SSIEM 2007

Annual Symposium of the European Society on Inborn Errors of Metabolism

Hamburg, 4.9.2007 - 7.9.2007

ERNDIM Meeting on Diagnosis of Peroxisomal Disorders - Clinical Pointers

Jutta Gärtner

Georg August University Göttingen

Dept. of Pediatrics and Pediatric Neurology

Genetic Disorders of Peroxisomes

- **Multiple deficiencies - peroxisome biogenesis disorders (PBD)**
  - Zellweger syndrome spectrum (ZSS)
  - Rhizomelic chondrodysplasia punctata (RCDP)
- **Single function deficiencies**
  - peroxisomal ß-oxidation (D-bifunctional protein deficiency, ...)
  - X-linked adrenoleukodystrophy (X-ALD)
  - others

PBD - Zellweger Syndrome Spectrum

Mutated Gene	Patient #	Phenotype	%
PEX1	124	ZSS	54
PEX5	3	ZSS	1
PEX12	9	ZSS	4
PEX6	27	ZSS	12
PEX10	5	ZSS	2
PEX26	11	ZSS	5
PEX16	1	ZSS	<1
PEX2	3	ZSS	1
PEX7	44	RCDP	19
PEX3	2	ZSS	<1
PEX13	1	ZSS	<1
PEX19	1	ZSS	<1
*PEX14**	1	ZSS	<1

ZSS: *PEX1* mutations most common

PEX7 mutations only → RCDP

all other *PEX* mutations → ZSS

modified from Gould and Valle, 2000
**Shimozawa N et al, 2004*

PBD - Zellweger Syndrome Spectrum

Mutated Gene	Patient #	Phenotype	%
PEX1	124	ZSS	54
PEX5	3	ZSS	1
PEX12	9	ZSS	4
PEX6	27	ZSS	12
PEX10	5	ZSS	2
PEX26	11	ZSS	5
PEX16	1	ZSS	<1
PEX2	3	ZSS	1
PEX7	44	RCDP	19
PEX3	2	ZSS	<1
PEX13	1	ZSS	<1
PEX19	1	ZSS	<1
*PEX14**	1	ZSS	<1

Genotype-phenotype correlation:

type of mutation and not the mutated *PEX* gene determines disease severity

modified from Gould and Valle, 2000
**Shimozawa N et al, 2004*

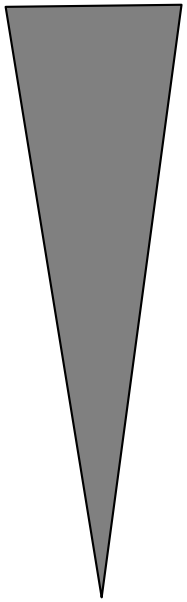
PBD - Zellweger Syndrome Spectrum

- Besides classical forms also late clinical onset forms with secondary deterioration
- PBD is a differential diagnosis of late-infantile onset leukencephalopathy

Genetic Disorders of Peroxisomes - cMRI Findings

Neuroradiological features in PBD and ß-oxidation defects - Summary

- Polymicrogyria
- Pachygyria
- Leukencephalopathy
- Germinoytic cysts
- Brain atrophy



Impact of cMRI for PBD and ß-Oxidation Defects

cMRI findings can be highly suggestive for PBD or ß-oxidation defects

further diagnostic work-up even in the absence of characteristic biochemical and/or clinical findings

X-linked Adrenoleukodystrophy - General

Incidence

1:20.000 males (1:16.000 males and females)

Clinical phenotypes

- cerebral demyelinating forms
  - childhood and adolescent cerebral ALD
  - adult cerebral form
  - 35 % of males with AMN

- adrenomyeloneuropathy (AMN)
  - adult males (20-40y)
  - heterozygous women > 35 years

- Addison’s disease only

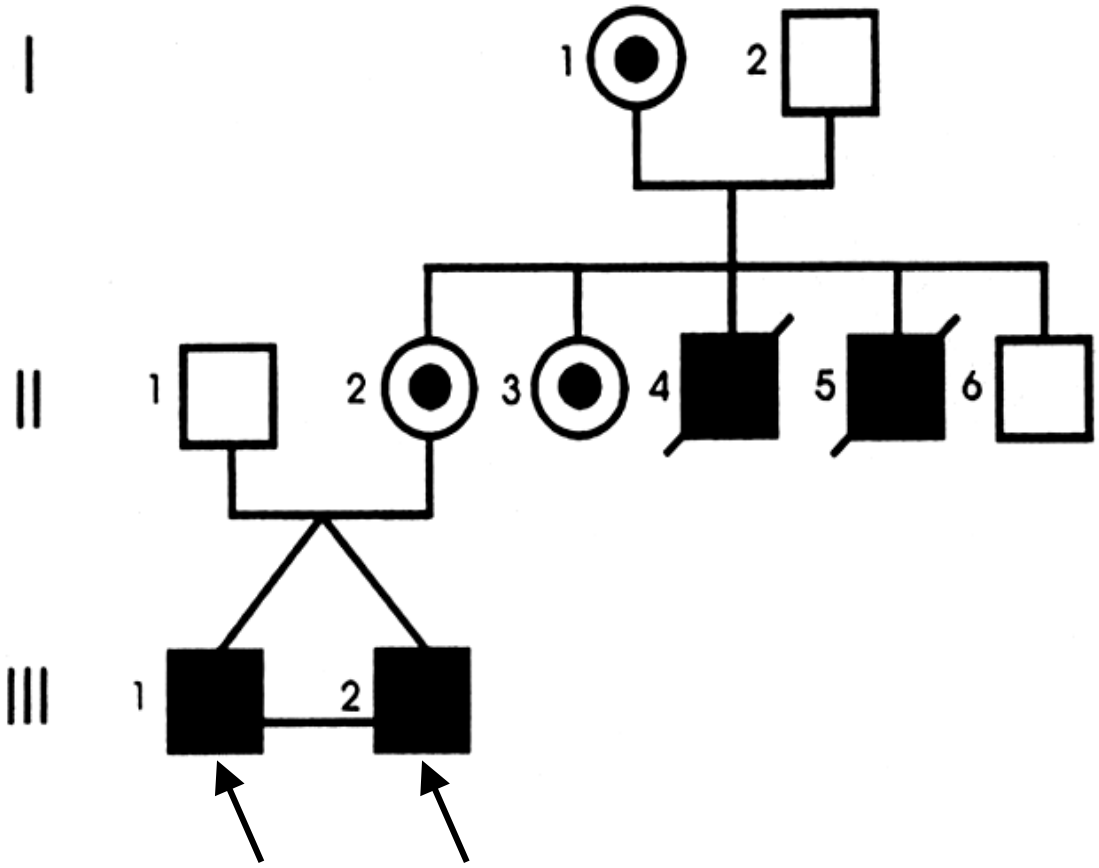
X-linked Adrenoleukodystrophy - *ALD* Gene

- Localization
  chromosome Xq28
- Gene Product - ALDP, ABCD1
  75 kDa peroxisomal membrane protein
  ABC (ATP-Binding Cassette) transporter protein family
- Gene Defect
  primary cause for all clinical phenotypes of X-ALD

But

Malfunction of ALDP alone does not explain the various clinical phenotypes

X-linked Adrenoleukodystrophy - Pathophysiology



Monozygotic Twins with X-ALD and two distinct clinical phenotypes.

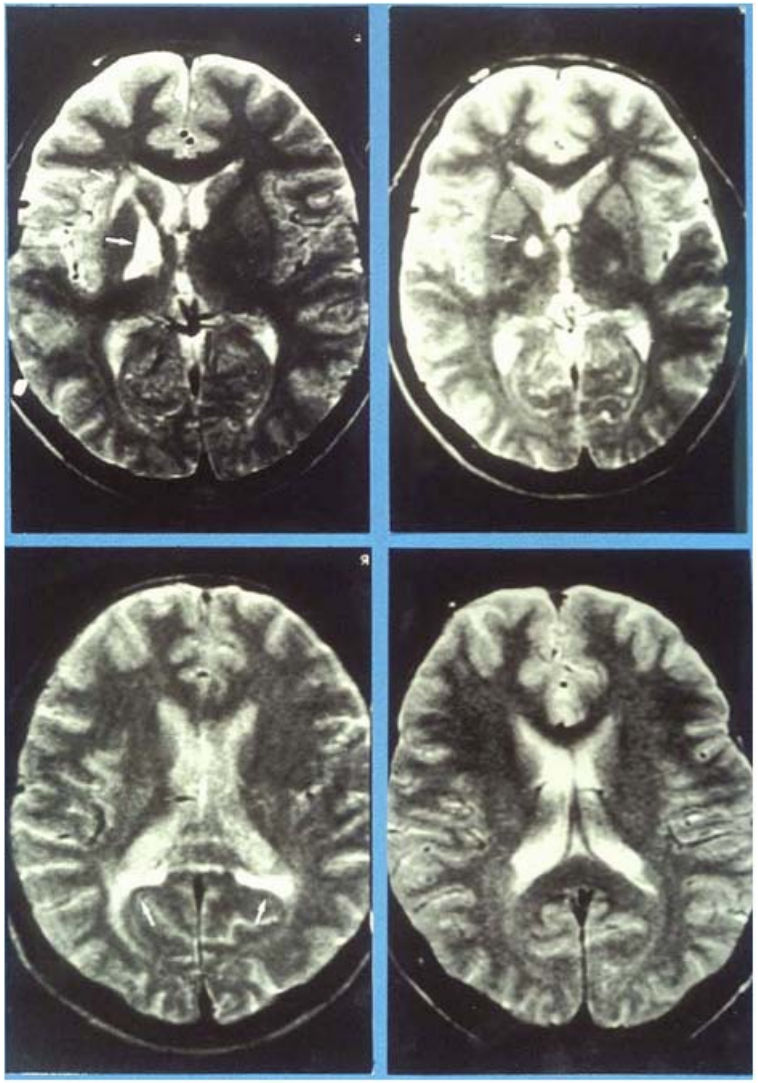
Korenke et al. 1996

X-linked Adrenoleukodystrophy - Pathophysiology

Current strategies to find modifiers

- candidate gene approaches
  - immune systeme
  - protein-protein-interaction partners
  - others
- global gene and protein expression profiles
  - transcriptomics
  - proteomics
- genome wide scans
  - susceptibility loci and genes

X-linked Adrenoleukodystrophy - Therapy



before after

Bone marrow transplantation (HSCT) can reverse or stabilize CNS demyelination in cALD

N Engl J Med, 1993
Lancet, 2000
Blood, 2004