89.47)	89.47 (71.92–89.47)	0.00	0.00	0.00
SF-36: PF	34	19	1	14	0.22 (−2.66–1.16)	−0.07 (−2.86–1.26)	0.00	−0.03	0.02
SF-36: PCS	34	21	0	13	50.11 (17.26–62.36)	49.16 (16.67–64.72)	−0.21	−0.17	−0.37

Average of 8 years between assessments: 0.75 points on the EDSS score

Huffnagel et al, 2019

Q1

Clinimetric tools often have limitations, for example a ”ceiling effect”. What is the “ceiling effect”?

a. Research subjects reach a maximum (or control level) score
b. Research subjects reach a minimum score

Q2

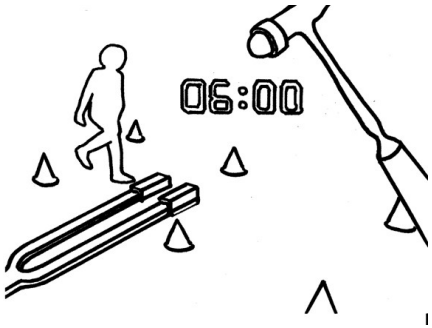
The 6 minute walk test often shows much variation in longitudinal assessments because

a. The people administering the test do not measure the distance accurately
b. The results are affected by many confounders (co-morbidity, motivation, test conditions)

Clinical trials in ALD are difficult

- 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)

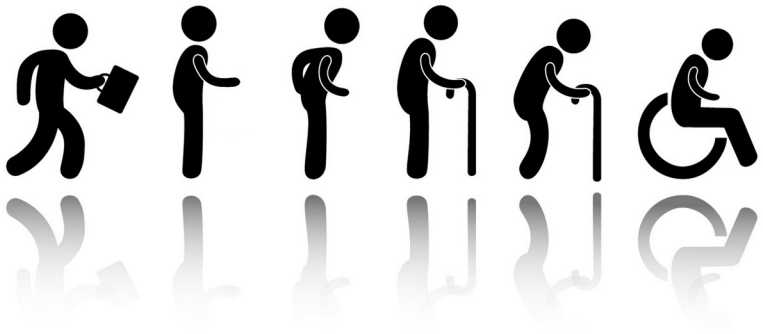


Huffnagel et al, 2019

New outcome measures are needed

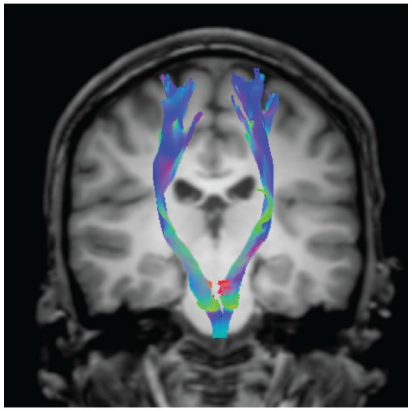
- Directly measure the underlying pathology
- Are sensitive to small changes in severity of spinal cord disease
- No “floor” and “ceiling” effect: more patients eligible (men in wheelchair and women)

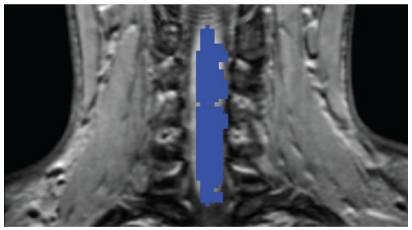
- Predictors to stratify patients (risk of cerebral ALD, rate of progression) also needed



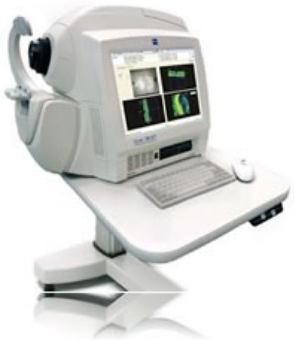
Towards objective outcome measures and predictors

qMRI
(like DTI and CSA)

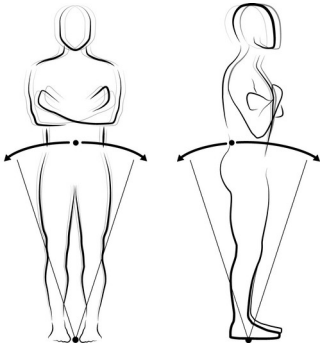




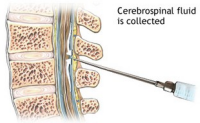
Optical coherence tomography



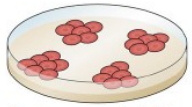
Sway and dynamometry



Plasma, CSF

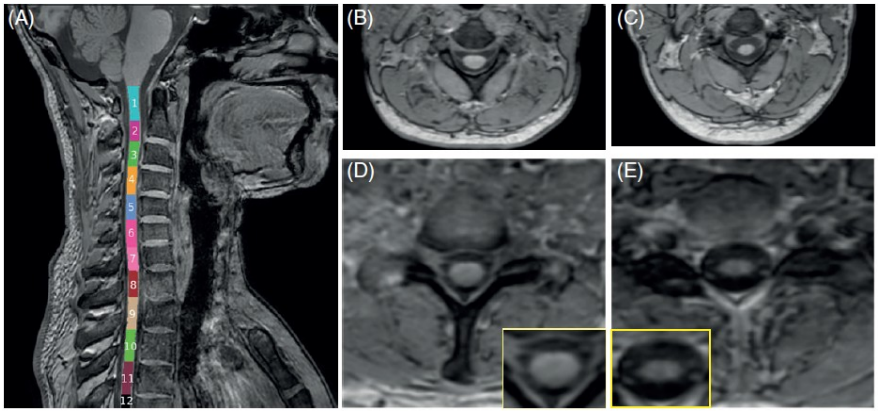


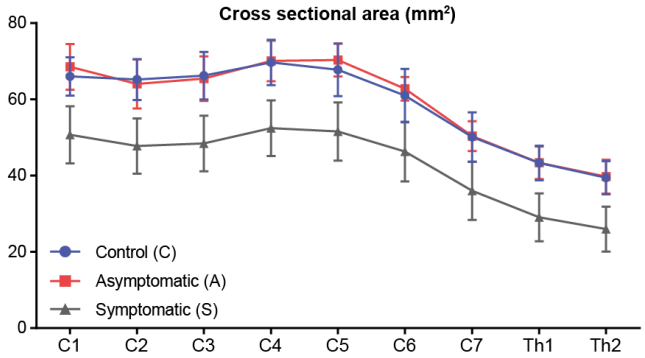
iPSC derived neuronal cells

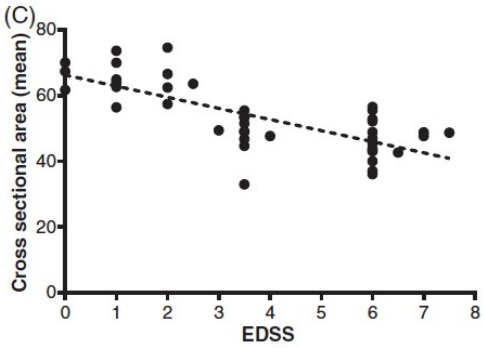


Wearable technology
(OPAL from APDM)

MRI: cross sectional area of spinal cord

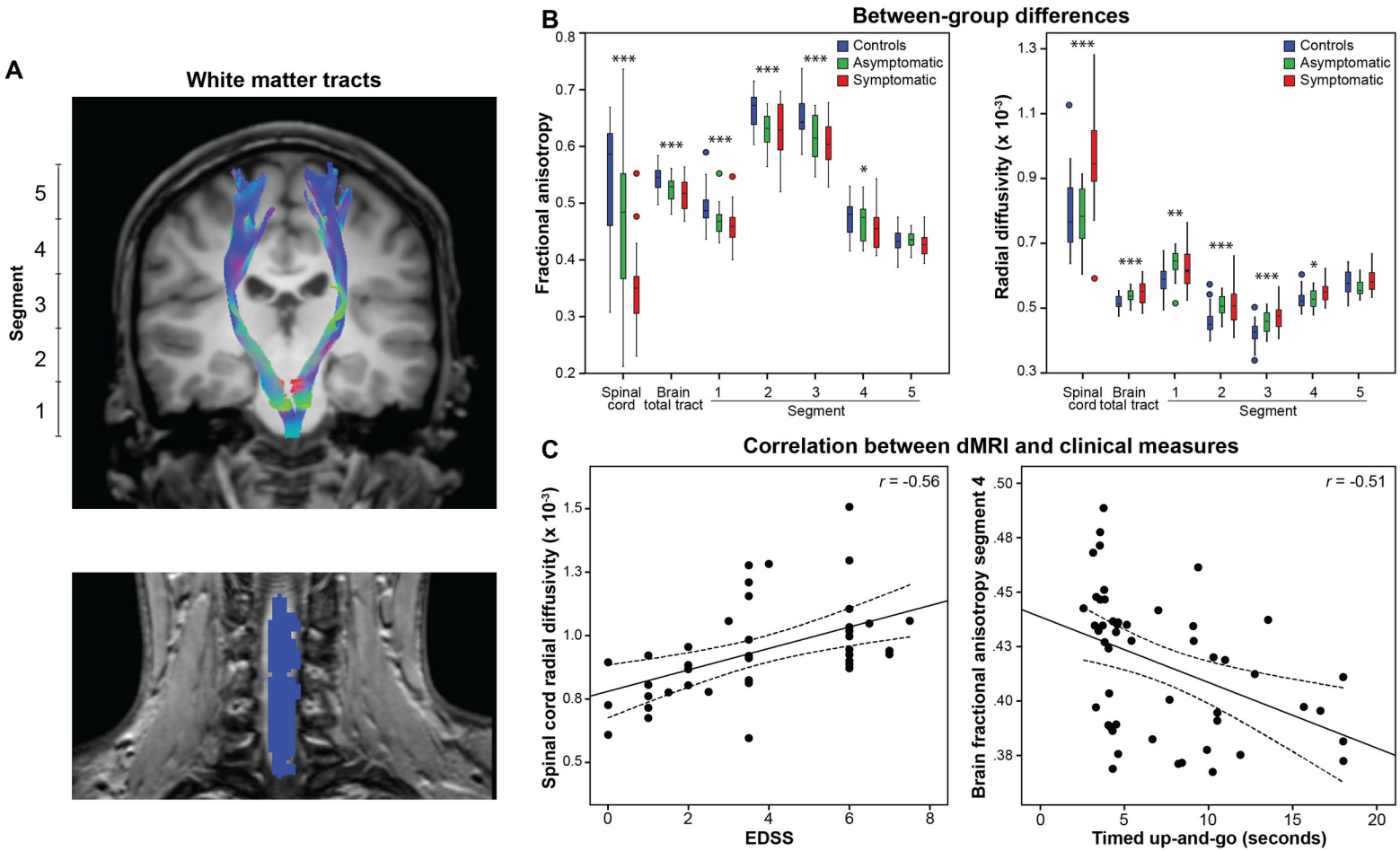






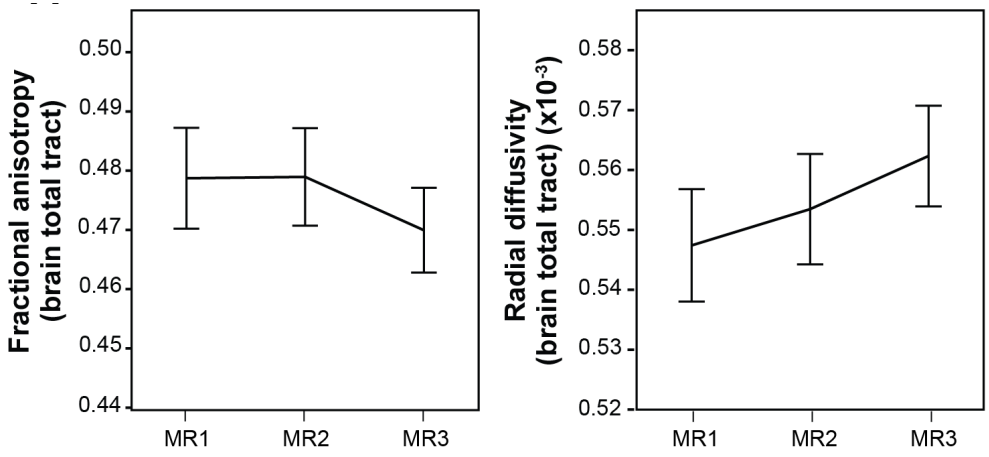
Van der Stadt, JIMD, 2020

MRI: DTI of motor tracts in brain and spinal cord



Dubey et al, 2005
Castellano et al, 2016
Huffnagel et al, Neurology, 2019

Changes in DTI parameters over time



Differences in FA and RD between controls and patients

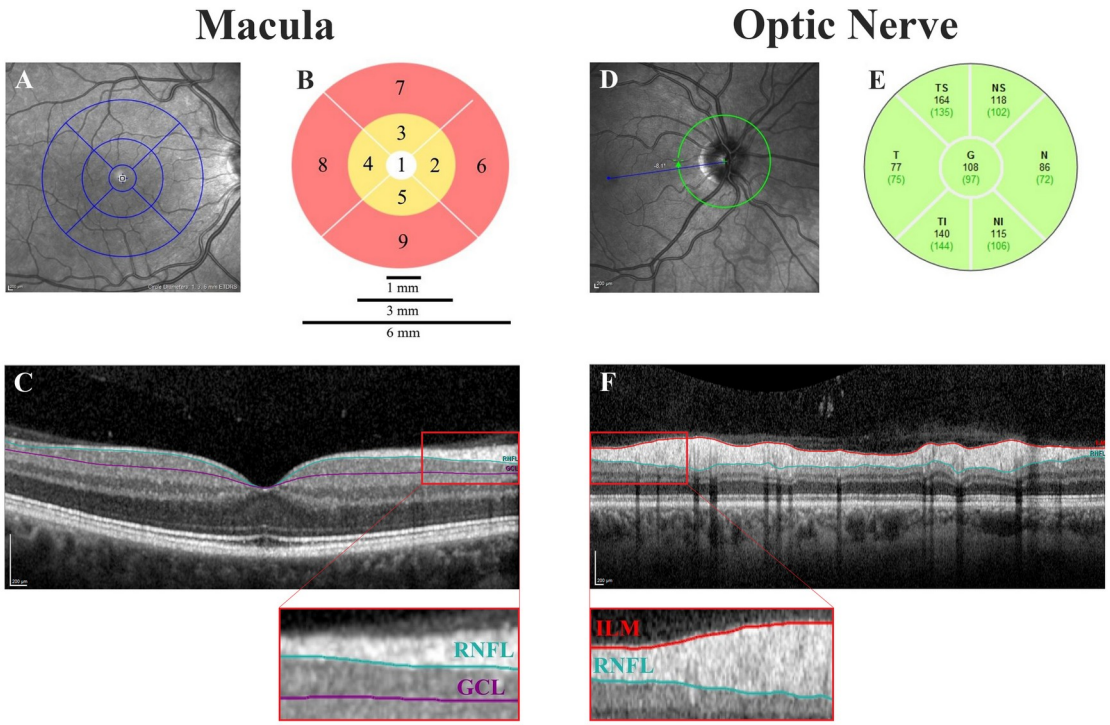
Differences beween asymptomatic and symptomatic patients

Correlates with changes in GUGO over time

Potentially useful outcome measure, but more data required and technical difficulties to be overcome

Huffnagel et al, neurology, 2019

Optical coherence tomography



Studies in MS suggest correlation between OCT parameters and neurologic outcome

Alonso et al, 2018
van Ballegoij et al, J Neurol, 2020
van Ballegoij et al, ACTN, 2021

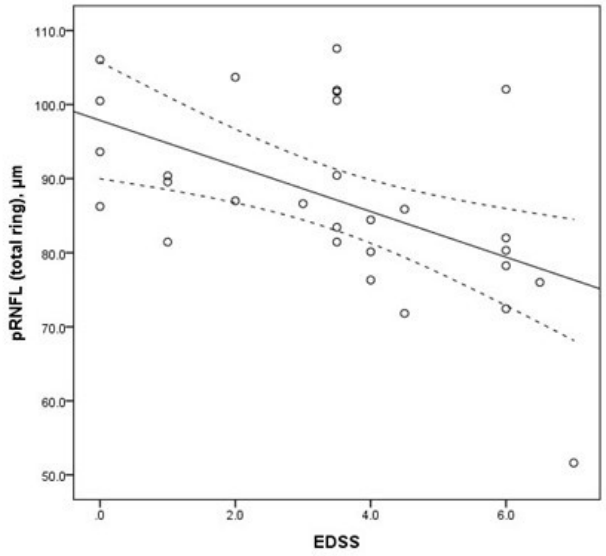
Cross-sectional OCT data

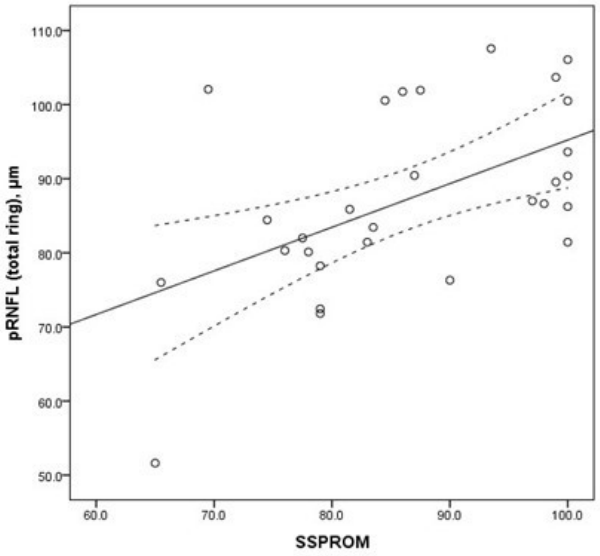
Table 1. Retinal nerve fiber layer thickness in controls, asymptomatic patients and symptomatic patients.

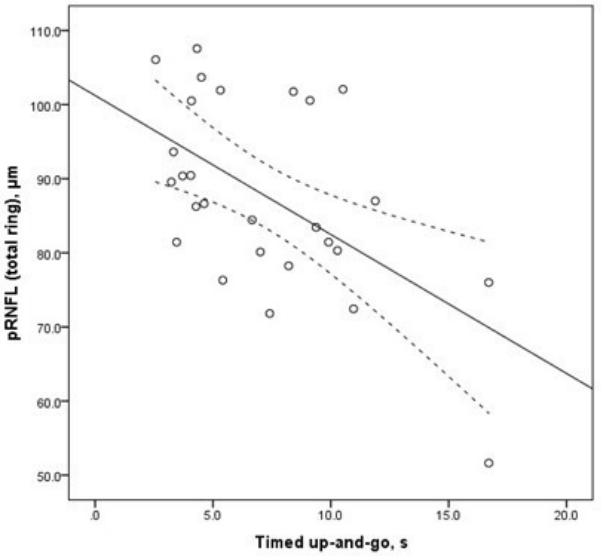
Men	Retinal layer	Region	Control (n=33)	Asymptomatic (n=9)	Symptomatic (n=20)	p-value	Cohen's d effect size		
							C vs A	C vs S	A vs S
	RNFL, µm	Total grid surface[a]	36.68 (3.67)	36.93 (2.99)	32.91 (3.78)	.001	.07	1.01	1.18
		Pericentral ring	28.45 (2.26)	27.77 (1.46)	27.12 (2.16)	.09	.36	.60	.35
		Peripheral ring	39.52 (4.23)	39.97 (3.57)	35.99 (4.35)	.002	.11	.82	1.00
	pRNFL, µm	Total [b]	91.30 (9.26)	93.13 (8.51)	84.77 (13.30)	.06	.21	.57	.75
		Superior	113.91 (13.62)	114.56 (12.50)	102.75 (16.44)	.02	.05	.74	.81
		Nasal	66.52 (10.37)	67.94 (10.54)	69.02 (13.14)	.80	.14	.21	.09
		Inferior	114.80 (16.00)	117.89 (10.55)	108.88 (18.22)	.29	.23	.35	.61
		Temporal	70.00 (13.99)	72.11 (15.31)	58.42 (12.83)	.005	.14	.86	.97
Women	Retinal layer	Region	Control (n=37)	Asymptomatic (n=10)	Symptomatic (n=23)	p-value	Cohen's d effect size		
							C vs A	C vs S	A vs S
	RNFL, µm	Total grid surface[a]	36.81 (3.54)	35.73 (3.54)	36.51 (4.44)	.67	.31	.07	.19
		Pericentral ring	27.44 (1.92)	27.13 (2.58)	27.71 (2.13)	.72	.14	.13	.25
		Peripheral ring	39.98 (3.15)	38.66 (3.90)	39.49 (5.25)	.61	.37	.11	.18
	pRNFL, µm	Total [b]	95.04 (8.16)	92.74 (8.62)	89.19 (9.87)	.06	.27	.65	.38
		Superior	118.16 (14.28)	111.88 (9.82)	102.58 (12.98)	<.001	.51	1.14	.81
		Nasal	68.77 (10.14)	73.80 (15.88)	70.55 (11.29)	.60	.38	.17	.24
		Inferior	120.96 (15.01)	122.53 (13.19)	117.44 (19.17)	.65	.11	.20	.31
		Temporal	72.28 (10.89)	62.75 (7.60)	66.20 (9.39)	.01	1.01	.60	.40

van Ballegoij et al, J Neurol, 2020

Cross-sectional OCT data



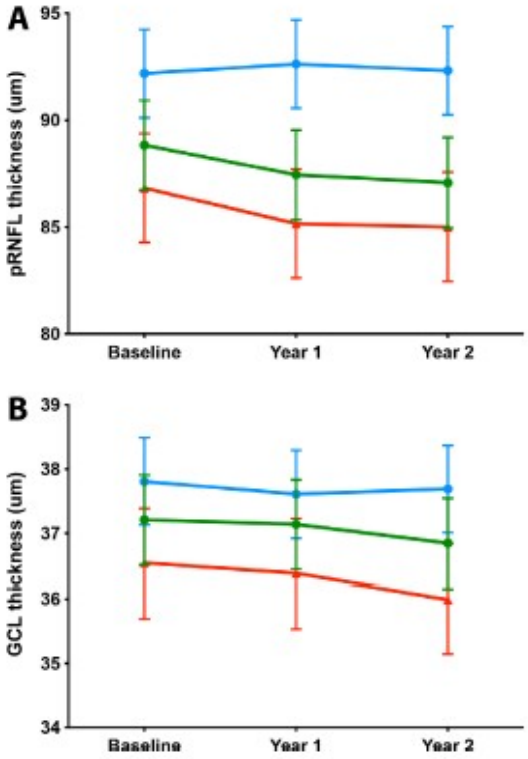




Promising data (cross-sectional) in men and women with ALD

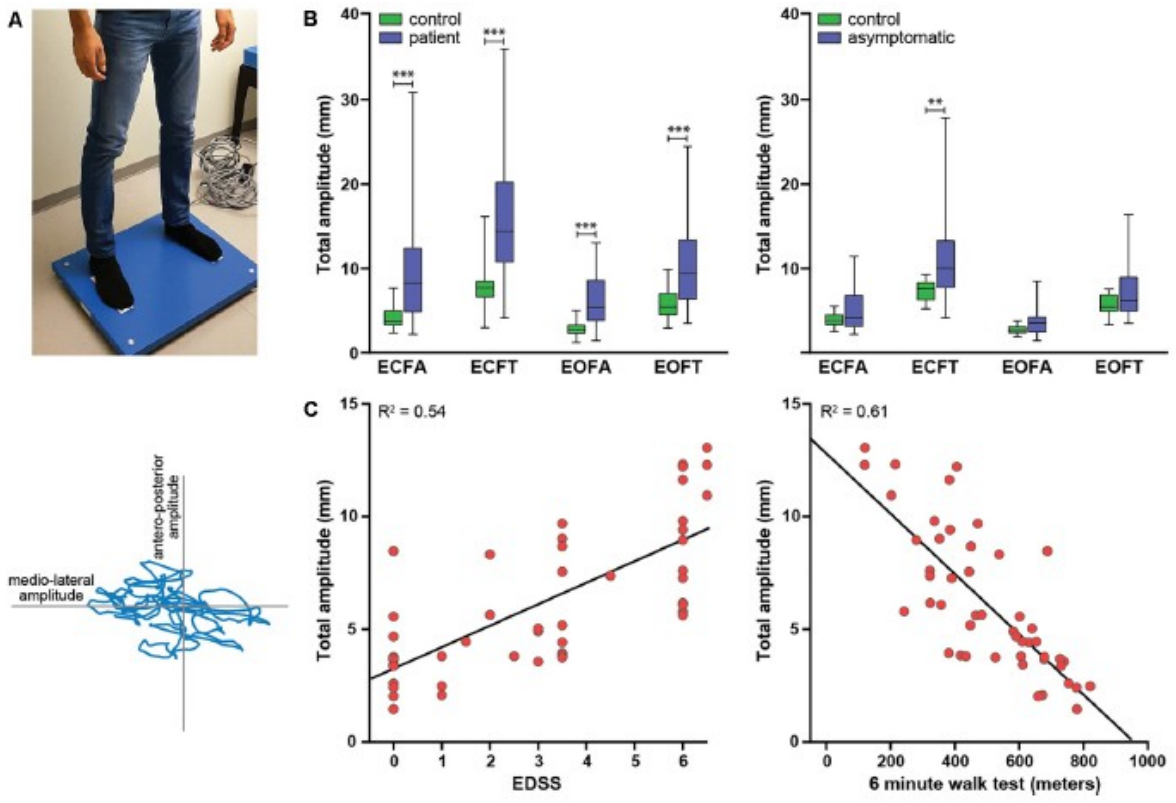
van Ballegoij et al, J Neurol, 2020

Longitudinal OCT data



Van Ballegoij et al, ACTN, 2021

Force plate analysis



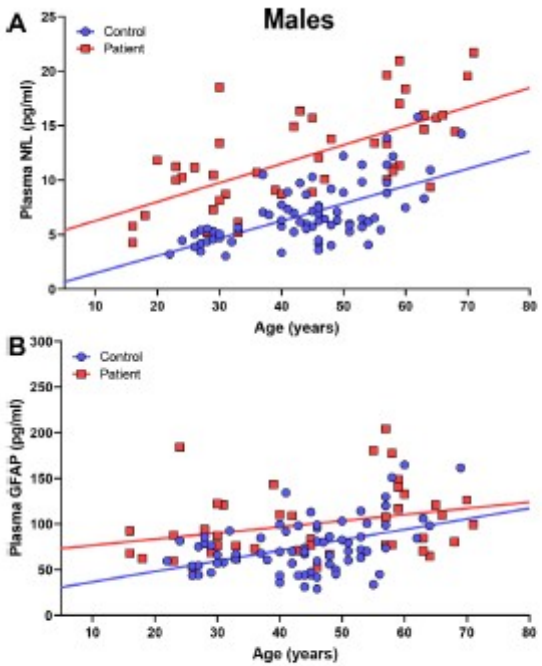
Van Ballegoij, Frontiers Physiol, 2021

Q3

Body sway in the EC-FT condition is mainly affected by:

a. Dorsal column dysfunction
b. Corticospinal tract dysfunction

Neurofilament light and GFAP

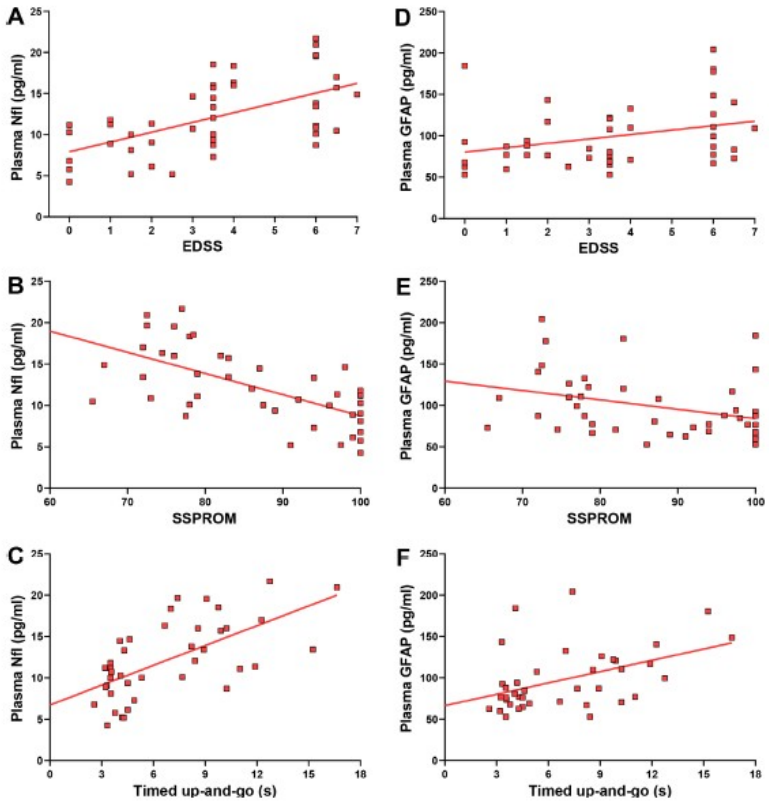


Males	Patient (n=45)	Control (n=74)	p-value	Effect size
Age, years	44.0 ± 16.7	44.1 ± 10.8	0.978	
NfL, pg/ml	11.2 (9.0-15.7)	6.2 (5.2-8.4)	<0.001	0.49
GFAP, pg/ml	87.0 (71.0-120.7)	70.1 (55.6-93.1)	<0.001	0.13

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

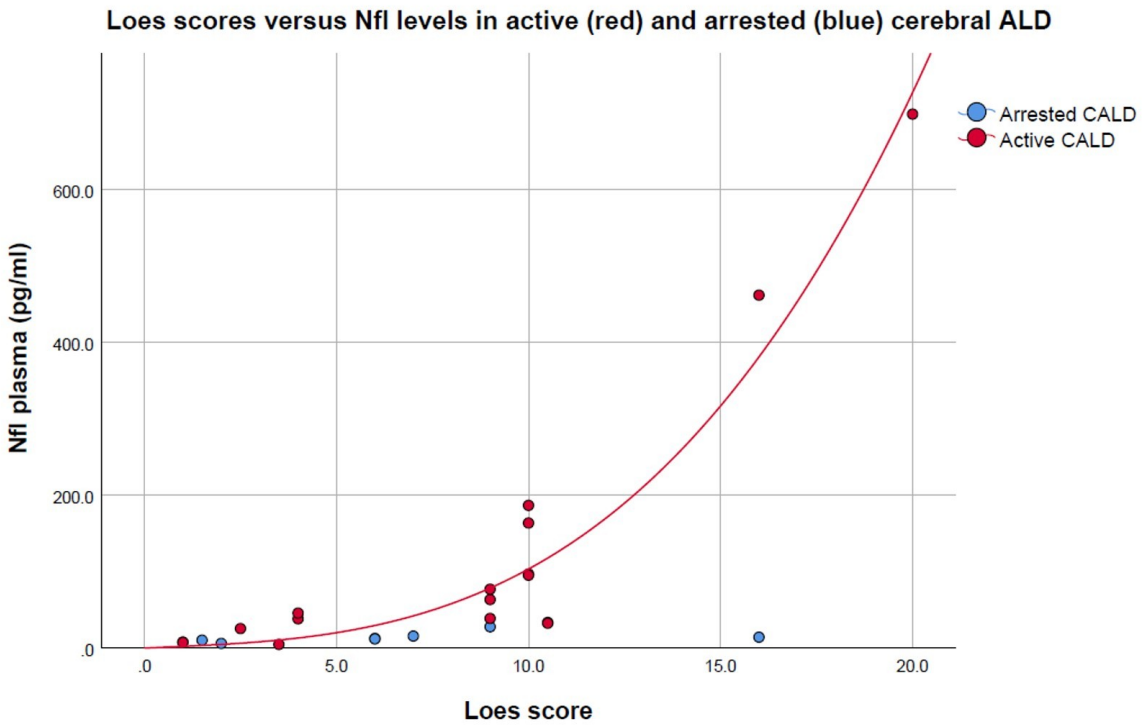
Van Ballegoij et al, ACTN, 2021

Neurofilament light and GFAP



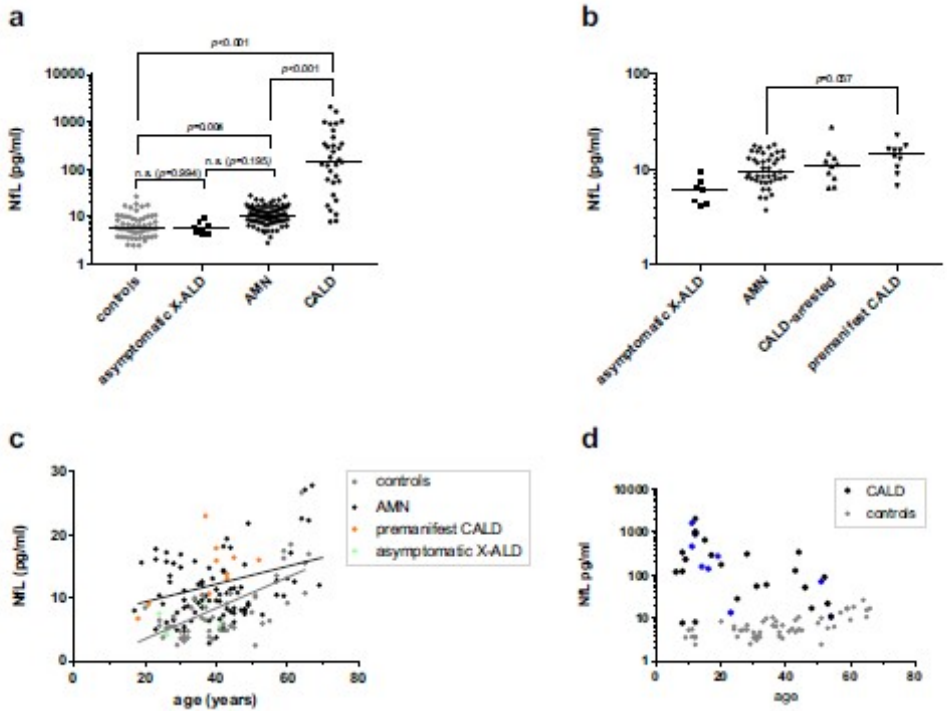
Van Ballegoij et al, ACTN, 2021

Neurofilament light



Unpublished data

Neurofilament light

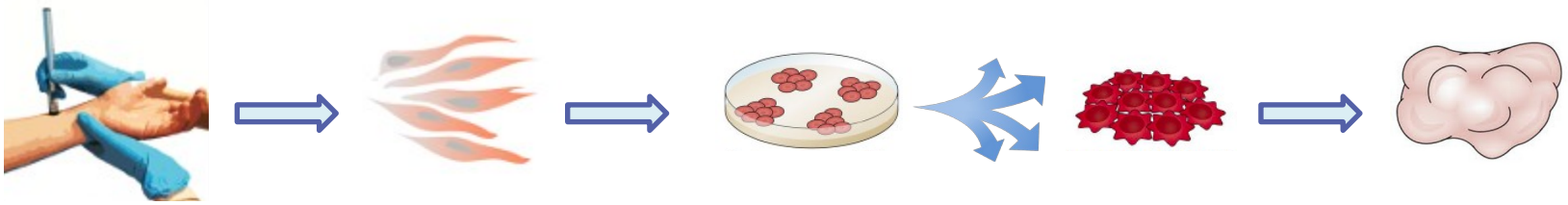


Weinhofer et al, Nature Comm, 2021

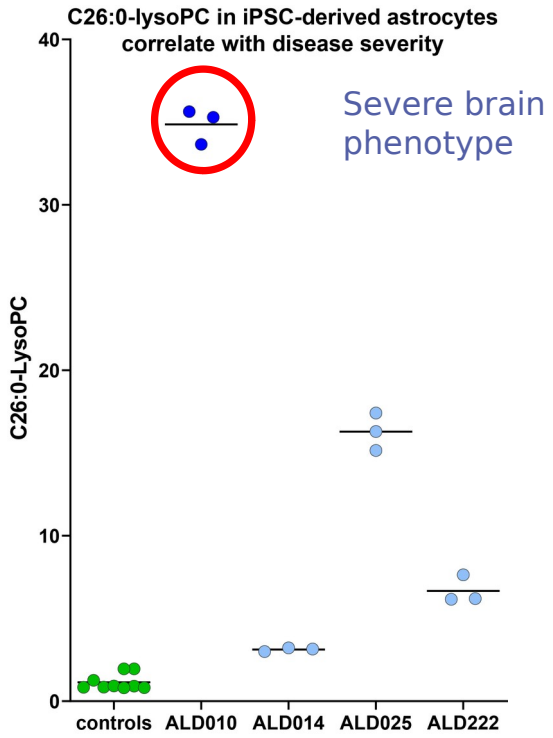
Human induced pluripotent stem cell (iPSC)-derived organoids

Advantages

- iPSC: Human-based and represent patient-own genetics
- Organoids: Mimic complex 3D brain-like structures
- Allow high-throughput screening



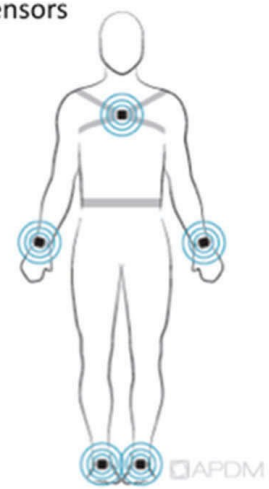
VLCFA levels in iPSC derived astrocytes seem to correlate with disease severity



New projects: new technologies and other diseases

- MTI and other MRI protocols
- OPAL movement lab: no formal testing, patients just move!

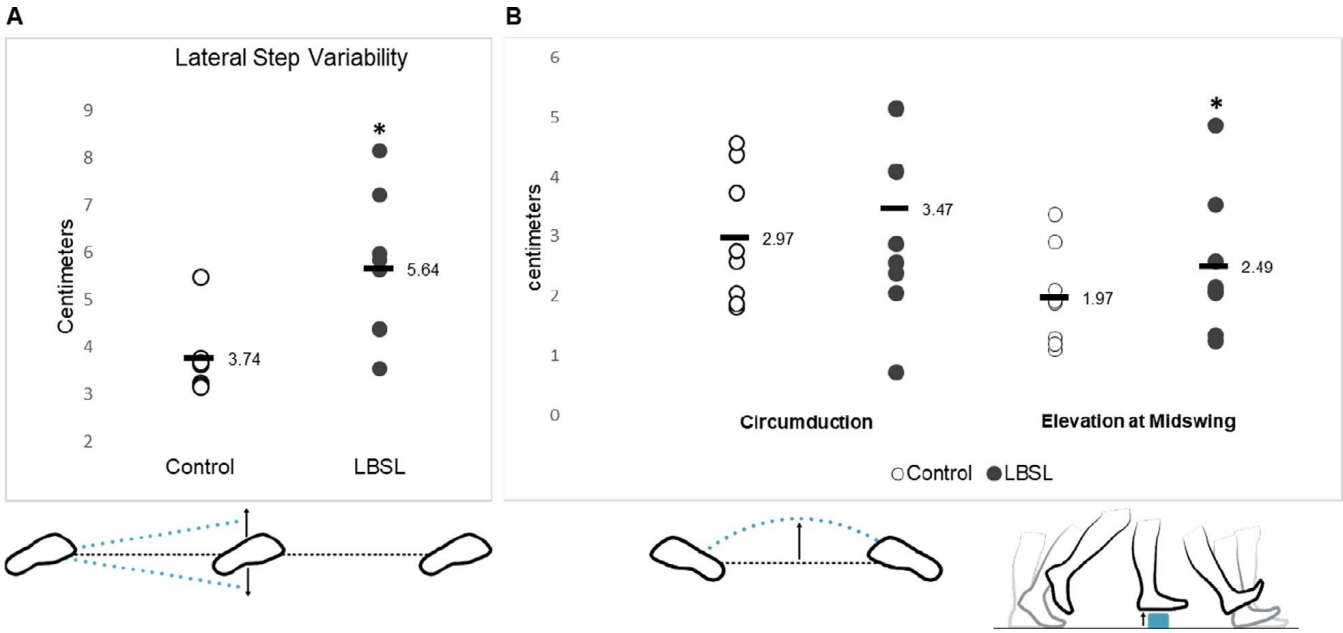
A. Location of Opal sensors



B. Example of sensor attached to the wrist

C. Size of Opal sensors

Gait analysis with wearables



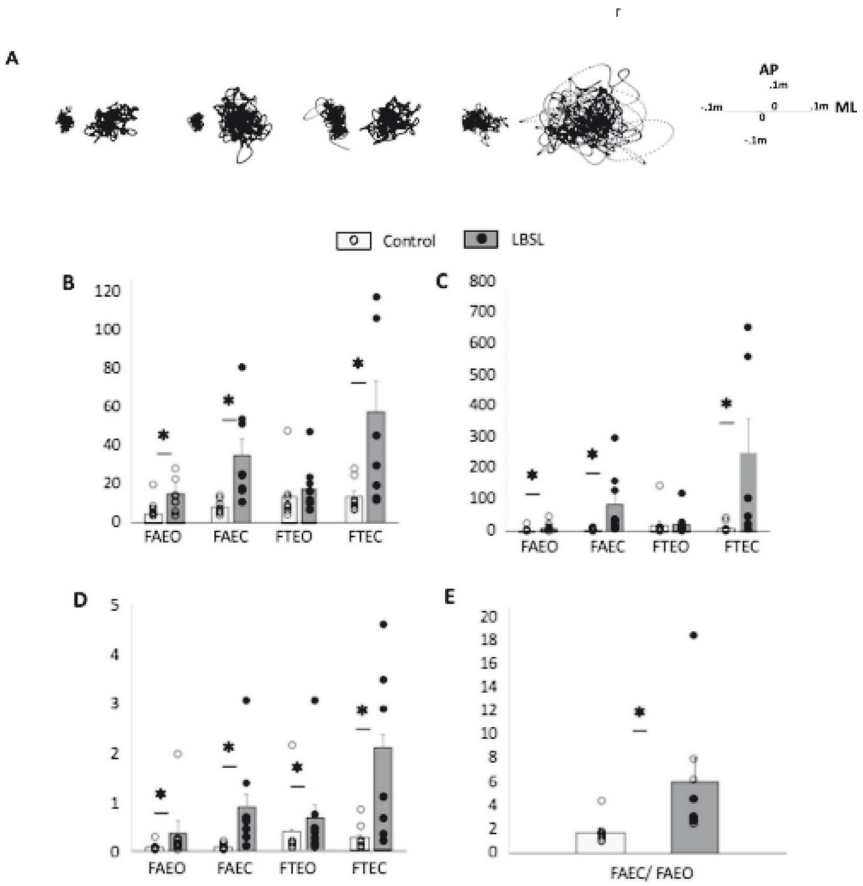
Different parameters can be selected for specific disorders

Can be incoporated in current assessment

Remote assessment is possible

Smith Fine et al, ACTN, 2022

Gait analysis with wearables



Smith Fine et al, ACTN, 2022

To summarize

- Genetic and biochemical defect known, but pathophysiology poorly understood
- Clinical features and natural history systematically studied, but questions remain
- Due to the slow progression clinical trials are difficult, new outcome measures are needed
- New biomarkers look promising as surrogates
- Predictors for cerebral ALD are needed to optimize follow-up and to stratify patients for trials

European Reference Network
for rare or low prevalence complex diseases

Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

NEXT Webinar

‘Antisense oligonucleotide mediated exon skipping therapy development for Duchenne muscular dystrophy takes more than an oligonucleotide’

by Annemieke Aartsma-Rus,

Leiden University medical Center, the Netherlands

29. March 2022