CLINICAL PRESENTATIONS OF PEROXISOMAL DISORDERS

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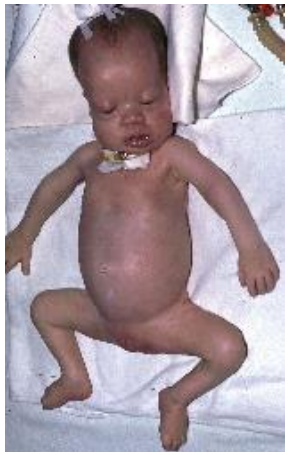
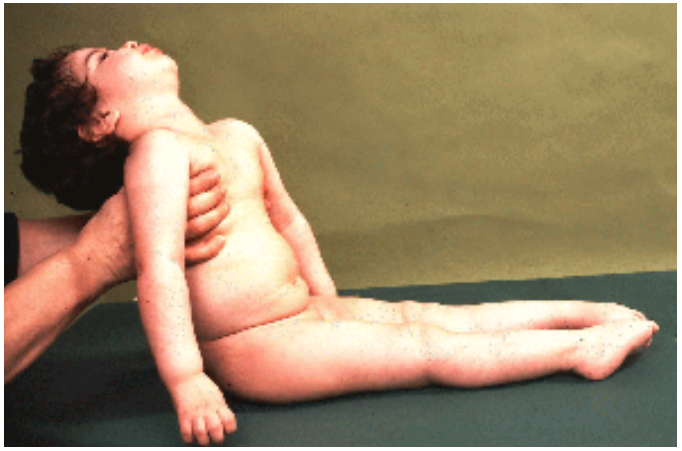
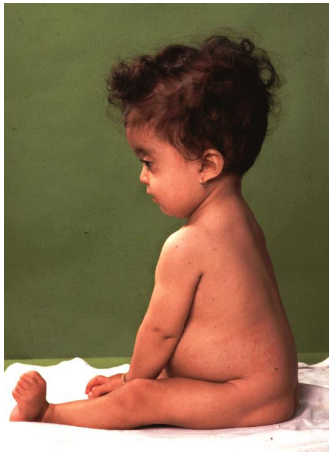
Clinical diversity of genetic peroxisomal disorders



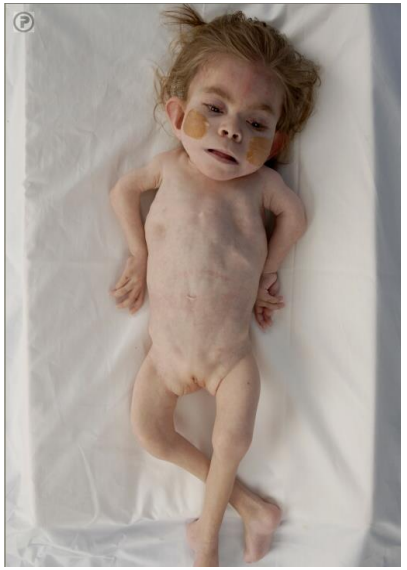
Zellweger syndrome



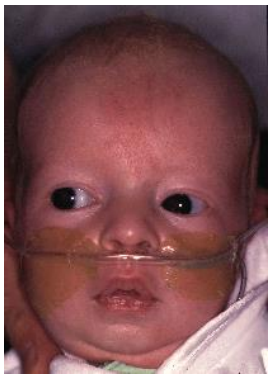
Neonatal adrenoleukodystrophy



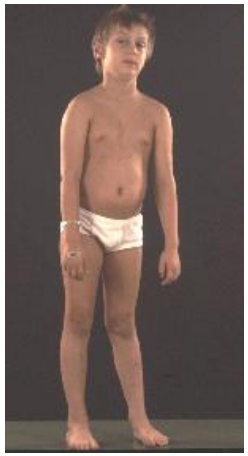
Infantile Refsum disease



Rhizomelic chondrodysplasia punctata



Isolated peroxisomal β-oxidation defect



X-ALD

X- AMN

And many more ……

CLASSIFICATION OF PEROXISOMAL DISORDERS

1. **PEROXISOME BIOGENESIS DISORDERS**
   - **Zellweger syndrome**
   - **Neonatal adrenoleukodystrophy**
   - **Infantile Refsum disease**

   Zellweger spectrum disorders

   - **Rhizomelic chondrodysplasia punctata**

   RCDP spectrum disorders

2. **SINGLE ENZYME DEFICIENCIES**
   - **Disorders of ether phospholipid biosynthesis (RCDP type 2/3)**
   - **Disorders of peroxisomal ß-oxidation**
     - *** X-linked adrenoleukodystrophy**
     - *** Acyl-CoA oxidase deficiency**
     - *** D-bifunctional protein deficiency**
     - *** 2-Methylacyl-CoA racemase deficiency**
     - *** SCPx deficiency**
   - **Disorders of peroxisomal fatty acid-α-oxidation (Refsum)**

THE CLINICAL SPECTRUM OF

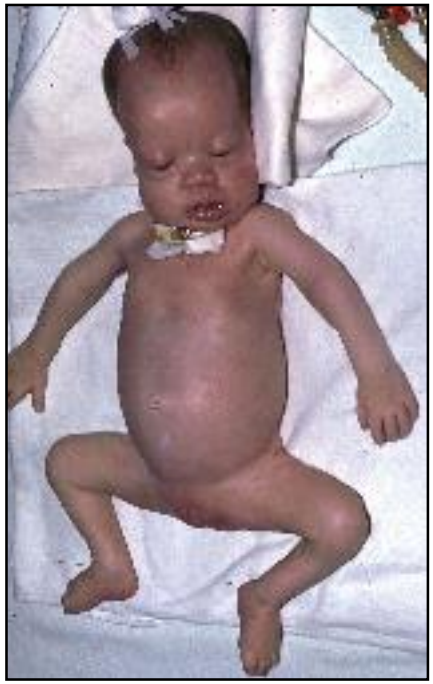
Zellweger Spectrum Disorders
+ Acyl-CoA oxidase deficiency
D-Bifunctional Protein deficiency

Rhizomelic Chondrodysplasia Punctata Spectrum
Type 1, 2, 3
Type 4, 5

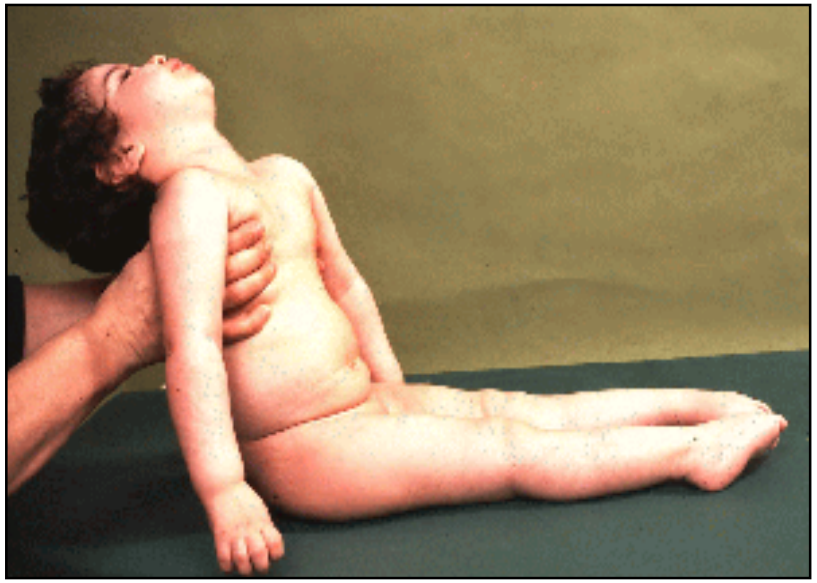
X-Linked Adrenoleukodystrophy Spectrum
Adrenocortical insufficiency
Progressive myelopathy and peripheral neuropathy (male and female)
Cerebral adrenoleukodystrophy

Zellweger spectrum disorders

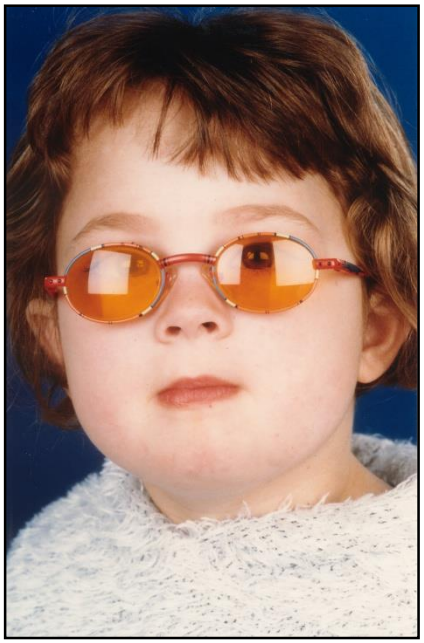
Peroxisome biogenesis disorders
“generalized peroxisomal disorders”



Zellweger syndrome



Neonatal adrenoleukodystrophy



Infantile Refsum disease

Phenotype variants with overlapping clinical signs

ZSD: Characterized by the absence of functional peroxisomes and a deficiency of multiple peroxisomal metabolic pathways

- **Plasma**
  - ↑ VLCFAs
  - ↑ Pristanic acid and phytanic acid (diet and age dependent)
  - ↑ DHCA and THCA (in most but not all patients)
  - ↑ Pipecolic acid
- **Erythrocytes**
  - ↓ Plasmologens
- **Skin fibroblasts**
  - ↓ α and ß-oxidation
  - ↑ VLCFAs
  - ↓ DHAPAT activity
  - IF α-catalase: absence of import-competent peroxisomes

ZELLWEGER SPECTRUM DISORDERS
CLINICAL PRESENTATION

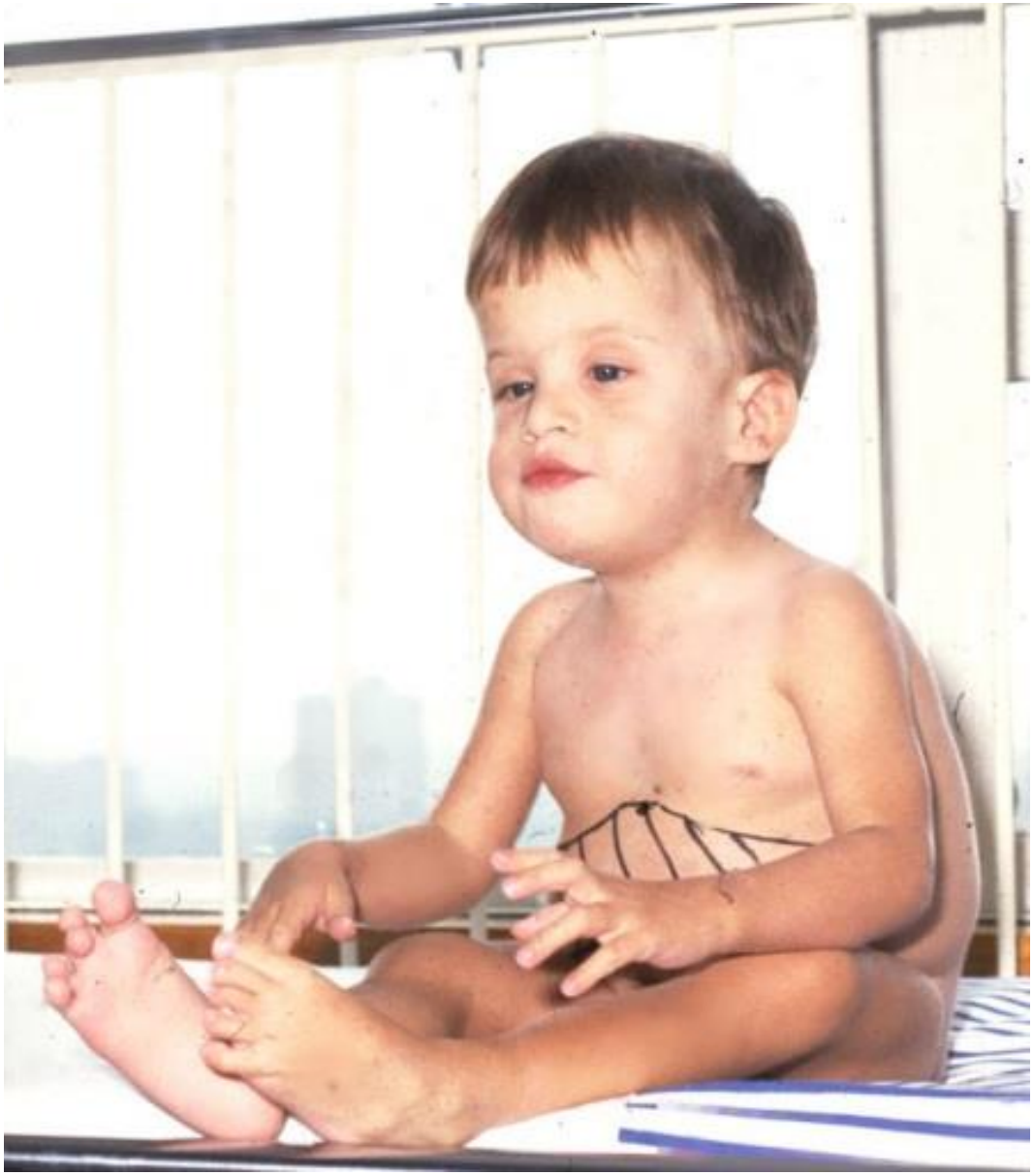
Most frequent combination

- **Cognitive and motor dysfunction**
- **Retinopathy**
- **Hearing defect**
- **Liver dysfunction**

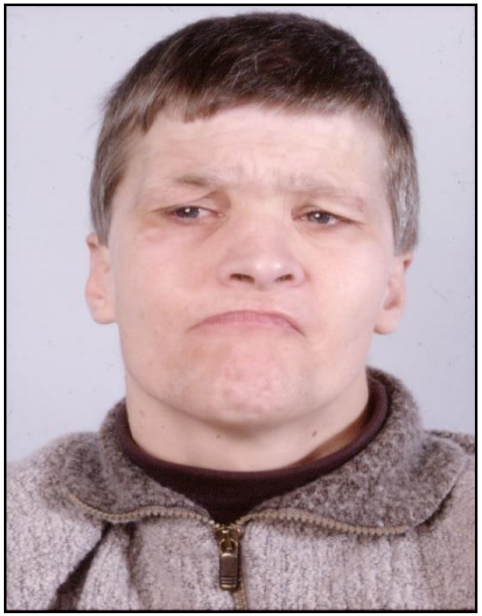
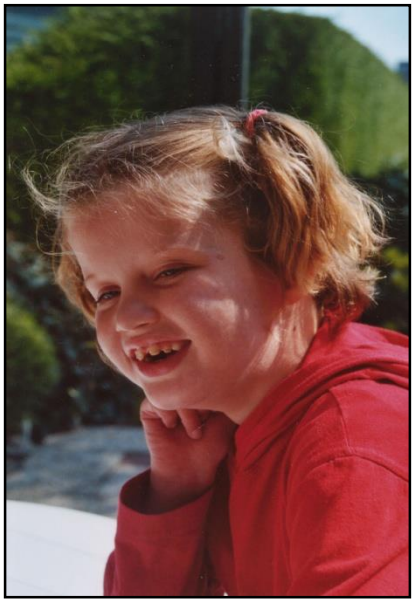
- **Visual impairment**
- **Very mild cognitive impairment**

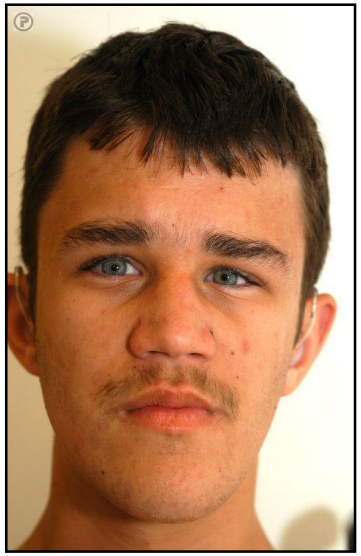
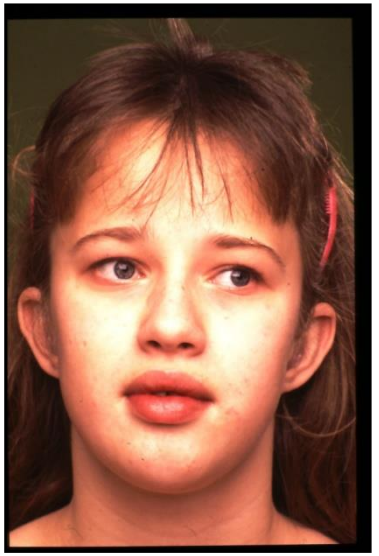
- **Ataxia**
- **Polyneuropathy**

ZSD – Liver phenotype



Zellweger spectrum disorders – Mild phenotype

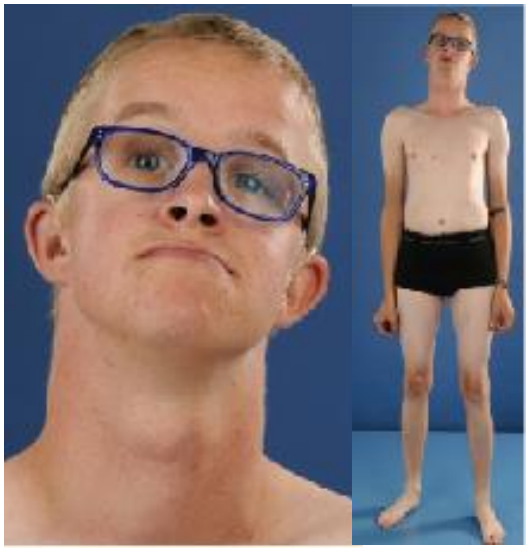



ZSD
Progressive neurological manifestations

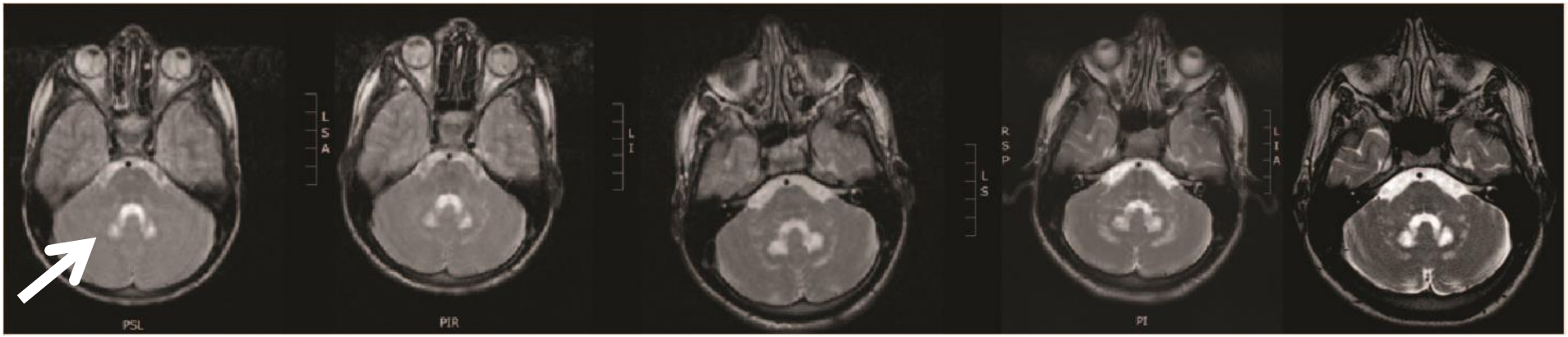
3 years

14 years

16 years

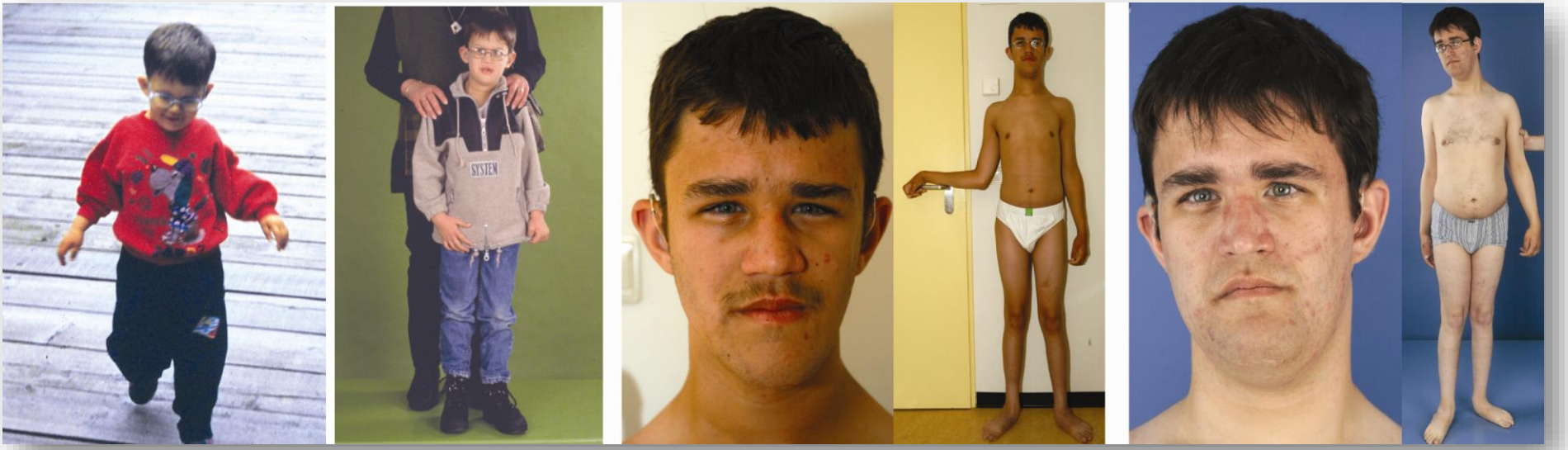


22 years

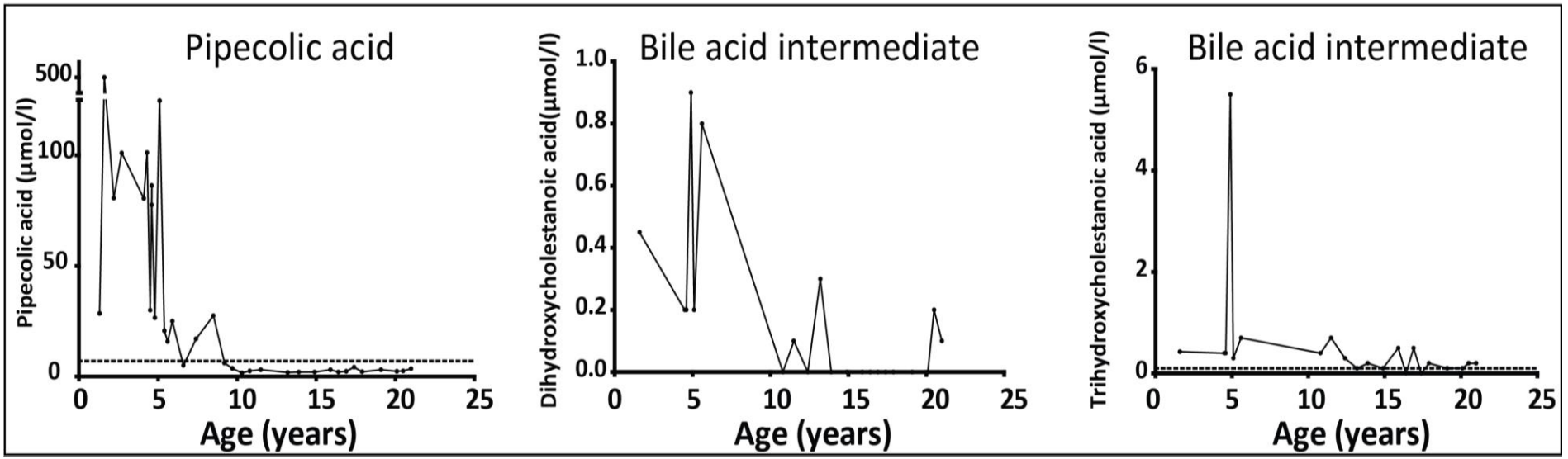


11 years 14 years 17 years 18 years 22 years

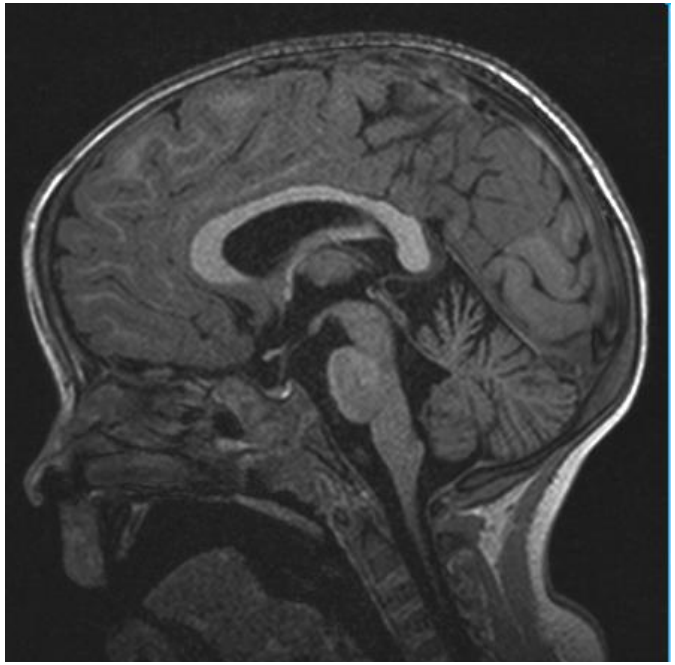
ZSD
Progressive neurological manifestations
Normalization of biochemical abnormalities

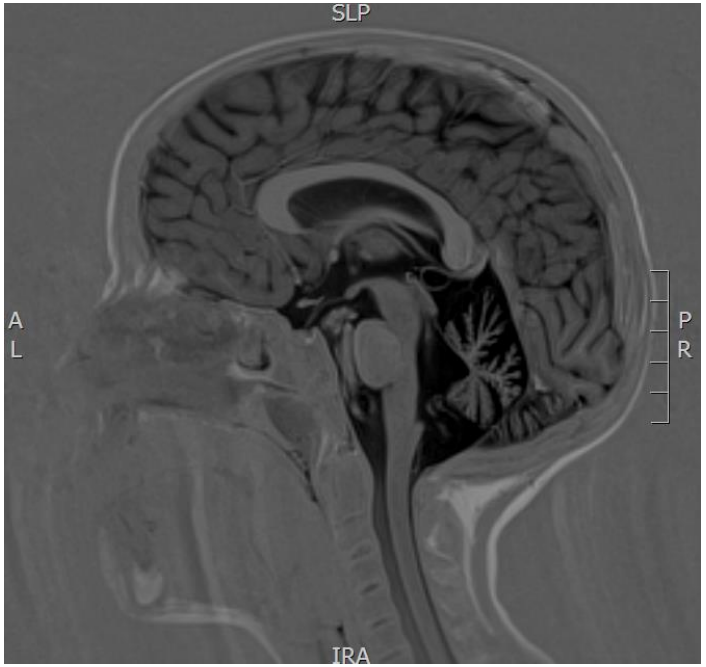


3 years 7 years 15 years 23 years



Zellweger spectrum disorder – Ataxia



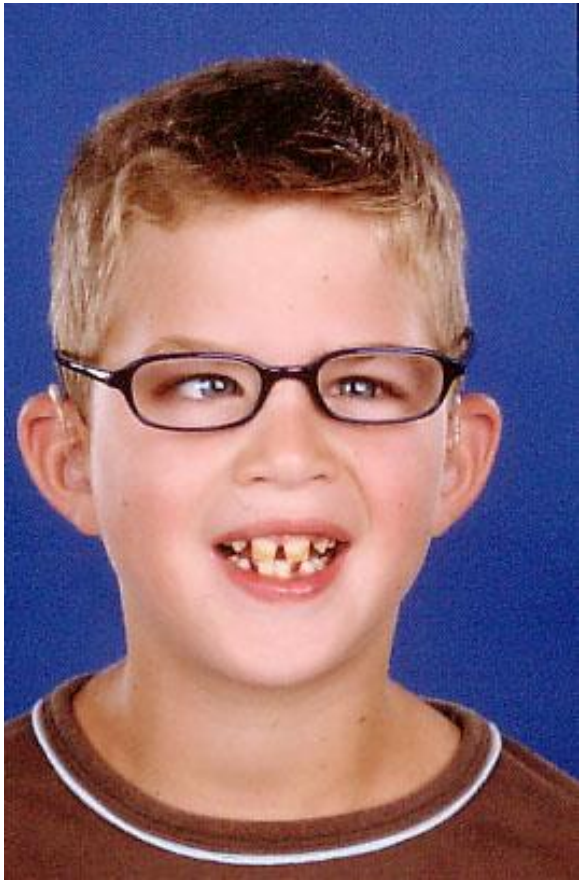


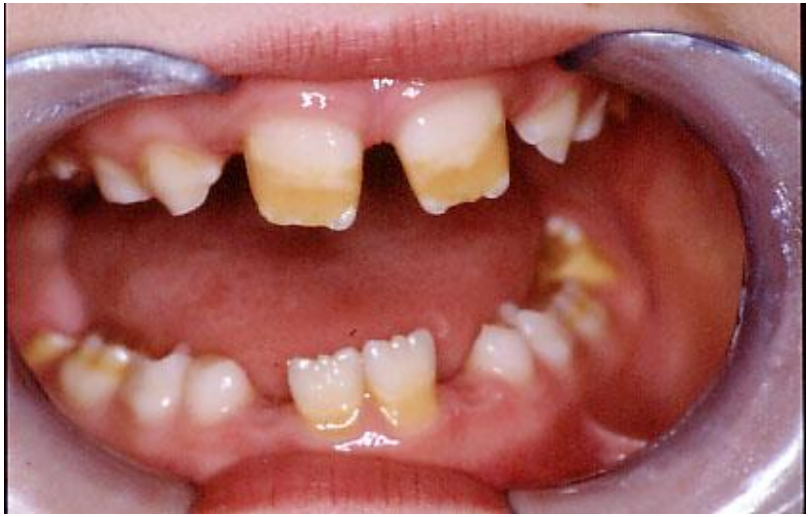
5 yrs

8 yrs

- T_1-weighted mid sagittal MRI
- Progressive atrophy of the vermis

6 yrs





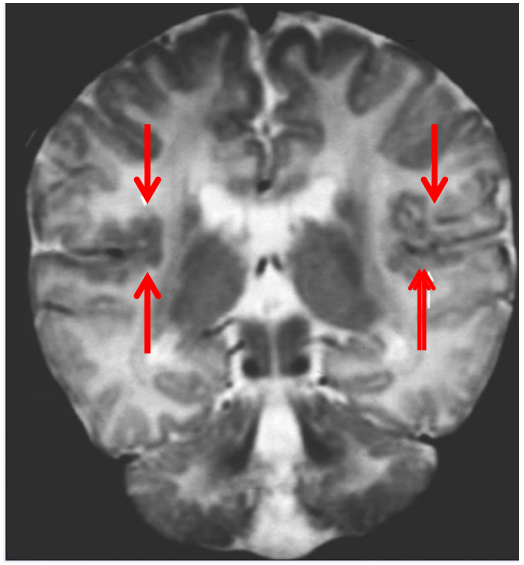
• D-Bifunctional protein deficiency

- **Most frequent single enzyme defect that mimics Zellweger spectrum phenotypes**

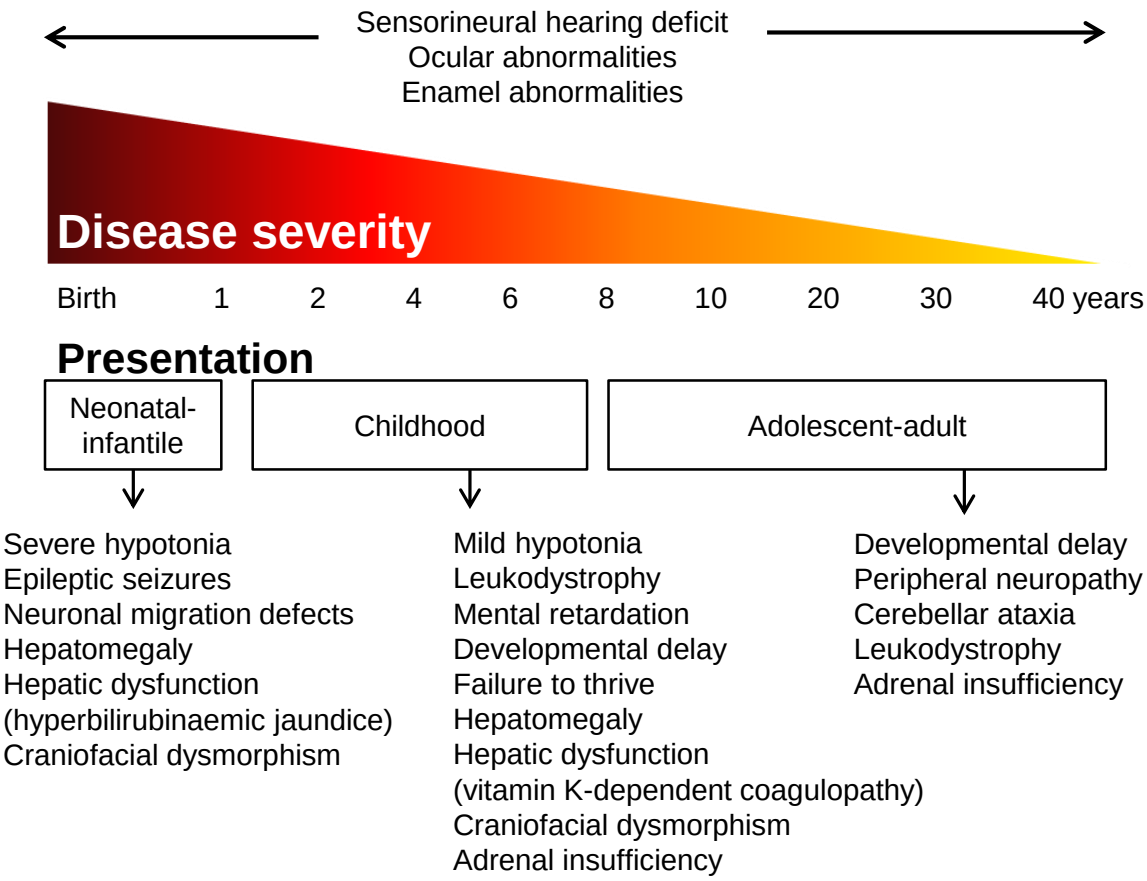
- **Differs fundamentally from peroxisome assembly disorders – single enzyme defect, peroxisomes intact**

D-bifunctional protein deficiency

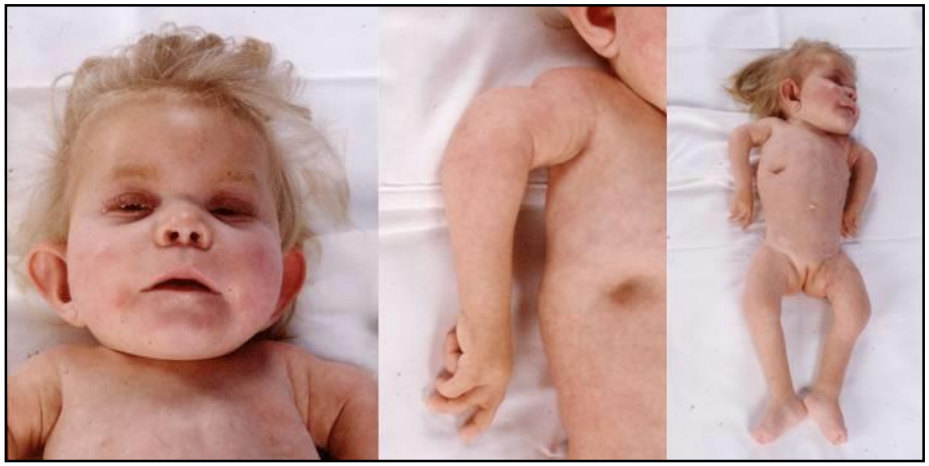
- Early onset clinical symptoms
- Often neonatal hypotonia / seizures
- Severe developmental delay and peripheral neuropathy
- Often neuronal migration abnormality and cerebellar pathology (88%)



T_2-weighted MRI, perisylvian polymicrogyria

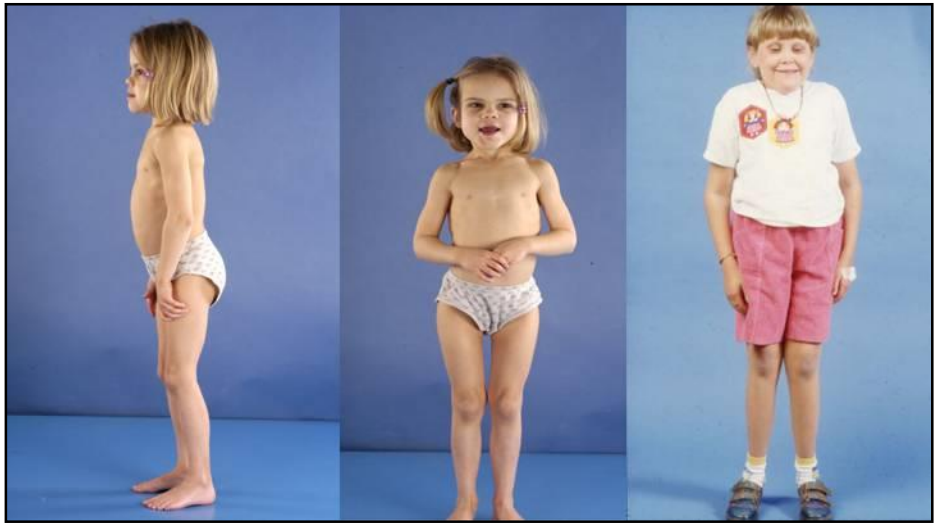

Sensorineural hearing deficit
Ocular abnormalities
Enamel abnormalities
Disease severity
Birth
1
2
4
6
8
10
20
30
40 years
Presentation
Neonatal-infantile
Childhood
Adolescent-adult
Severe hypotonia
Epileptic seizures
Neuronal migration defects
Hepatomegaly
Hepatic dysfunction
(hyperbilirubinaemic jaundice)
Craniofacial dysmorphism
Mild hypotonia
Leukodystrophy
Mental retardation
Developmental delay
Failure to thrive
Hepatomegaly
Hepatic dysfunction
(vitamin K-dependent coagulopathy)
Craniofacial dysmorphism
Adrenal insufficiency
Developmental delay
Peripheral neuropathy
Cerebellar ataxia
Leukodystrophy
Adrenal insufficiency

Rhizomelic chondrodysplasia punctata spectrum



Severe type

- NEAR ABSENCE OF DEVELOPMENT
- PLASMALOGENS < 5% IN RBC

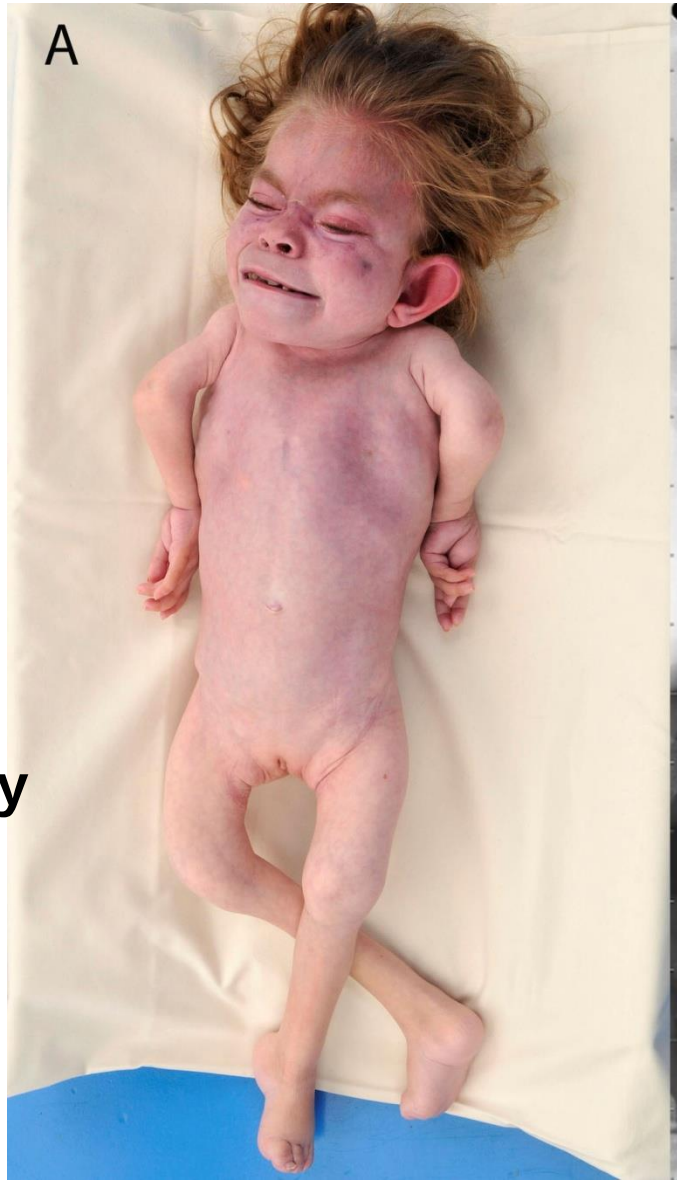


Milder type

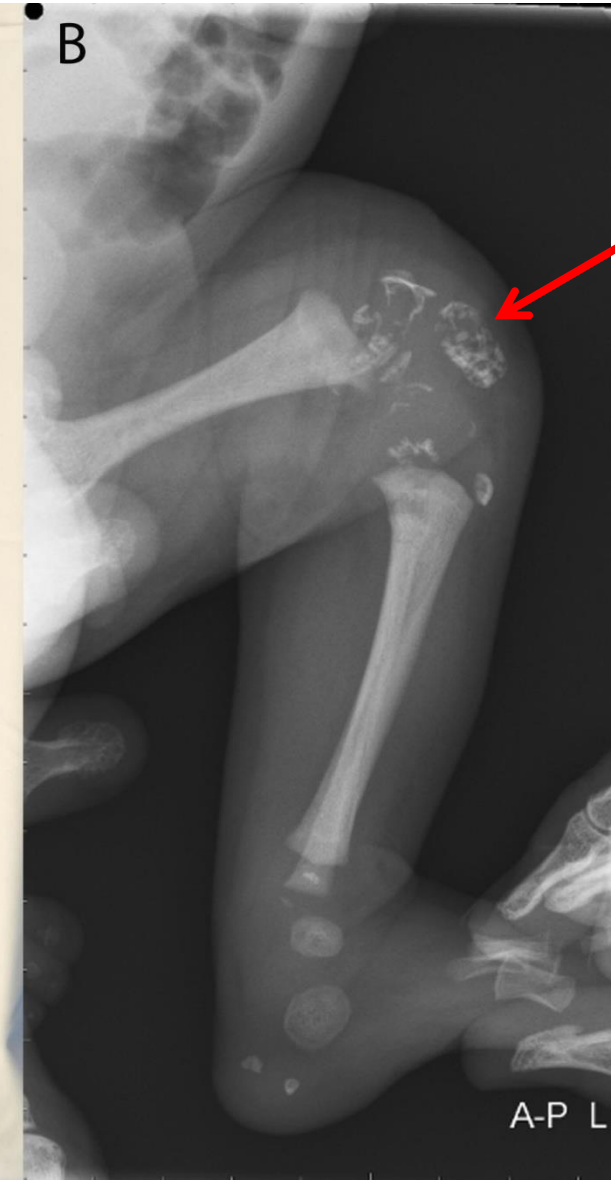
- UNSUPPORTED WALKING
- TELEGRAM STYLE SENTENCES
- PLASMALOGENS > 35% IN RBC

RCDP

- **Growth retardation, rhizomelia**
- **Cataracts**
- **Developmental delay**
- **PLASMALOGENS ↓**



11 years



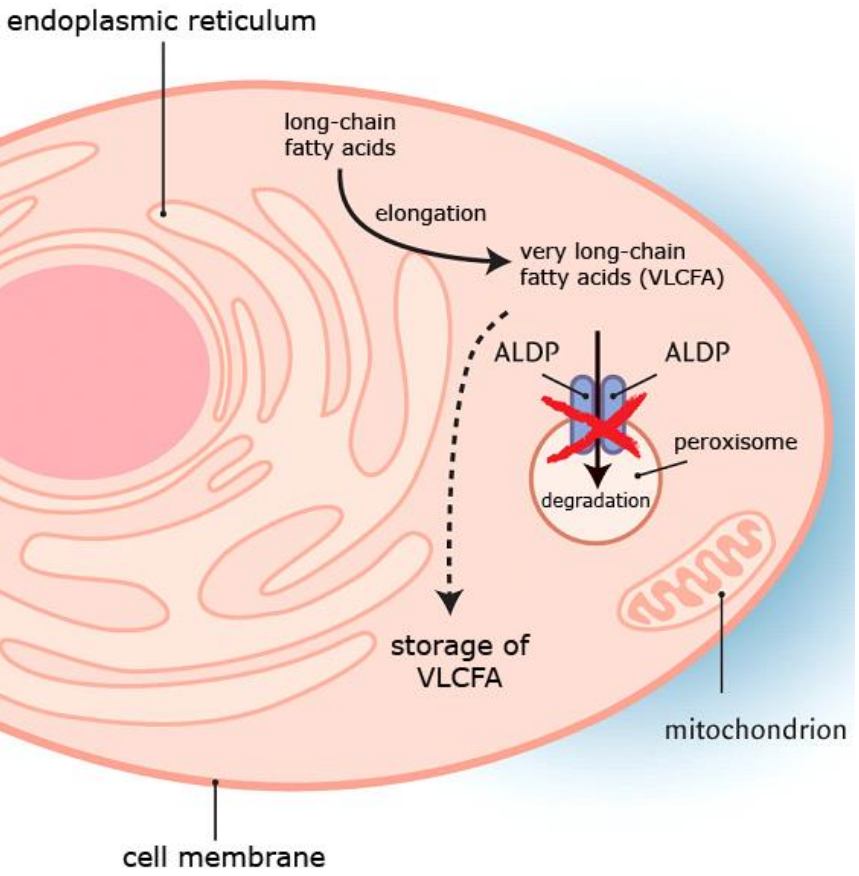
1 day old
punctate stippling

Rhizomelic chondrodysplasia punctata type I: severe type

Summary

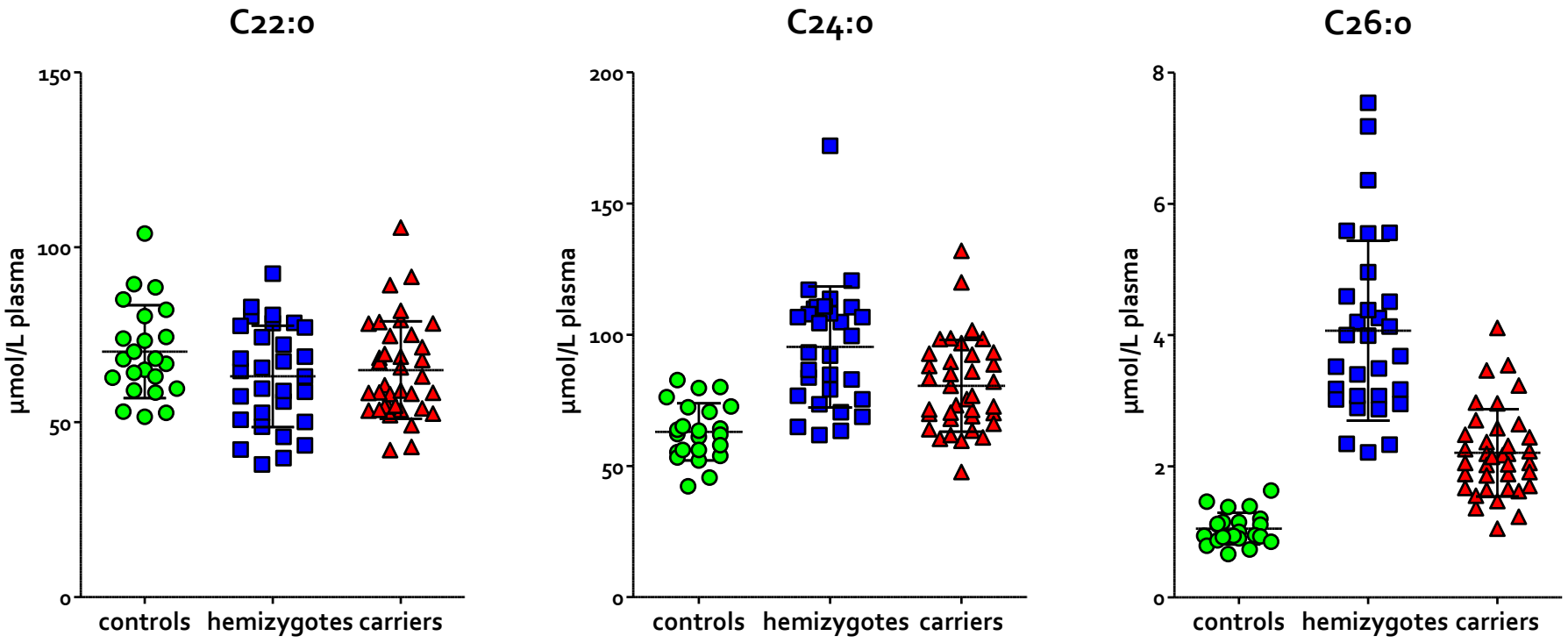
- Variability in **Zellweger** spectrum disorders and **RCDP** spectrum disorders is much larger than generally appreciated
- Biochemical abnormalities can fluctuate to normalize with time in Zellweger spectrum disorders
- Patients present a (slowly) progressvie disease course

Introduction: genetics and biochemistry of ALD



- Peroxisomal metabolic disease
- Mutation in *ABCD1* gene (X-linked)
- Accumulation of C26:0
- >10.000 patients in Europe
- Clinical spectrum
- Men and women affected

Introduction: genetics and biochemistry of ALD



Introduction: clinical features of ALD

1910

Aus dem pathol.-anatom. Universitätsinstitute (Vorstand: Hofr. Prof. Weichselbaum) und dem Karolinen-Kinderspitale (dirig. Primararzt:

Die Encephalitis periaxialis diffusa

(nebst Bemerkungen über die Apraxie des Lidschlusses).

Von

Paul Schilder.

Mit 11 Textabbildungen.

(Eingegangen am 19. März 1924.)

Bronzekrankheit und sklerosierende Encephalomyelitis.

(Diffuse Sklerose.)

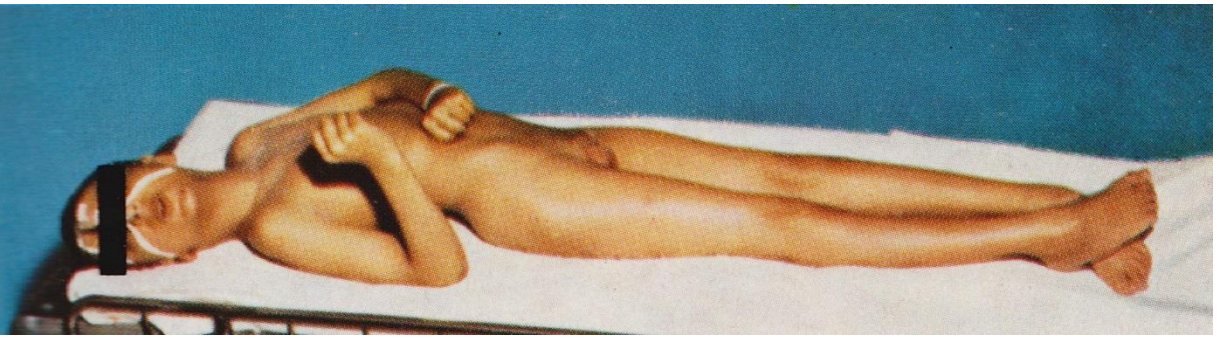
Von

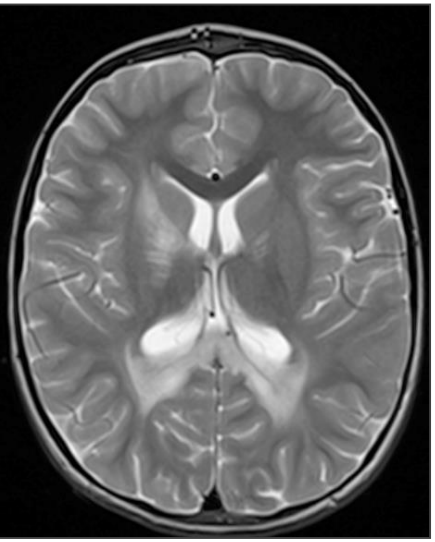
E. Siemerling und **H. G. Creutzfeldt.**

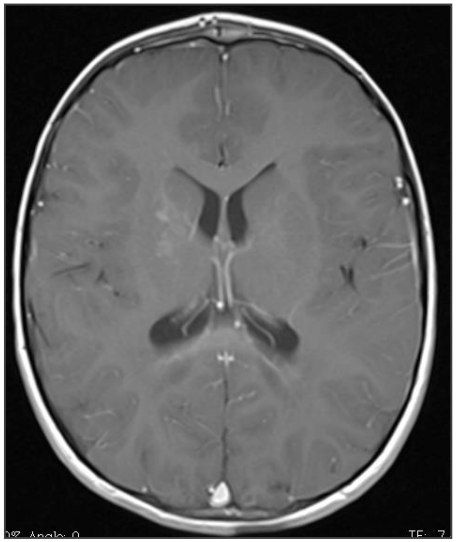
Mit 10 Textabbildungen.

(Eingegangen am 28. Dezember 1922.)

Introduction: Clinical features of ALD



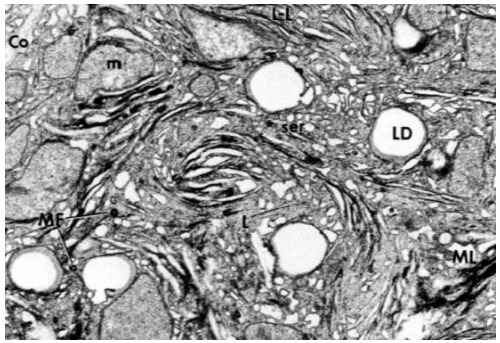




T2 T1 gadolinium

1972: inclusions in adrenal glands

1976: accumulation of VLCFA



Introduction: Clinical features of ALD

- > 80% of male patients develop adrenocortical failure < 18 years
- Often only glucorticoid deficient, in contrast to auto-immune Addison
- Often first symptom of X-ALD

Introduction: Clinical features of ALD

Reports of heridatery spastic paraperesis with adrenal failure

In the 1970s identified as ALD by two different groups

J. Neurol. 213, 237—250 (1976)

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

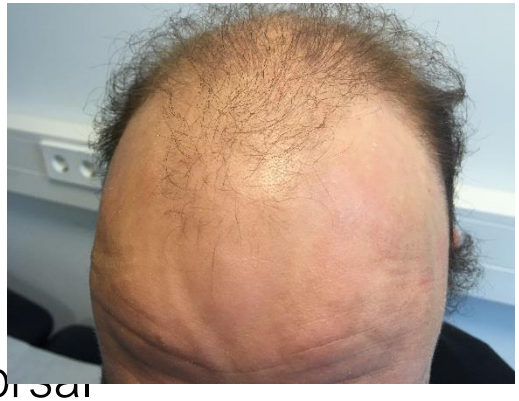
H. Budka, E. Sluga, and W.-D. Heiss

Neurological Institute and Neurological Clinic, University of Vienna

Received May 13, 1976

Extension of the phenotype thanks to the biomarker!

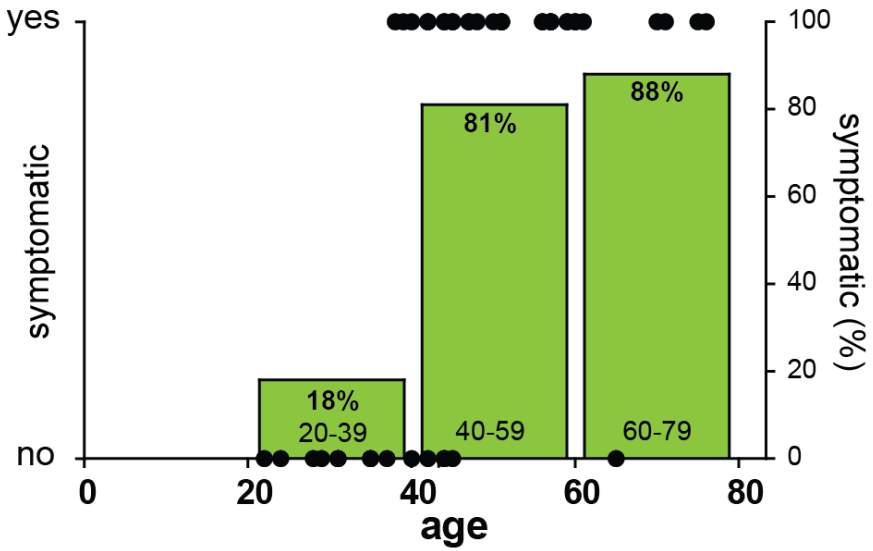
Introduction: Clinical features of ALD



- Onset variable but usually in the 3rd decade
- Thin hair, early balding
- Slowly progressive myelopathy with prominent dorsal column and spinothalamic tract involvement
- Neurophysiological testing: (axonal) peripheral neuropathy, clinically less relevant
- Arms are not affected

Introduction: Clinical features of ALD

Women with ALD

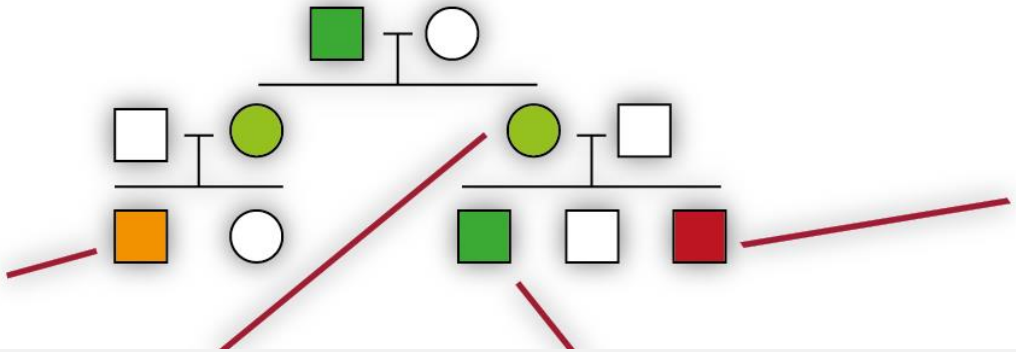


Myelopathy (prominent fecal incontinence)
Peripheral neuropathy (clinically less relevant)
Symptomatic status highly age dependent

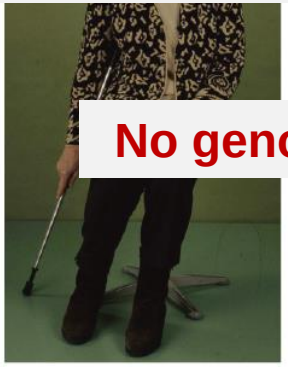
Women are patients!

Clinical spectrum of ALD: “classic view”

adrenal insufficiency



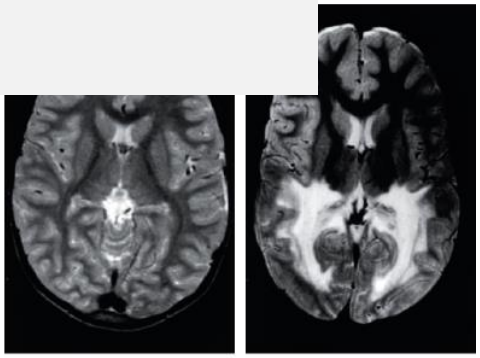
Is this true?
Do we know natural history?



symptomatic carrier

adrenomyeloneuropathy

No genotype-phenotype correlation!



childhood cerebral ALD

Cerebral ALD is not rare in adulthood

Frequent occurrence of cerebral demyelination in adrenomyeloneuropathy

Marlijn de Beer, MD
Marc Engelen, MD, PhD
Björn M. van Geel, MD, PhD

ABSTRACT

Objective: To study the frequency of additional cerebral demyelination in Dutch patients with adrenomyeloneuropathy (AMN).

Methods: Consecutive patients with AMN from the Dutch X-linked adrenoleukodystrophy cohort

Women with ALD develop symptoms

doi:10.1093/brain/awt361 Brain 2014: 137; 693–706 | 693

BRAIN
A JOURNAL OF NEUROLOGY

X-linked adrenoleukodystrophy in women: a cross-sectional cohort study

Marc Engelen,[1,2] Mathieu Barbier,[3,*] Inge M. E. Dijkstra,[4] Remmelt Schür,[2] Rob M. A. de Bie,[1] Camiel Verhamme,[1] Marcel G. W. Dijkgraaf,[5] Patrick A. Aubourg,[3,6] Ronald J. A. Wanders,[4] Bjorn M. van Geel,[7] Marianne de Visser,[1] Bwee T. Poll-The[1,2] and Stephan Kemp[2,4]

>60 years: about 90% of women have symptoms

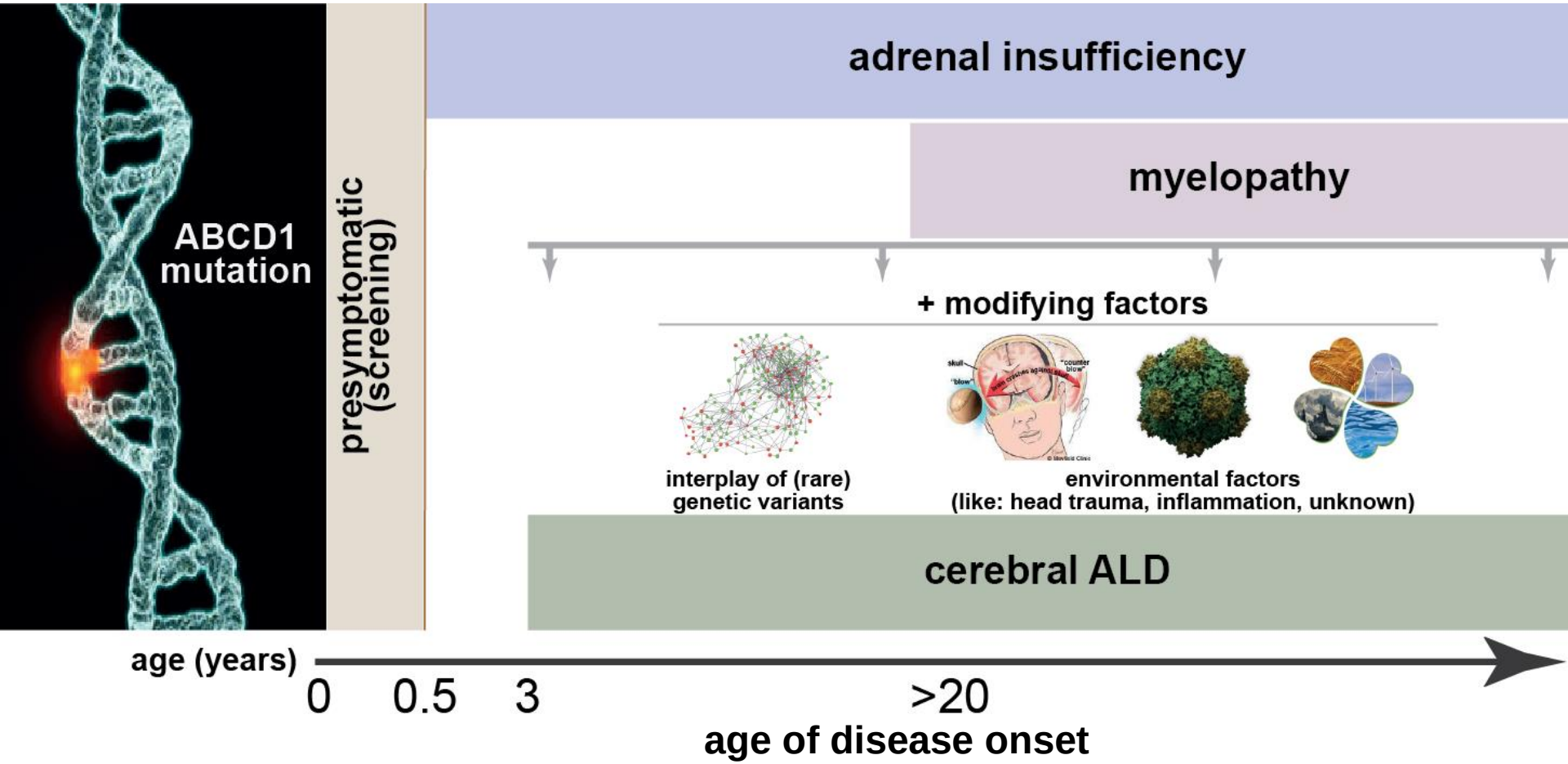
Men still develop myelopathy after succesful HSCT

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

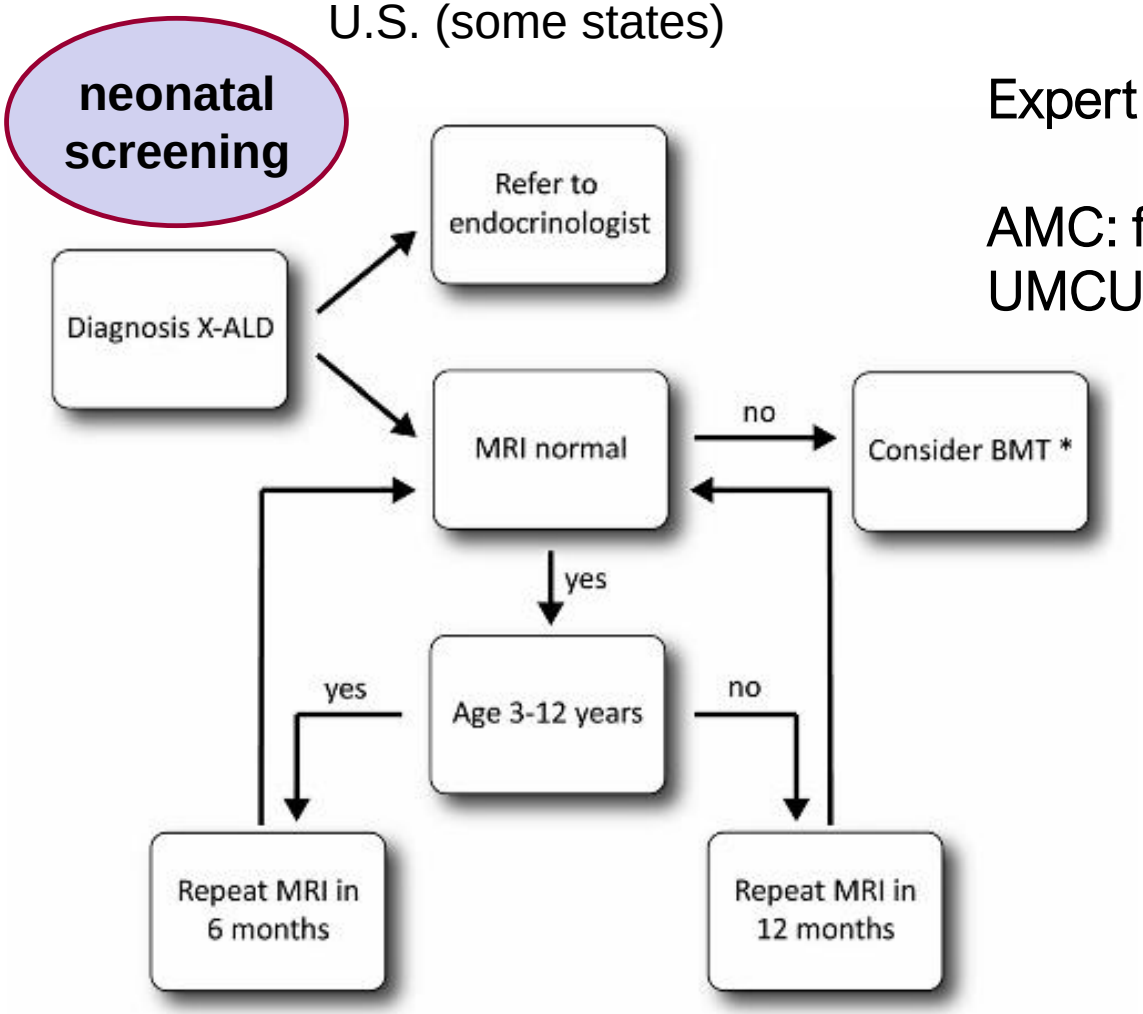
Attenuated?

Clinical spectrum of ALD: current view



Follow-up

U.S. (some states)



Expert centers

AMC: follow-up
UMCU: HSCT

Key clinical problems

- Clinical course unpredictable

  Intensive follow-up while not all men develop cerebral ALD

- Natural history not well known on quantitative outcomes

  Clinical trial readiness

- No curative treatment for the majority of patients

Medicijnstudie bij patienten met X-ALD

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Patients and parents