Hematopoietic Stem Cell Transplantation for Adrenoleukodystrophy

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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 \( \approx 1:20,000 \) 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

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


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

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

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

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

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

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
- Episodic incontinence: 1
- Total incontinence: 2
- Nonfebrile seizures: 1

Possible Total: 25

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?