Hematopoietic Stem Cell Transplantation for Adrenoleukodystrophy

2011 NHLBI Pediatric Workshop

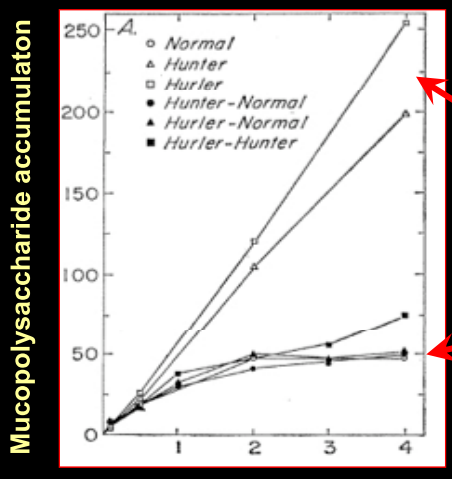
Sept. 14, 2011

Paul Orchard, M.D.

Division of Pediatric Blood and Marrow Transplant

University of Minnesota

Hypothesis: Cross-Correction will Modify Outcomes in Genetic Diseases



Lysosomal Disease

Hurler/Hunter cells alone

Hurler/Hunter cells with NL cells

Fratantoni, Hall, Neufeld. Science; 1968, 162; 853: 570-2

Adrenoleukodystrophy

- Frequency ≈**1:20,000** births
- X-linked peroxisomal disorder
- Defect in ABCD1 gene; many described mutations
- Defective metabolism of very long chain fatty acids (VLCFA)
- Affected boys have high plasma VLCFA; establishes the diagnosis

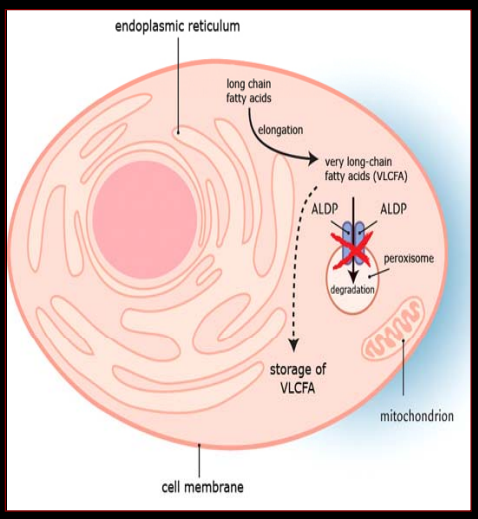


Figure: Dr. S. Kemp, Emma Children's Hospital, Amsterdam, Netherlands

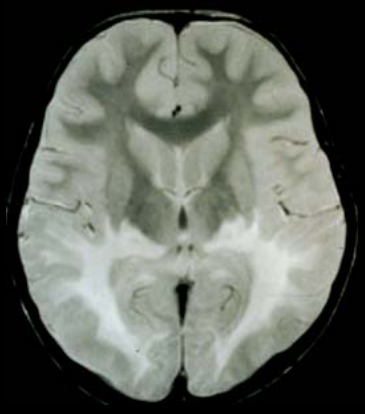
Clinical Characteristics: ALD

1.	Childhood Cerebral-ALD (C-ALD)	30-35%
	– Mean 7.2 yrs; (2.75-10 yrs)	
2.	Adolescent C-ALD	4-7%
	– 11-21 age group; slower progression	
3.	Adrenomyeloneuropathy (AMN) alone	40-46%
	– Spinal cord disease; 40% develop C-ALD	
4.	Adult C-ALD	2-5%
5.	Ponto-cerebellar disease (adolescent/adult)	1-2%
6.	Addisonian alone	50%
7.	Asymptomatic; incidence decreases with age	Rare > 40yrs

Indication for Transplantation For Adrenoleukodystrophy

Evidence of Active Cerebral ALD

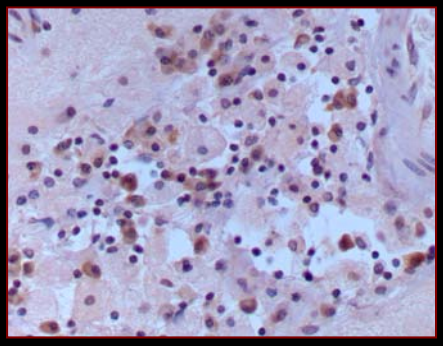
- Characteristic white matter changes on MRI
- Evidence of active inflammation/blood brain barrier disruption (gadolinium enhancement)



Problem #1: Can't Predict Phenotype

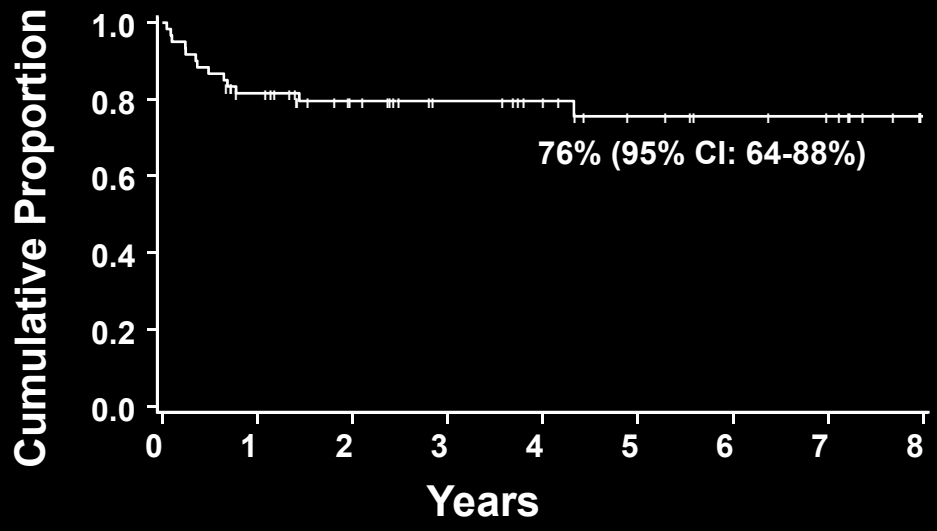
HSCT for Cerebral-ALD How Does it "work"?

- Stop cerebral inflammatory process with BMT regimen
- However, as gene product is a peroxisomal membrane protein, no "cross-correction" as seen in lysosomal diseases
- Oligodendrocyte responsible for myelination; not provided with BMT



- It is thought that donor derived microglia provide "protection" for oligodendrocyte population

Overall Survival: All Transplanted ALD Patients (n=60)



Miller, W. et al. Blood, 2011; 18(7):1971-8

Grading Radiographic Severity

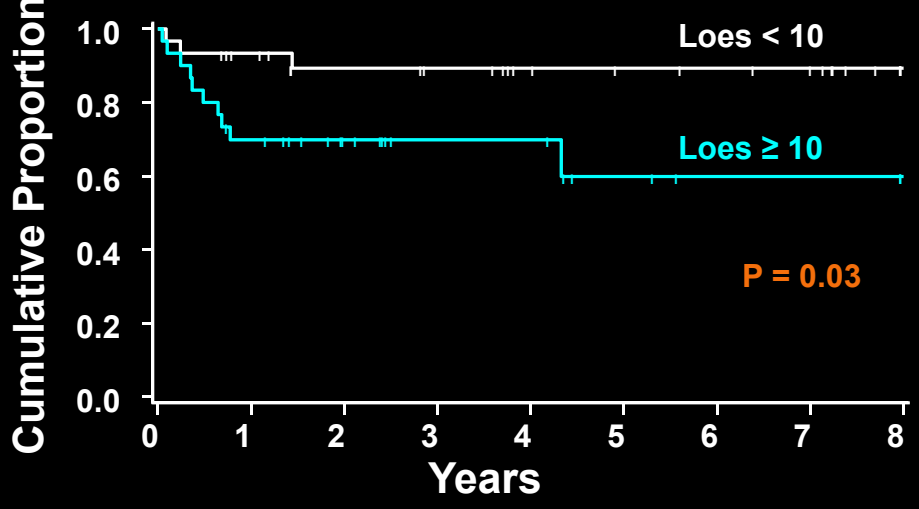
Loes scoring System: (0 – 34)

point assignment based upon demyelination-atrophy in loci:

- parieto-occipital WM
- antero-temporal WM
- frontal WM
- corpus callosum
- visual pathways
- auditory pathways
- pyramidal system
- basal ganglia
- anterior thalamus

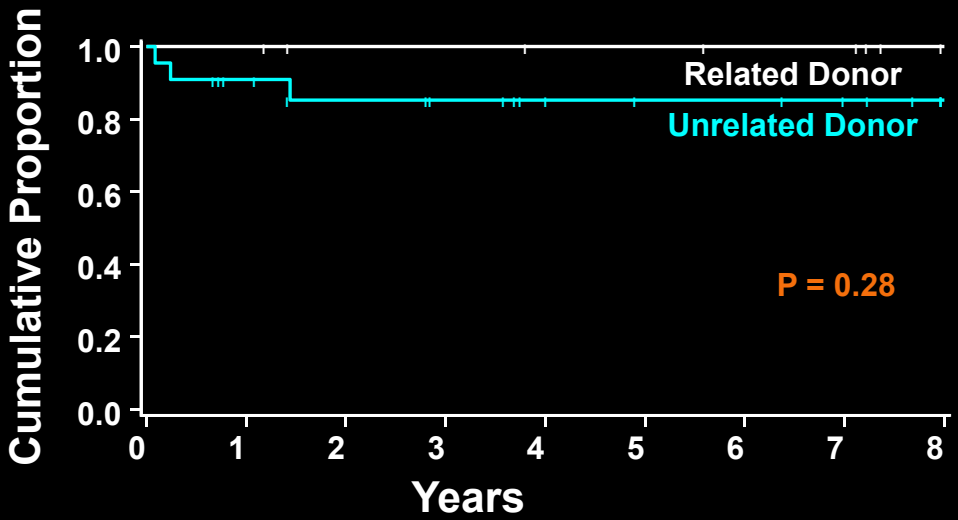
Loes DJ et al. AJNR Am J Neuroradiol 1994;15:1761-1766

Survival by pre-Transplant Loes Score
Early vs. Late Disease



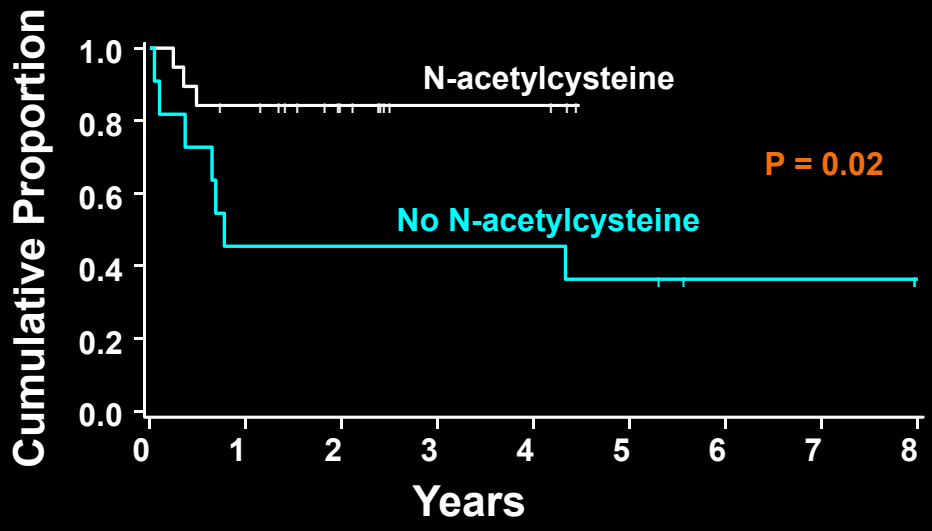
Problem #2: In late diagnosis, outcomes poor; different approach

Survival by Graft Source; Early Cerebral ALD
(Loes Score <10; N=30)



Miller, W. et al. Blood, 2011; 18(7):1971-8

Addition of NAC to Advanced ALD Transplant (Loes Score >10; N=30)



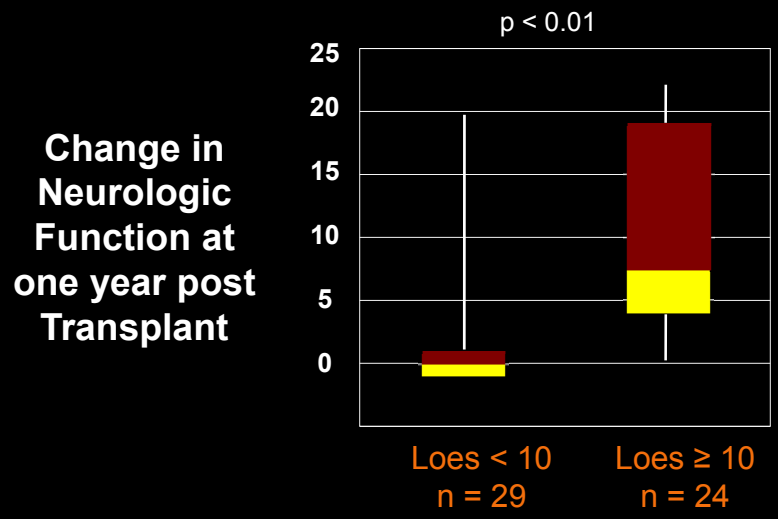
Miller, W. et al. Blood, 2011; 18(7):1971-8

Cerebral-ALD: Determining Clinical Severity Moser/Raymond Scale

Hearing/auditory processing problems	1
Aphasia/apraxia	1
Loss of communication	3
Vision impairment/fields cut	1
Cortical blindness	2
Swallowing difficulty or other CNS dysfunction	2
Tube feeding	2
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Spastic gait (needs assistance)	2
Wheelchair required	2
No voluntary movement	3
Episodes of incontinency	1
Total incontinency	2
Nonfebrile seizures	1
Possible Total	**25**

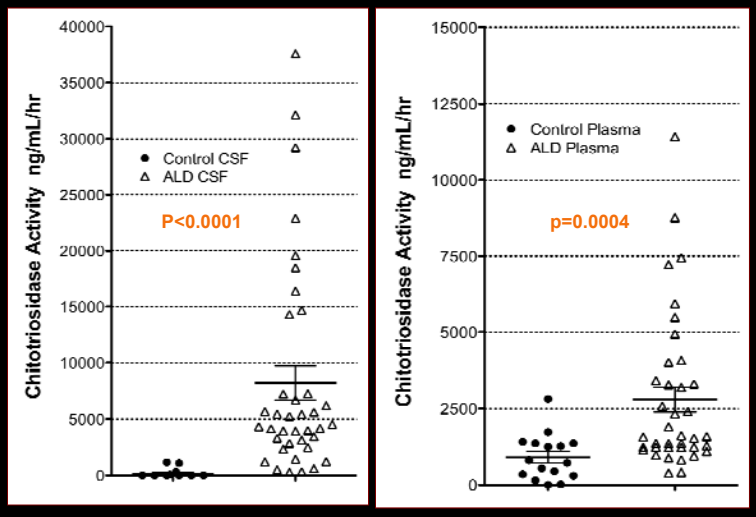
from Moser, et al; Arch Neurol 2005;62:1073-1080

Change in Neurologic Function Score

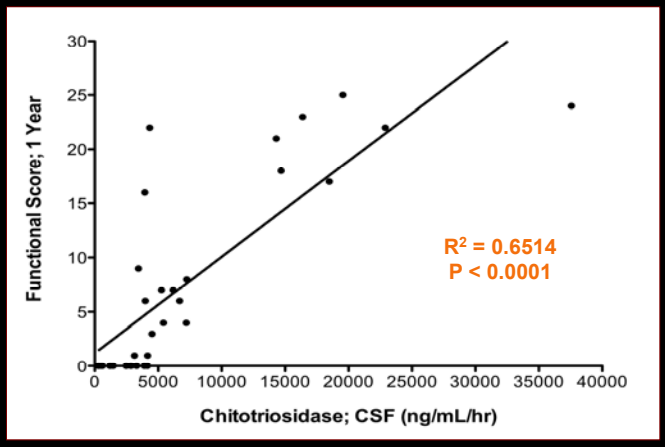


Problem #3: Within Early/Advanced groups, can we predict function?

Chitotriosidase Testing Pre-Transplantation in Cerebral Adrenoleukodystrophy



Pre-BMT CSF Chitotriosidase vs. Functional Score at 1 year



Conclusions: Allogeneic Transplantation for ALD

- Cannot yet predict who is at risk for cerebral disease, which is the target group for transplantation
- Important to identify cerebral disease EARLY in the course of disease; done by repeat MRI if known ALD patient
  - If identified early; good outcomes with current transplant approaches
  - If advanced disease; survival & neurologic status post transplant poor with current approaches, but no alternative therapy for these boys
- Future beneficial approaches may include newborn screening, biologic assessments of risk, modification of transplant procedures to decrease risk and prevent deterioration during therapy

Current Obstacles:
Cellular Therapy for ALD

- Don't clearly understand the biology of the disease, nor treatment with transplantation
- Clinical/functional, radiographic monitoring not standardized
- Rare disease, limited numbers of patients exist for design of new prospective trials – need cooperative studies
- How to integrate new approaches (gene therapy) as choices
- As early diagnosis critical in achieving acceptable outcomes. Can studies identify who will develop cerebral ALD?
  - Possible prospective trials monitoring evidence of inflammation, oxidative stress, etc. May lead to preventive therapy
  - How to design and pay for a national trial covering years?