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)

DG ‚Leukodystrophies'
17 March 2020

Joint webinar series

X-linked Adrenoleukodystrophy

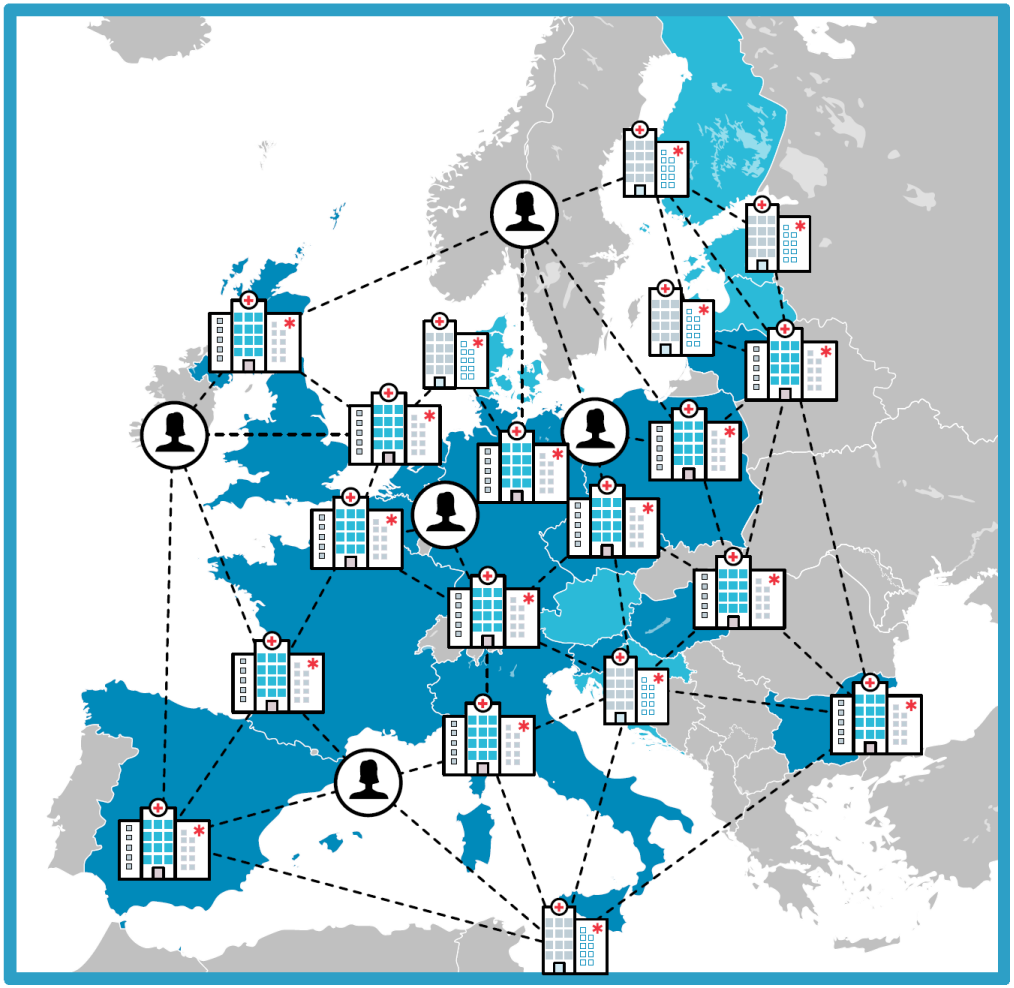
Marc Engelen
University Medical Centers Amsterdam, the Netherlands

General information about the webinars

- RARE neurological, neuromuscular and movement disorders
- 30-35min presentation
- 15min Q&A session at the end (please write your questions in the Q&A)
- Target audience: neurologists, residents, paediatric neurologists, geneticists and other para-medical personnel involved in patient care
- Recorded Webinar and presentation to be found at the latest 2 weeks after on: http://www.ern-rnd.eu/education-training/past-webinars/
- For more information on this diseases group visit: http://www.ern-rnd.eu/disease-knowledge-hub/leukodystrophies/
- Post-webinar survey (2-3min): satisfaction, topic/speaker ideas for next webinars

European Reference Network for RARE Neurological Diseases (ERN-RND)

- **Countries with Full Members**
- **Countries with Affiliated Partners**

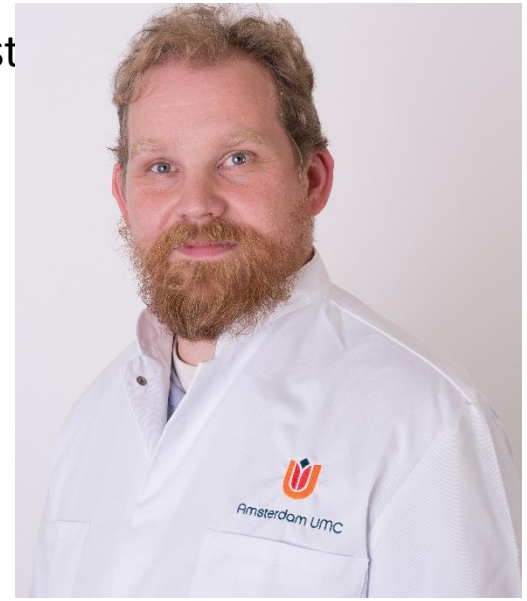


ERN-RND covers 6 disease groups:

1. Ataxia and HSP
2. Leukodystrophies
3. Dystonias /NBIA/Paroxysmal disorders
4. Chorea and HD
5. FTD
6. Atypical Parkinsonism

Speaker: Marc Engelen

- MD, PhD University of Amsterdam
- (Pediatric) neurologist, Amsterdam Leukodystrophy Center, Amst Medical Centers
- Follows are large cohort of patients with X-linked Adrenoleukodystrophy
- Local PI for the Minoryx ADVANCE study



Institutional Logo,
‚Speakers' picture or disease related picture

Webinar outline

- X-linked adrenoleukodystrophy: biochemistry and genetics
- X-linked adrenoleukodystrophy: clinical features
- X-linked adrenoleukodystrophy: diagnosis
- X-linked adrenoleukodystrophy: follow-up and treatment

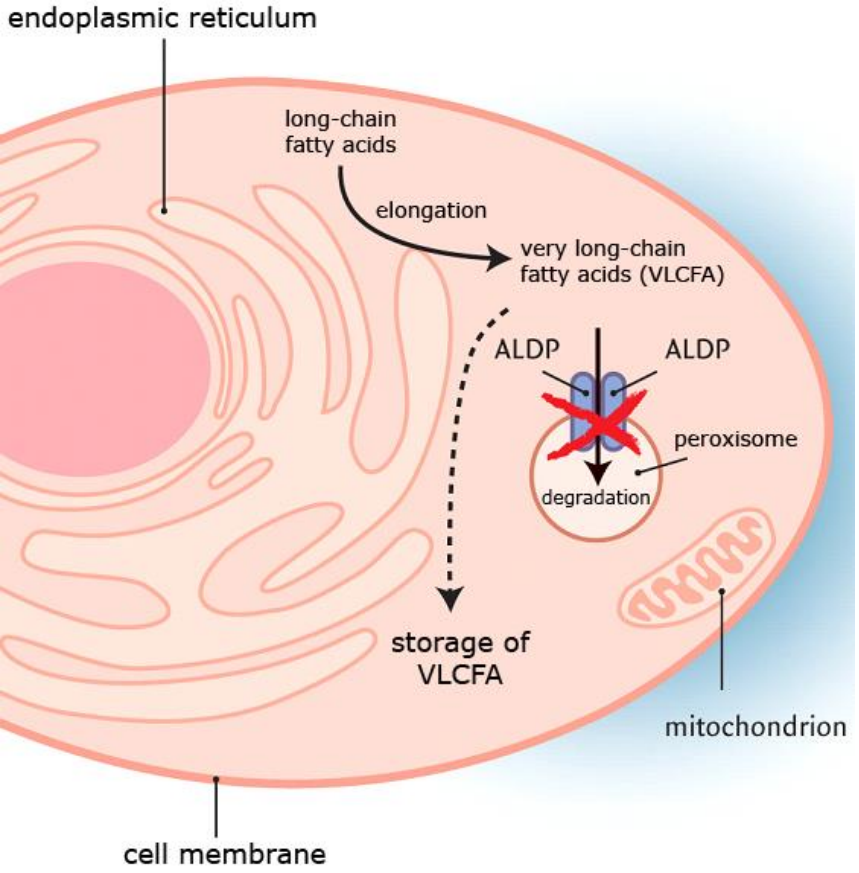
Institutional Logo,
‚Speakers' picture or disease related picture

Learning objectives

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

- describe the clinical features of X-ALD
- know the diagnostic procedures to confirm the diagnosis
- know about treatment options

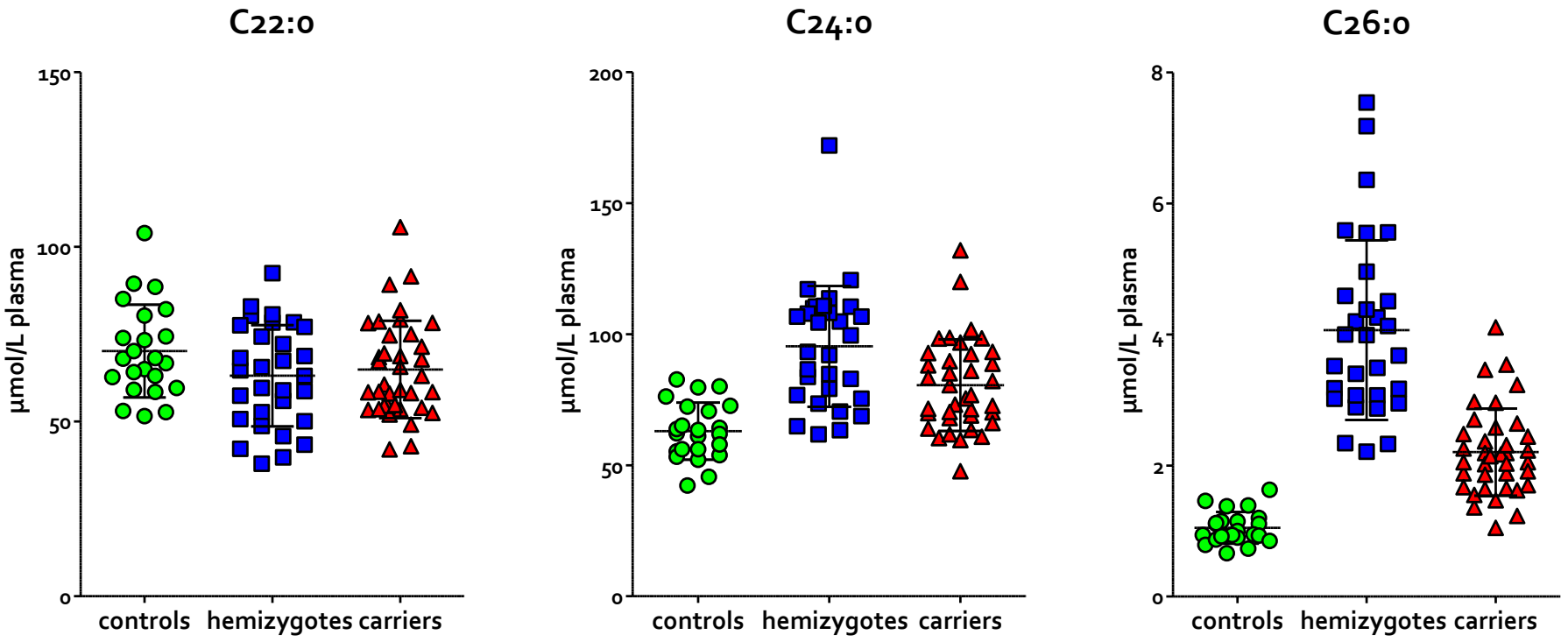
Biochemistry and genetics



- 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

Biochemistry and genetics



Kemp et al, Nature Reviews Endo, 2016

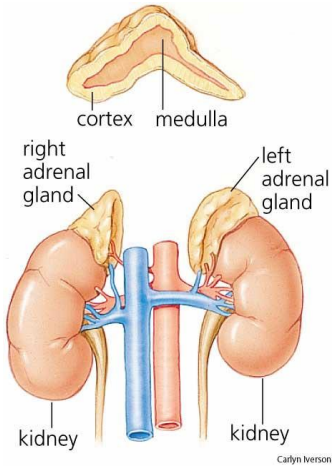
Question 1

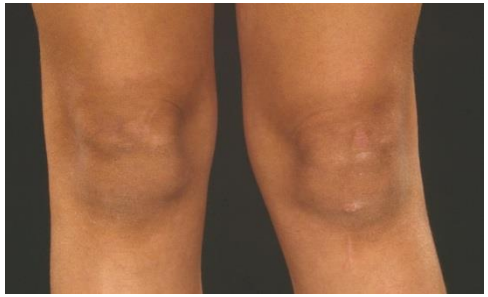
Which statements are correct?

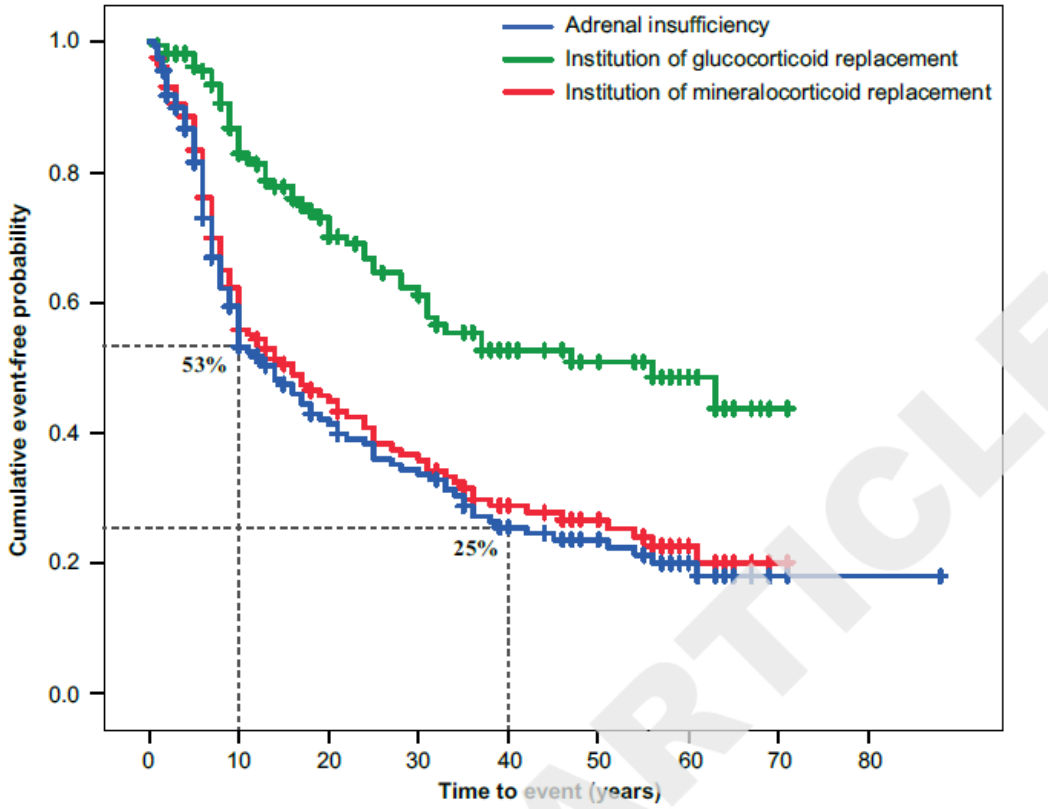
Adrenal failure in ALD:

a. Occurs in male and female patients.
b. Always occurs before the age of 18 years.
c. Is always the first manifestation of the disease.
d. Glucocorticoid production is affected more than mineralocorticoid production

Clinical features: adrenal failure

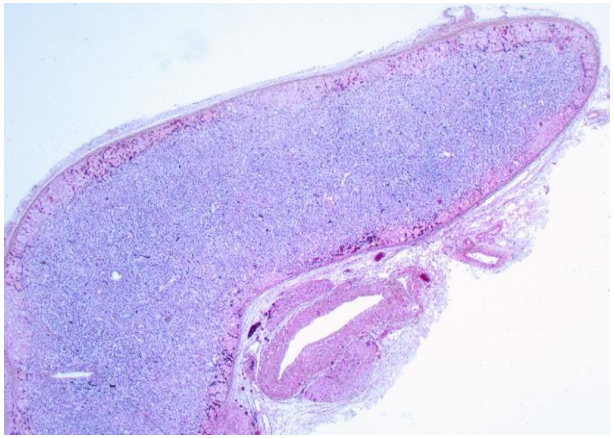


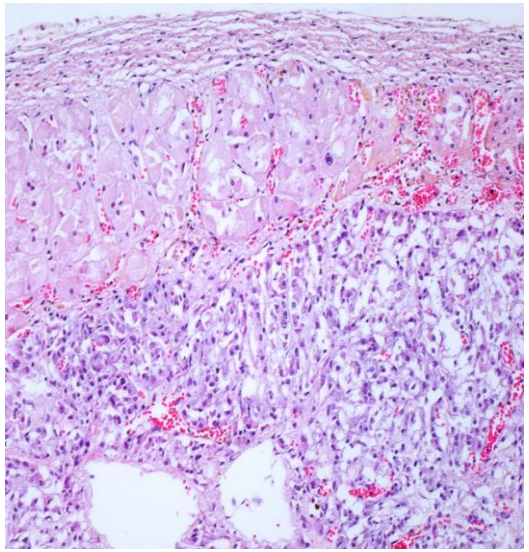


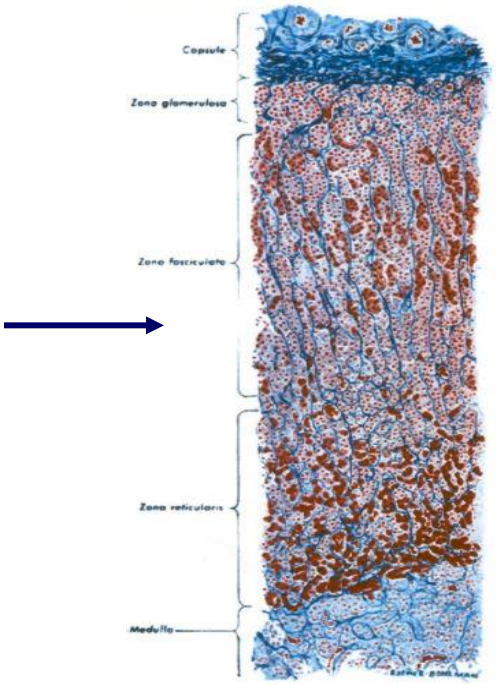


Huffnagel et al, JCEM, 2019

Clinical features







Courtesy of Dr. N.I. Wolf, Amsterdam Leukodystrophy Center / Amsterdam University Medical Centers

Question 2

Which statements are correct?

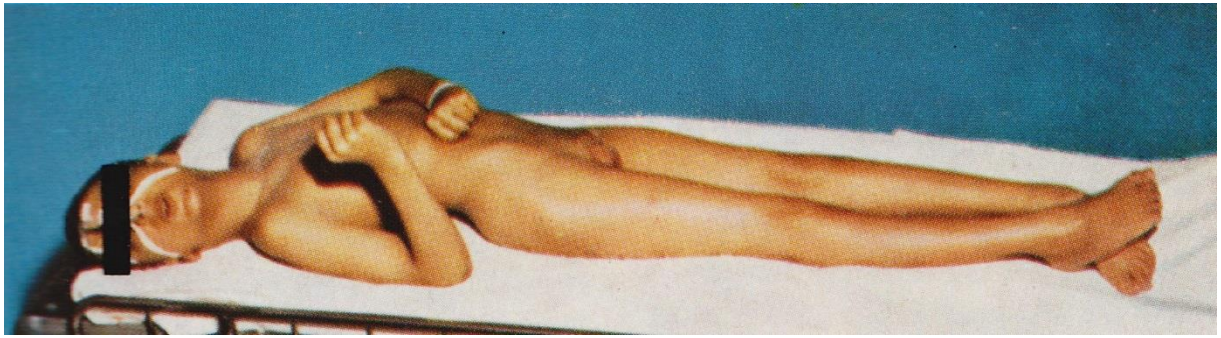
Cerebral ALD:

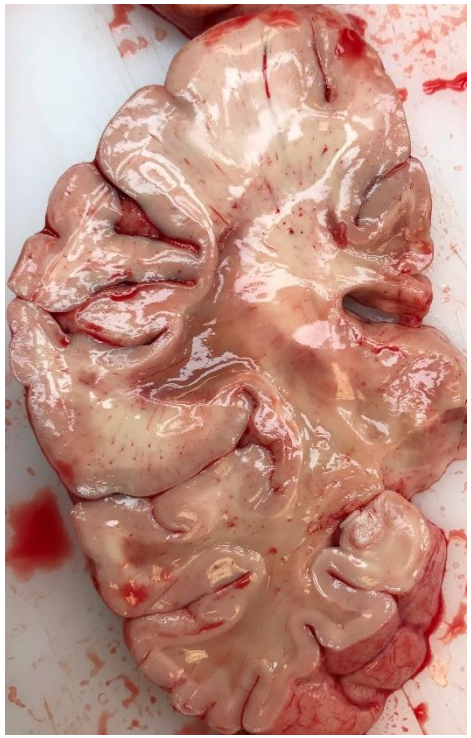
a. Occurs in children but not in adults.
b. Usually starts in the splenium of the corpus callosum.
c. Is always relentlessly progressive if not treated by HCT.
d. Lesions can show gadolinium enhancement just behing the leading edge

Clinical features: cerebral ALD

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

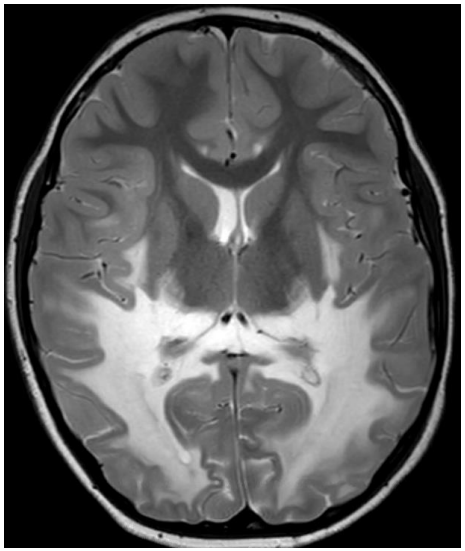
- neuropsychological and psychiatric deficits
- focal neurological deficits
- seizures
- untreated usually progressive

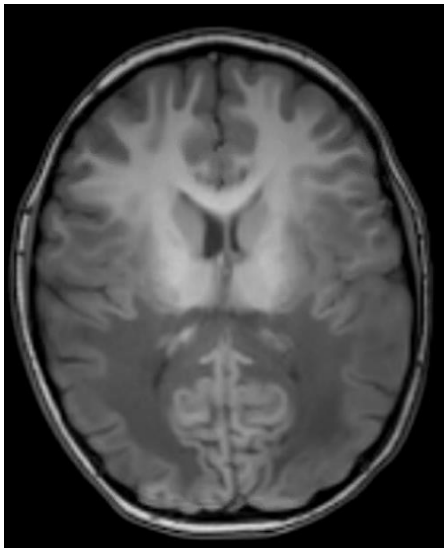


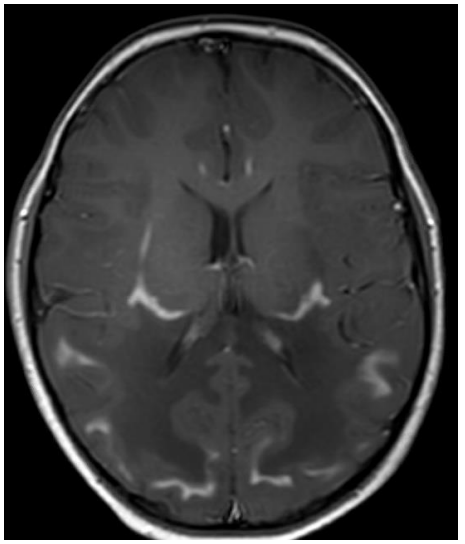


Engelen et al, OJRD, 2012
Powers et al, Clin Neuropathol, 1985

Clinical features



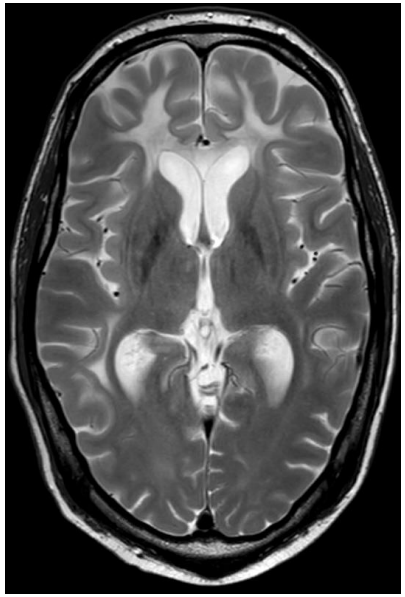


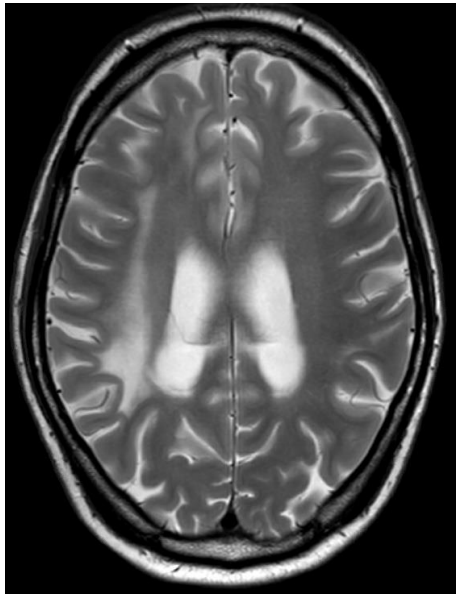


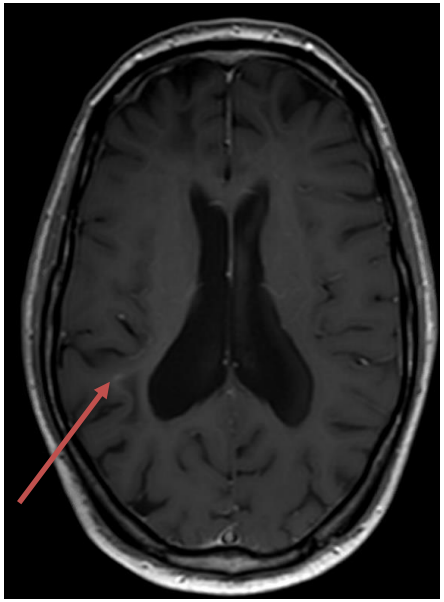
80% start in splenium and extends into occipital, parietal and frontal white matter

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

Clinical features

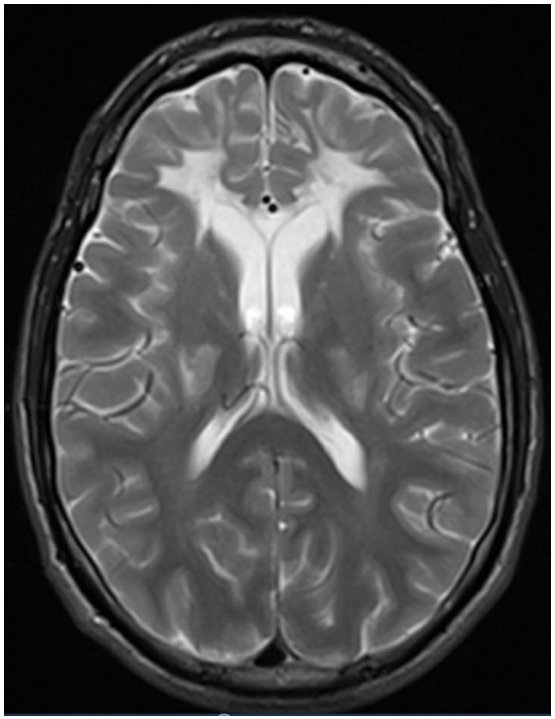


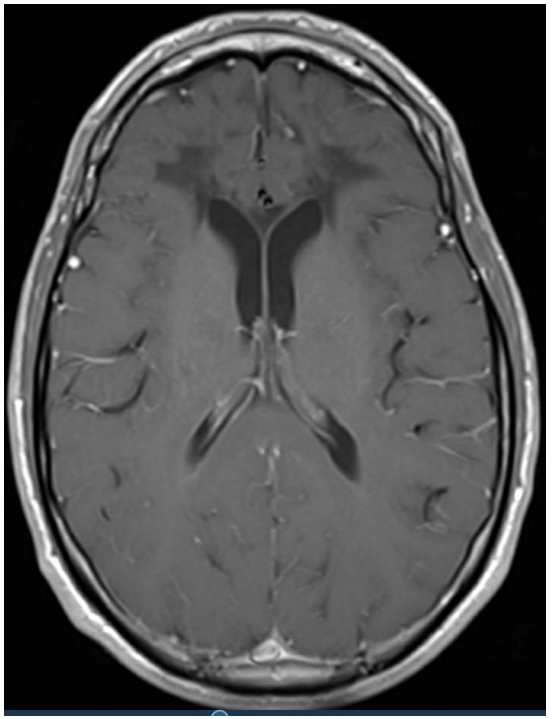




20% start in genu and extend into frontal white matter
Enahncement can be subtle (wait 5 – 10 min after contrast administration!)
Rarely in posterior fossa initially

Clinical features





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

Probably not so rare

Eichler et al, Arch Neurol, 2007

Clinical features

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, Nature Reviews Endo, 2016

Question 3

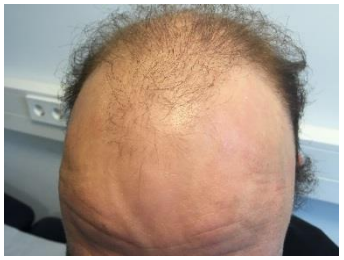
Which statements are correct?

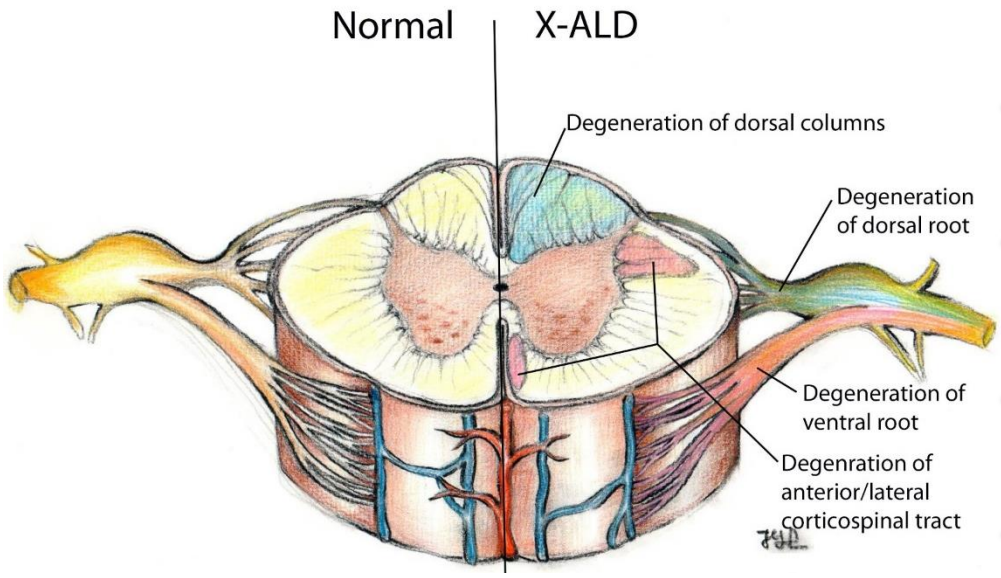
The spinal cord disease in ALD:

a. (Virtually) never occurs before the age of 18.
b. Is characterized by early loss of vibration sense.
c. Affects men and women.
d. Is very rapidly progressive (over weeks to months)

Clinical features

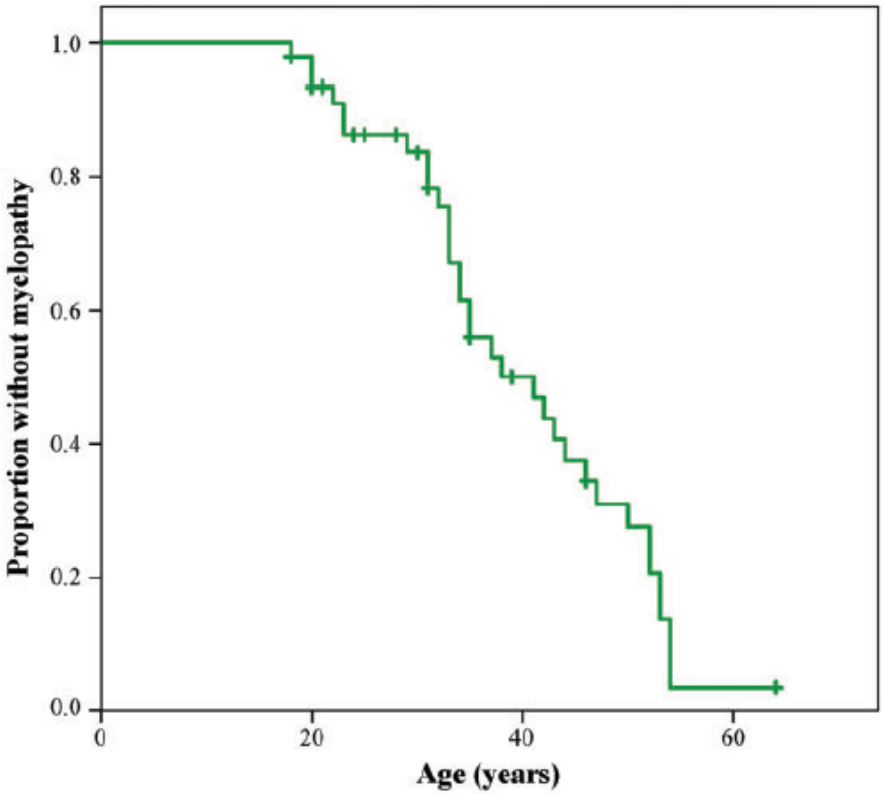
- Axonal degeneration in spinal cord and peripheral nerves
- All men and about 90% of women develop spinal cord disease
- “Core phenoype” in adulthood





Huffnagel et al, Brain, 2019

Clinical features



Spinal cord disease rare before early twenties and virtually always present before late fifties

Enormous variation in age of onset (and therefore
rate of progression)

Huffnagel et al, Brain, 2019

Clinical features

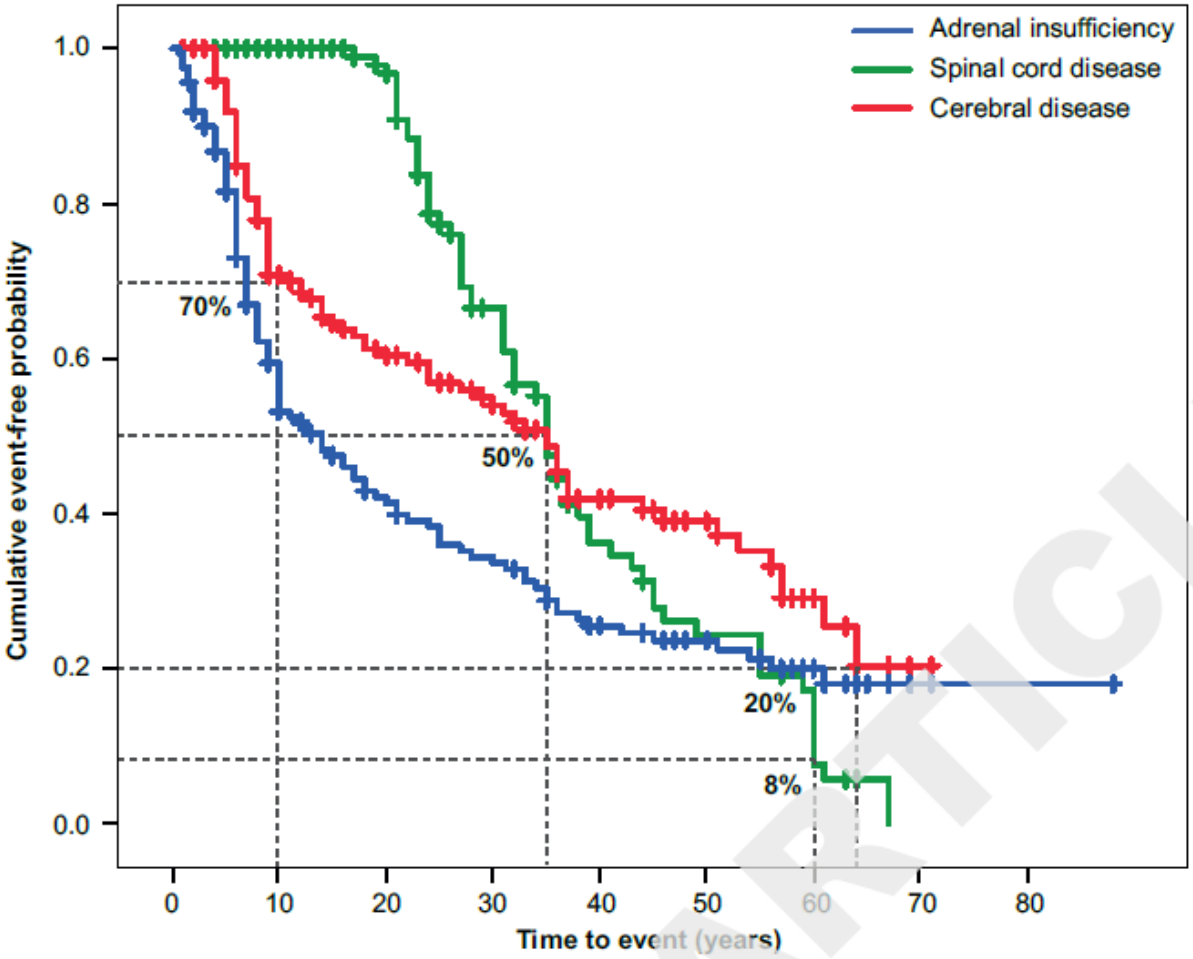
Outcome measure	Baseline	Follow-up	Change
EDSS	6.0 (0–7.0)	6.0 (2.0–7.0)	0.34 (0.03 to 0.65)
SSPROM	79.12 ± 10.67	76.34 ± 12.49	−2.78 (−4.93 to −0.63)
Timed up-and-go, s	7.99 ± 3.09	8.80 ± 3.50	0.82 (0.08 to 1.55)
6-minute walk test, m	429.0 (202.0–695.0)	400.5 (260.5–676.0)	−19.67 (−35.4 to −3.9)
mJOA	13.00 (12–18)	14.00 (10–18)	−0.24 (−0.69 to 0.21)
ALDS	88.65 (49.70–89.47)	88.65 (39.58–89.47)	0.48 (−2.09 to 3.06)
ICIQ-MLUTS	17.04 ± 8.87	17.17 ± 9.31	0.13 (−1.71 to 1.97)
SF-36 physical component	−1.43 (−4.95–0.47)	−1.65 (−5.29–0.71)	0.00 (−0.34 to 0.34)

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

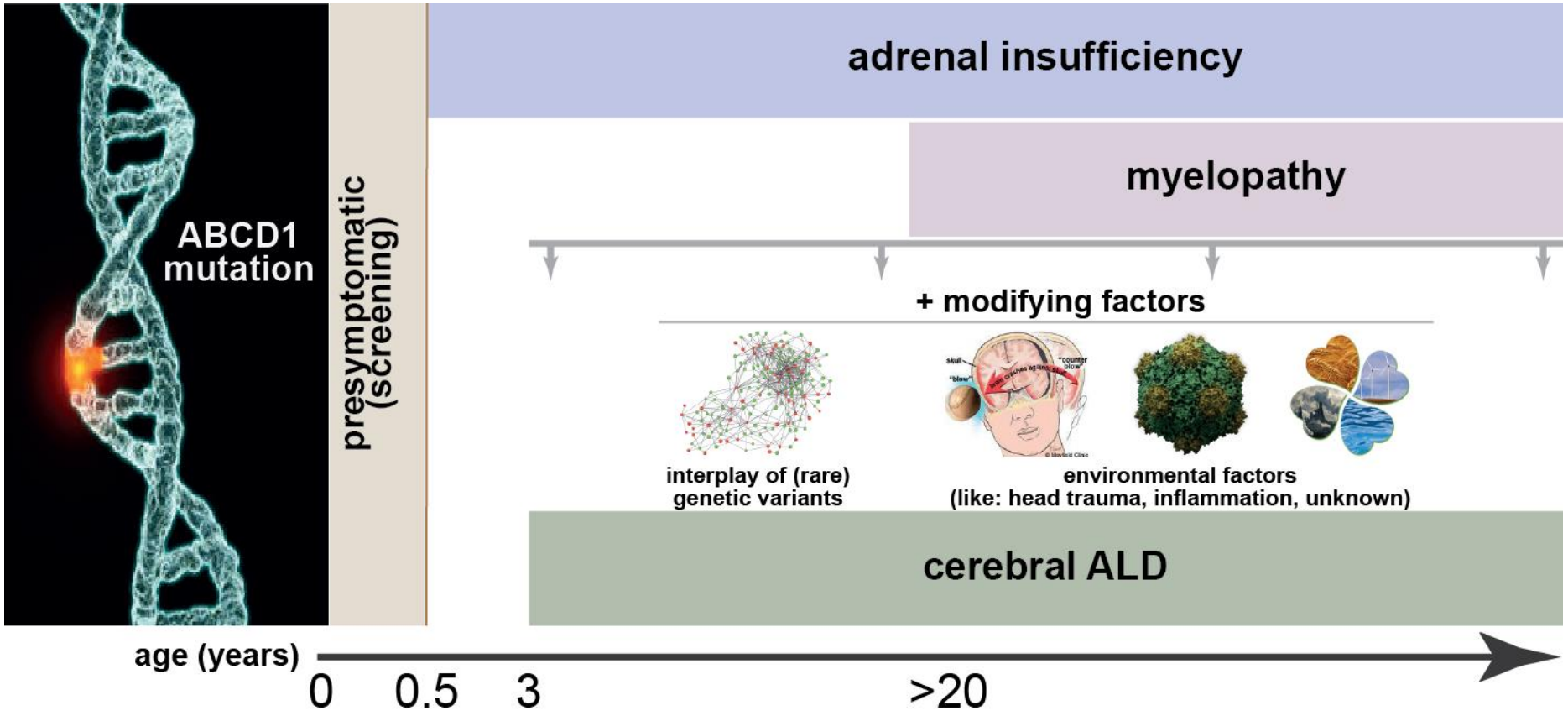
Huffnagel et al, Brain, 2019

Clinical features



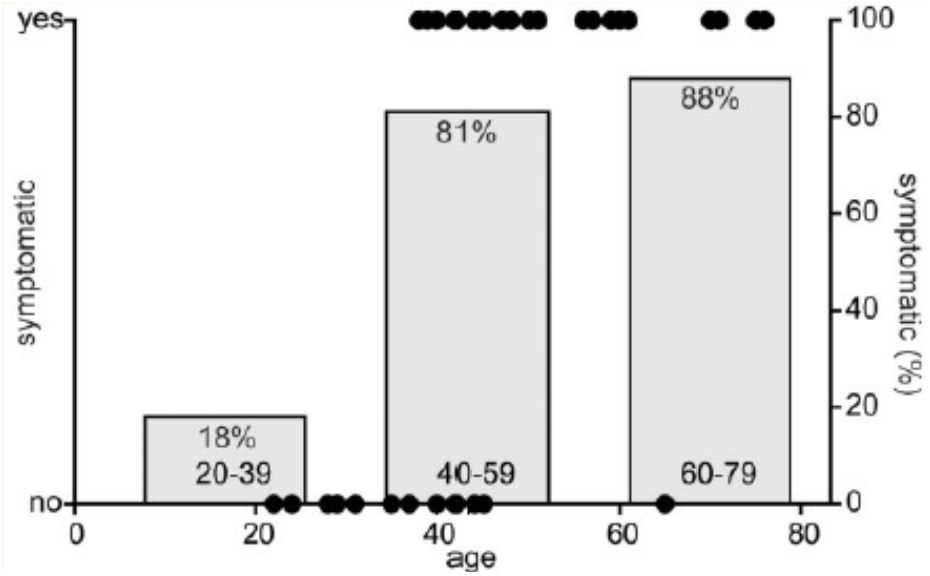
Huffnagel et al, JCEM, 2019

Clinical features



Kemp et al, Nature Reviews Endo, 2016

Clinical features



- In women age of onset is later
- In women progression is slower (over decades)
- Adrenal failure and cerebral ALD are very rare

Engelen et al, Brain, 2014

Clinical features

Table 5 Progression rates

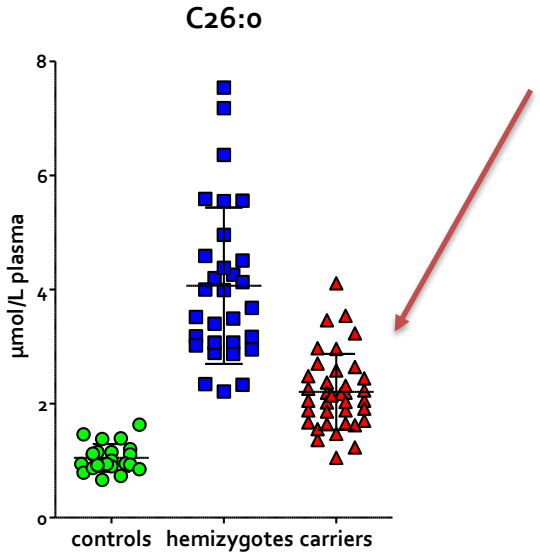
	N	Clinical progression	Stable score	Improvement score	Baseline (range)	Follow-up (range)
EDSS	32	21	11	0	2.75 (0–6)	3.5 (1.5–6)
ALDS	34	10	17	7	89.47 (71.92–89.47)	89.47 (71.92–89.47)
SF-36: PF	34	19	1	14	0.22 (−2.66–1.16)	−0.07 (−2.86–1.26)
SF-36: PCS	34	21	0	13	50.11 (17.26–62.36)	49.16 (16.67–64.72)

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

Huffnagel et al, OJRD, 2019

Diagnosis

- In men: plasma VLCFA (C26:0 and C26:0/C22:0 ratio).
- Confirmation by *ABCD1* mutation analysis

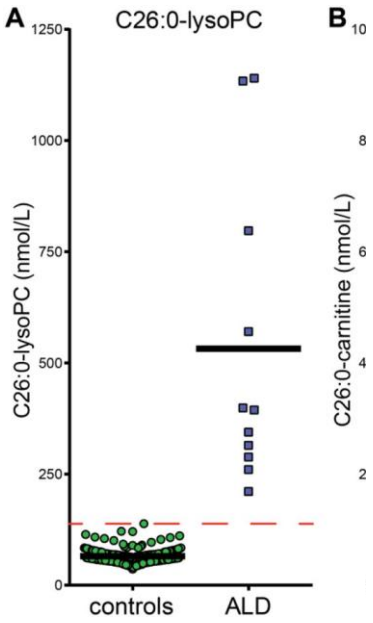


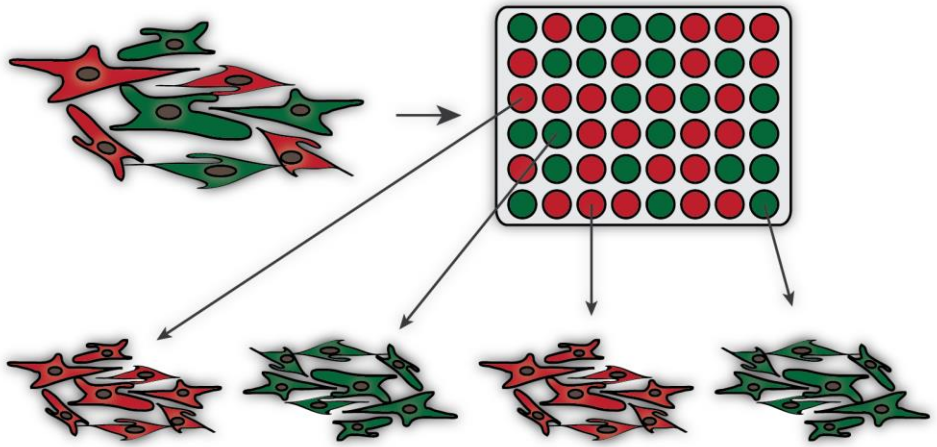
Diagnosis

- In women: plasma VLCFA (C26:0 and C26:0/C22:0 ratio) normal in 15%!

- *ABCD1* mutation analysis: however if VUS and VLCFA normal?

Diagnosis





C26:0-lysoPC
Male relatives with same VUS or mutation in *ABCD1*
Functional tests

Huffnagel et al, Mol Genet Metab, 2017
Schackmann et al, Mol Genet Metab, 2017

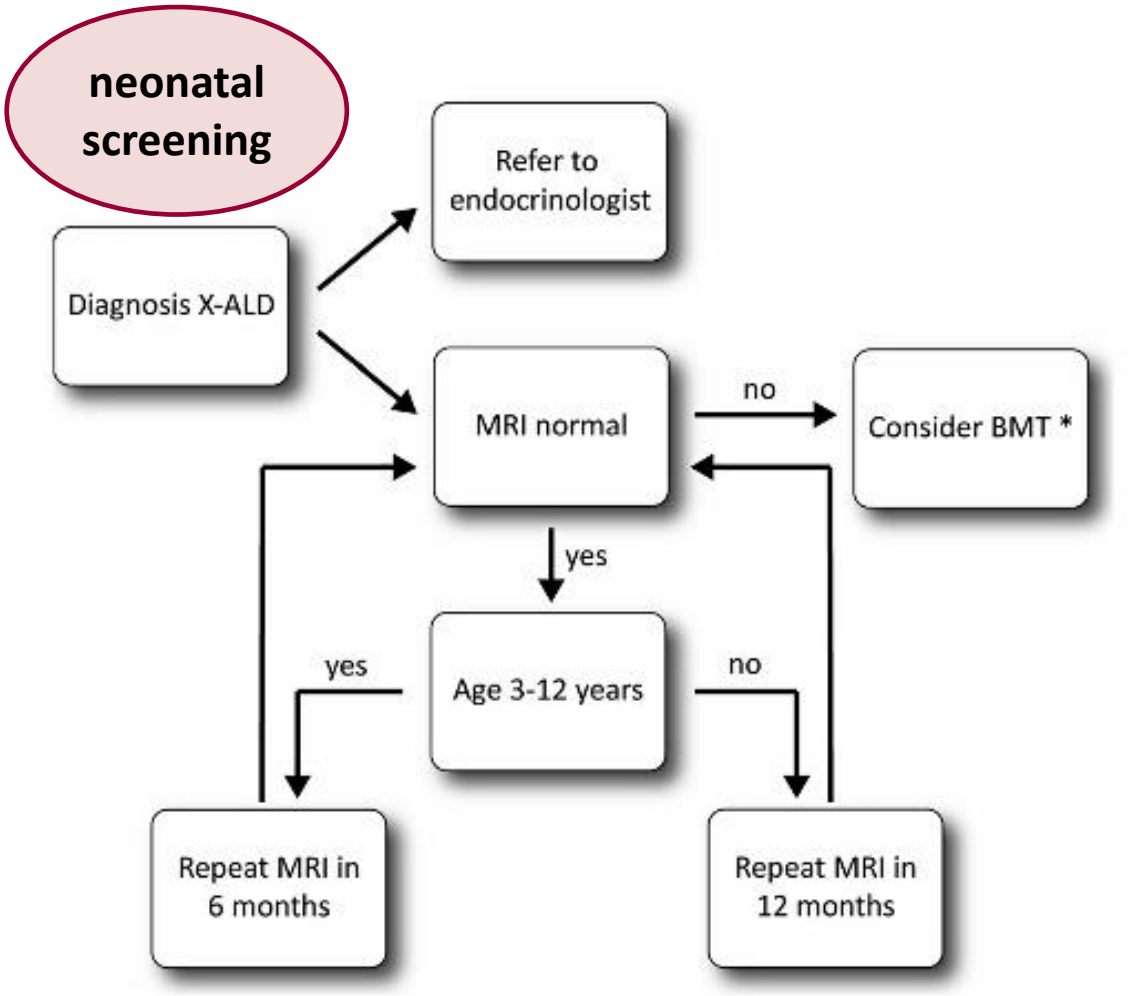
Diagnosis

- Newborn screening is implemented in part of the U.S., implementation study will start in the Netherlands

- Only boys in NL! See http://www.scanstudie.nl

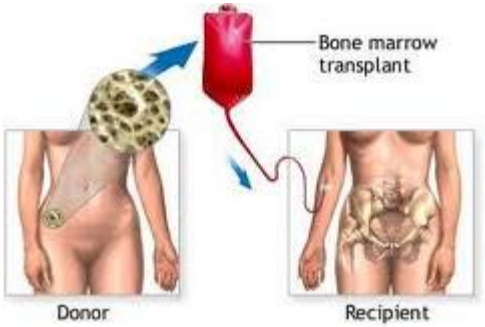
- Follow-up from early age

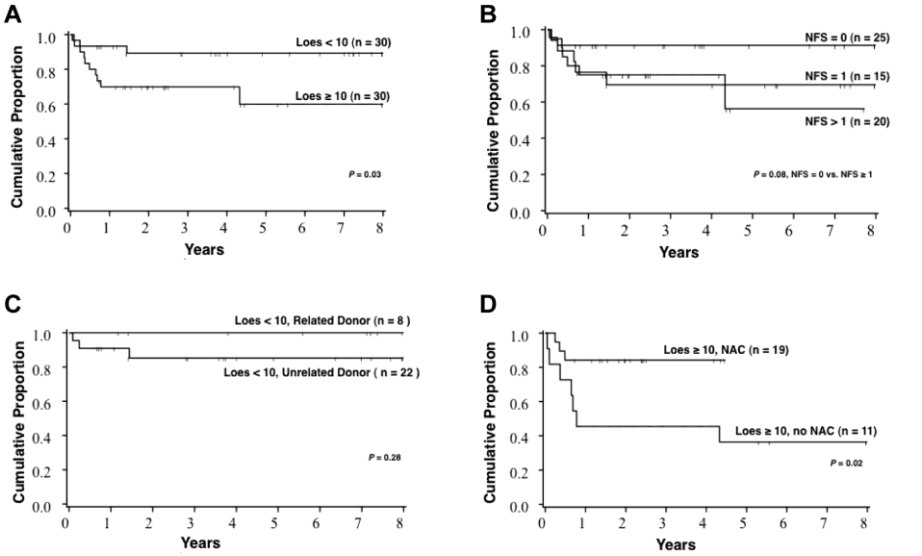
Follow-up and treatment



Engelen et al, OJRD, 2012

Follow-up and treatment





Survival estimates after HCT based on various patient and HCT characteristics. (A) All patients in the cohort stratified by Loes score at the time c

Prognosis (survival) poor if Loes score > 9
Modern insights: cognitive outcome poor if Loes score > 4.5

Miller et al, Blood, 2011
Pierpont, JAMA, 2017

Follow-up and treatment

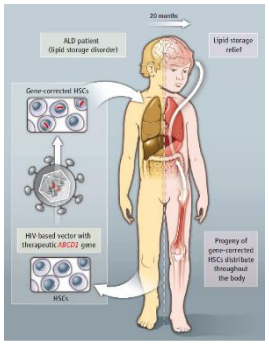
Table 1 Summary of clinical characteristics of the five patients

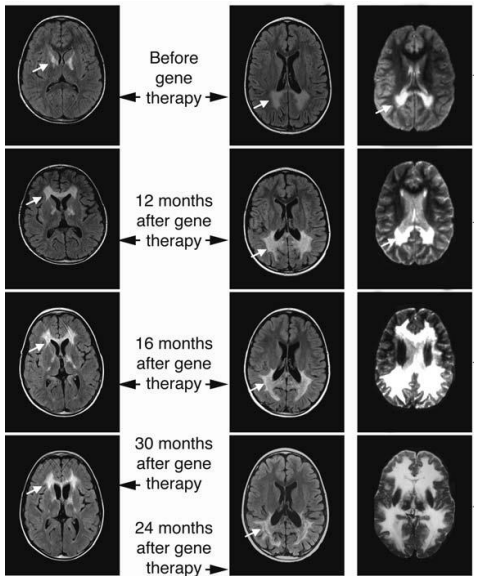
Transplantation					VLCFA pre-Tx		VLCFA post-Tx		Examination			
Patient	Age Tx	Donor	Chimerism	GvH	C26:0	C26/C22	C26:0	C26/C22	Age	AI	myelopathy	Mutation
A	4	sib	100 %	No	2.26	0.06	2.48	0.05	23	+	+	p.Ile657del
B	6	MUD	n.a.	No	2.56	0.08	1.6	0.08	18	+	−	not known
C1	9	MUD	100 %	No	n.a.	n.a.	0.77	0.02	25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

Follow-up and treatment





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Florian Eichler, M.D., Christine Duncan, M.D., Patricia L. Musolino, M.D., Ph.D., Paul J. Orchard, M.D., Satiro De Oliveira, M.D., Adrian J. Thrasher, M.D., Myriam Armant, Ph.D., Colleen Dansereau, M.S.N., R.N., Troy C. Lund, M.D., Weston P. Miller, M.D., Gerald V. Raymond, M.D., Raman Sankar, M.D., Ami J. Shah, M.D., Caroline Sevin, M.D., Ph.D., H. Bobby Gaspar, M.D., Paul Gissen, M.D., Hernan Amartino, M.D., Drago Bratkovic, M.D., Nicholas J.C. Smith, M.D., Asif M. Paker, M.D., Esther Shamir, M.P.H., Tara O'Meara, B.S., David Davidson, M.D., Patrick Aubourg, M.D., and David A. Williams, M.D.

No GVHD with autologous HCT after lentiviral gene therapy.

Follow-up and treatment

Only supportive care for the myelopathy of adulthood in men and women

Suppletion of hydrocortisone (and sometimes fludrocortisone) by endocrinologist

Progression over time (over years for men, decades for women)

Many trials planned (and 1 ongoing) for disease modifying treatments

Engelen et al, OJRD, 2012

Institutional Logo,
‚Speakers' picture or
disease related picture

Key Points /Conclusions

- Adrenoleukodystrophy is a not so rare neurometabolic disorder that is partially treatable!

- Women are patients and not carriers!

Suggested reading: Kemp et al, Nature Reviews Endocrinology, 2016.

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)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

DG ‚Leukodystrophies'
17 March 2020

European Reference Network | Neurological Diseases (ERN-RND)

This webinar has been supported by ERN-RND , which is partly co-funded by the European Union within the framework of the Third Health Programme "ERN-2016 - Framework Partnership Agreement 2017-2021."

Joint webinar series

THANK YOU

Next Webinar: 'Recognizing atypical parkinsonism'

14. April 2020, 15-16h CET