TRANSPLANTATION IN INHERITED NEUROMETABOLIC DISEASE

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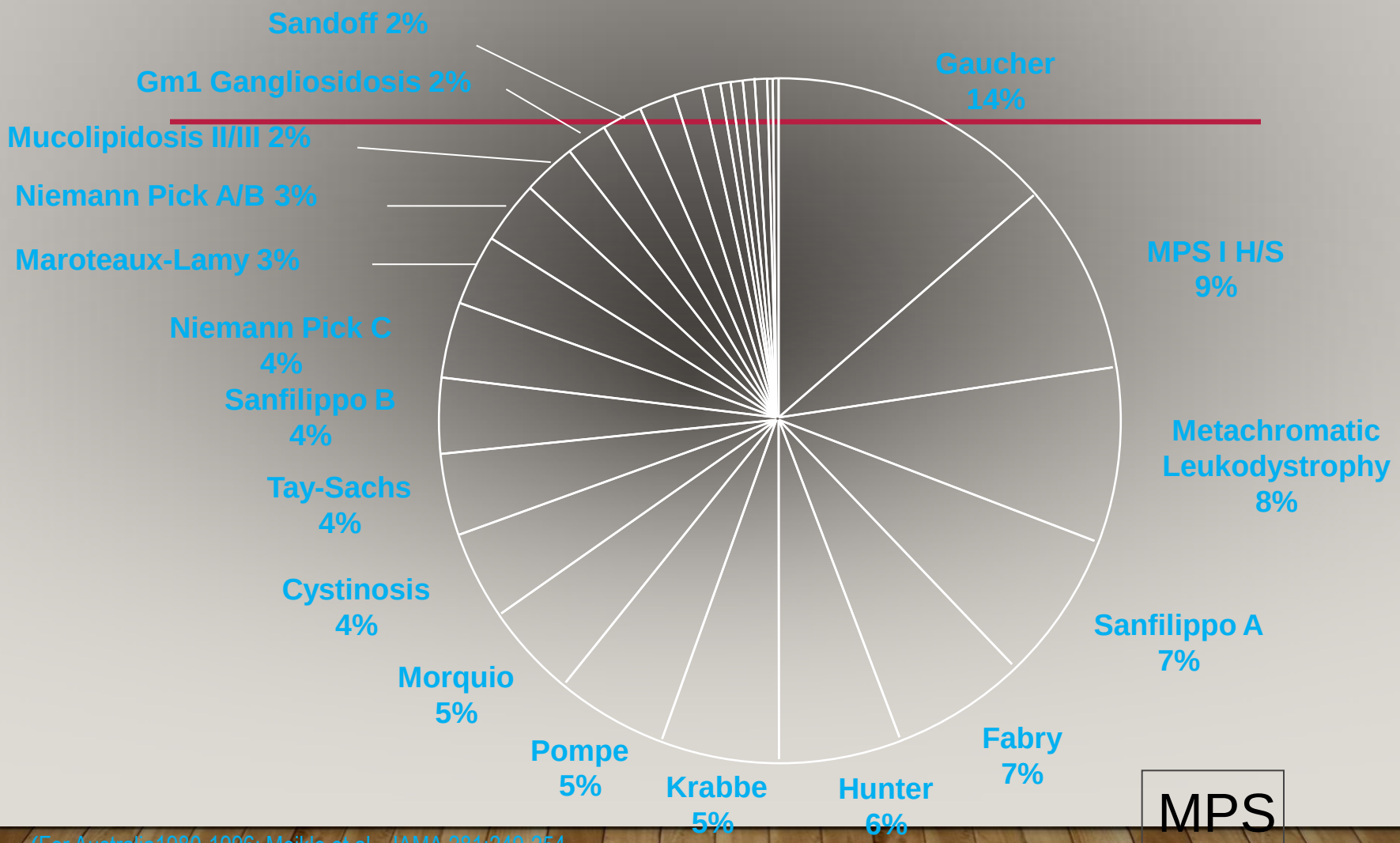
LYSOSOMAL STORAGE DISORDERS

- Inherited metaboloc disorders are a diverse group of diseases arising from genetic defect in lysosomal enzymes or peroxisomal function
- Devasting systemic processes affecting neurologic and cognitive function. Early death is a common outcome.

LYSOSOMAL STORAGE DISORDERS



(For Australia1980-1996; Meikle et al., JAMA 281;249-254

MPS 34%

EARLY DIAGNOSIS/EARLY TRANSPLANTATION

- Timely diagnosis and immediate referral for available treatments such as hematopoietic stem cell transplantation(HSCT) are essential steps in management
- Allogenic HSCT for IMD is performed using infusion of donor stem cells after immunosuppression and myelosuppression with a chemotherapeutic regimen

HOW HSCT COULD CORRECT AN IMD

- Cross –correction of metabolic defects with transferable lysosomal enzymes(direct transfer of enzyme from adjacent cell or mannose 6phosphate receptor endocytosis)
- Immunosuppression and decrease in perivascular inflammation in x-ALD
- Migration and growth of donor cells in liver (Kupffer cells),lungs(alveolar macrophages) and CNS microglia

INDICATIONS FOR HSCT

DISEASE:MPS	HSCT
Hurler(MPS IH)	Standard therapy
Hurler/Scheie(MPS IH/S	Optional
Scheie(MPS IS)	Optional
Hunter severe (MPS IIA)	Investigational
Hunter attenuated(MPS IIB)	Investigational
Sanfilippo(MPS III A/B/C/D)	Investigational
Maroteaux-Lamy(MPS VI)	Investigational
Sly(MPS VII)	Investigational

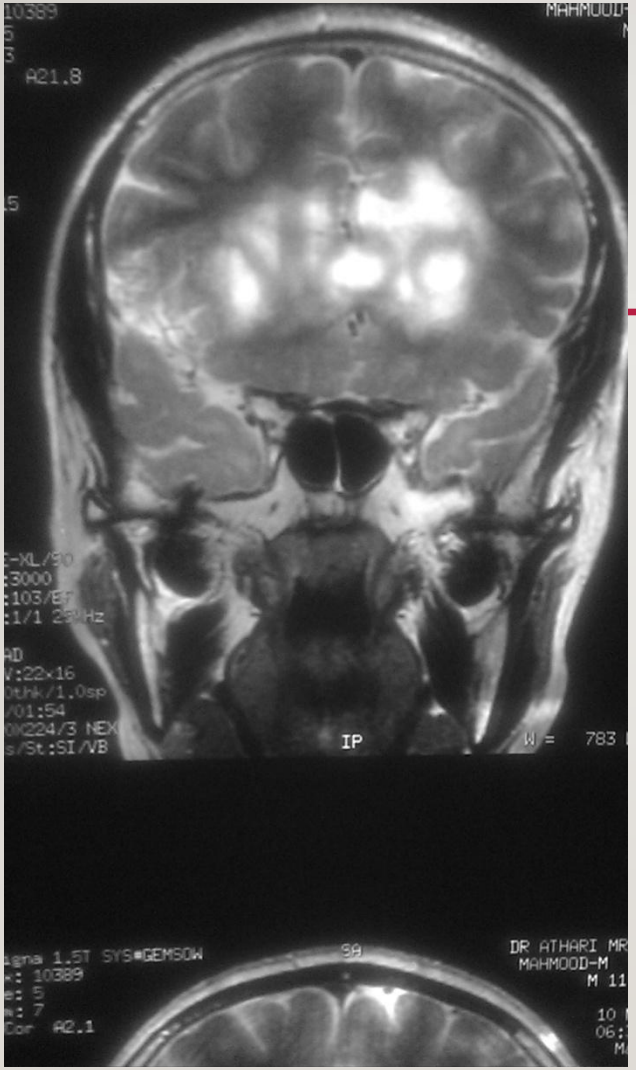
LEUKODYSTROPHY

- overall incidence is one in approximately 7600 live births

- . All leukodystrophies affect myelin, the insulation around nerves that enables rapid communication between neurons.

(demyelination), trigger abnormal myelin deposition

- (dysmyelination), or prevent myelin deposition
- (hypomyelination) in the CNS and/or peripheral nervous system (PNS) during development .
- more than 50 disorders are classified as leukodystrophies, and this number continues to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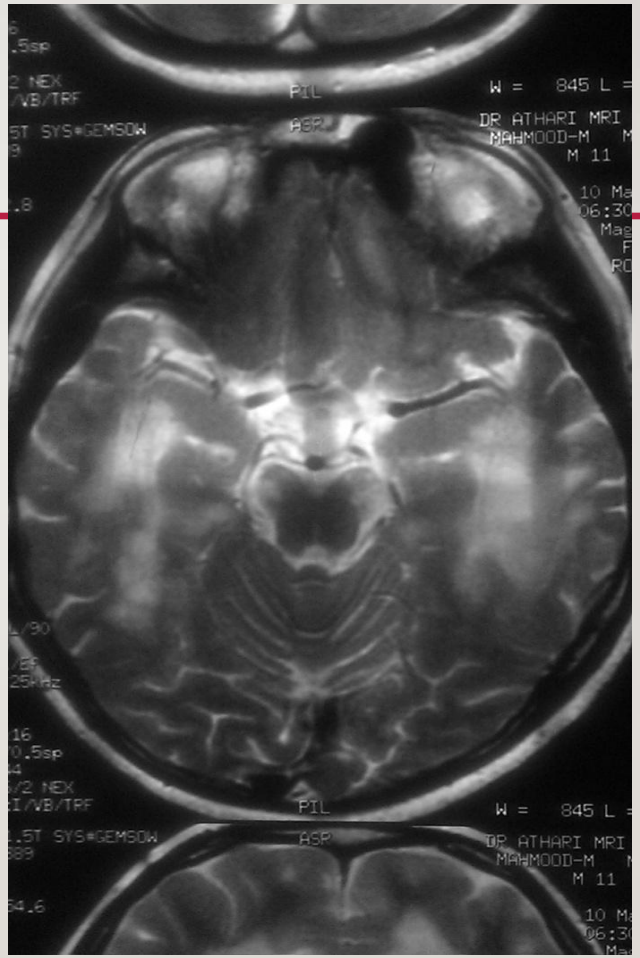
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INDICATIONS FOR HSCT

LEUKODYSTROPHIES	HSCT
• X linked ALD	• Standard therapy
• MLD:early onset	• Unknown
• MLD:late onset	• Standard therapy
• GLD:early onset	• Standard therapy
• GLD:late onset	• Optional

HSCT IS NOT EFFECTIVE

- Alexander syndrome
- Morquio syndrome
- Vanishing white matter disease
- Zellweger syndrome
- Fabry disease Canavan syndrome
- Cystinosis
- Cebrotendinous xanthomatosis
- Tay sachs/Sandhoff /GM1 Gangliodosis

HSCT EXPERIMENTAL REPORTS

- Wolman disease
- Alpha-Manosidosis
- Neiman –pick type B/C2
- Non neuropathic Gaucher disease (type 1)

Determining Whether HSCT is in a Patient's Best Interest

HSCT should be offered to patients for whom the potential benefit outweighs the inherent risks. Infants and children who have already experienced severe neurologic deterioration have symptoms that compromise their ability to tolerate high-dose chemotherapy. The presence of these symptoms shifts the risk-to-benefit assessment in an unfavorable direction.

Clinical Contraindications to HSCT
Inability to protect airway
Chronic aspiration
Uncontrolled seizures
Active or uncontrolled opportunistic infections
Severe scoliosis
Supplemental oxygen or need for assisted ventilation
Coma

Donor Selection

Optimal Donor

An HLA-matched, noncarrier sibling is the optimal donor choice for patients undergoing HSCT but is not available for most patients. Cord blood (CB) donors, when available, are preferred over unrelated bone marrow and peripheral blood stem cells.

Benefits of Cord Blood

Benefits of CB include rapid procurement, permissive HLA mismatching, and low rates of acute and chronic graft-versus-host disease (GVHD). Because the use of peripheral blood stem cells in pediatric recipients is associated with a higher incidence of acute and chronic GVHD, this donor source should only be used if other sources are unavailable or if the donor cannot undergo bone marrow harvest for medical reasons.

Special Considerations for Newborns Undergoing HSCT

In Utero Diagnosis

In families with a previously affected child, prenatal diagnosis is recommended. Mothers carrying an affected child should be followed by a high-risk obstetric team, and HSCT consultation should occur before delivery.

Delivery Planning

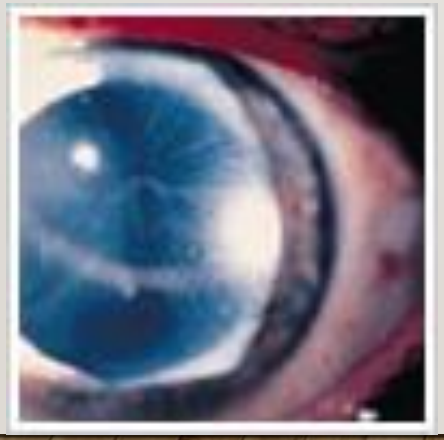
When possible, delivery should occur at the transplant center. For infants with EIKD, there is prior experience with inducing labor as soon as lung maturity is established.

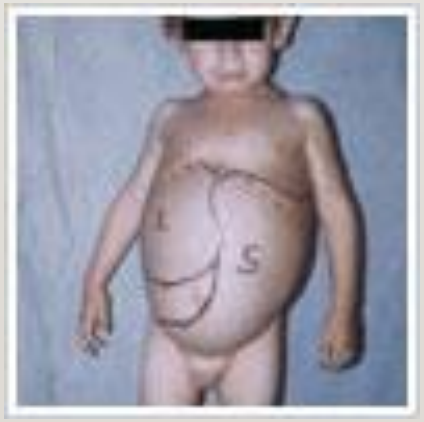
Cord Blood Collection

Cord blood should be collected and sent for HLA typing and disease confirmation. Standard newborn care should be provided during the first days of life.

HURLER SYNDROME

- The most severe form of MPS due to accomulation of glycosaminoglycan
- More than 500 HSCT scince 1980
- HSCT is effective treatment but must be performed early





HURLER SYNDROME

- What ~~is stem cell source? Normal HLA match sibling/unrelated cord~~ blood
- What is the conditioning regimen?standard BU/CY[EBMT 2005 guidline,eurocord-Duke university]
- How is survival after HSCT? 91%(4years)
- What is the role of enzyme replacement therapy?

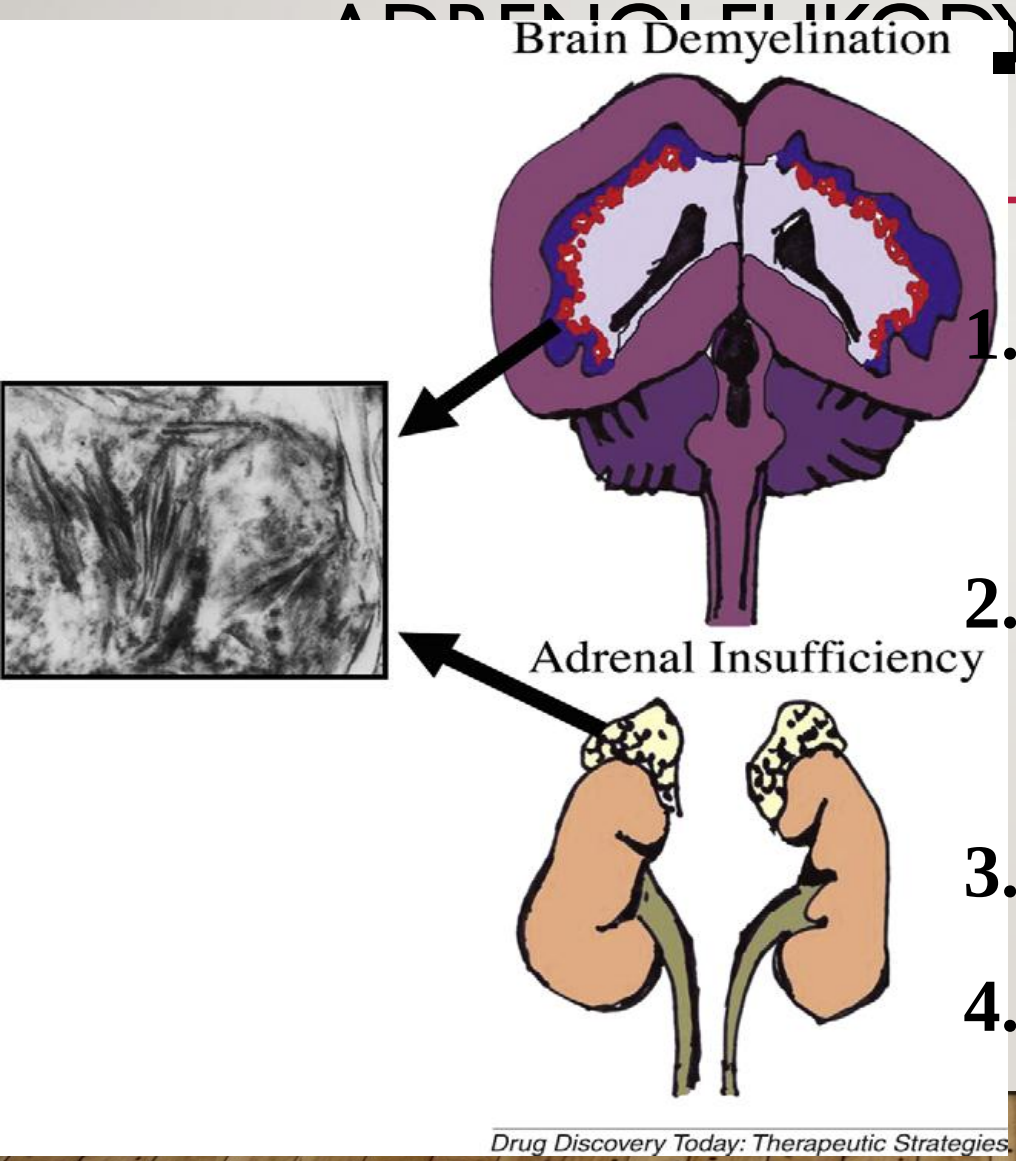
HURLER SYNDROME

- How is post transplant outcome?reduction of obstructive airway symptoms and hepatosplenomegaly, improvement of cardiovascular function,hearing ,vision,growth,hydrocephalus but not pretransplant cerebral damage

OTHER MPS SYNDROMES AND HSCT

- Hunter [MPS II] :8 boys successful HSCT French study/ ERT
- Sanphilipo[MPS III]: ERT is not available, HSCT data is not adequate 19 children in Duke university but only effective in two <2 years old children
- Marotexlamy[MPS VI]: Limited data,an option in patient who failed to ERT

ADRENOLEUKODYSTROPHY



- **4 major phenotypes of ALD**

1. **Cerebral ALD (CERALD)**
2. **Adrenomyeloneuropathy (AMN)**
3. **Addison disease**
4. **Asymptomatic status**

Drug Discovery Today: Therapeutics Strategies.2008.vol 5 :237-242

Table. X-Linked Adrenoleukodystrophy (X-ALD) Phenotypes

Phenotypes	Symptoms/ Signs	Age at Presentation, y	Diagnostic Test	Recommended Therapy
Males Cerebral (mild) (PIQ>80, MRI score <9) without AMN	Behavior changes, school failure, dementia, audiovisual	3-10 (common) 11-21 (intermediate) >21 (rare)	VLCFA, brain MRI	HSCT, adrenal HRT
Cerebral (severe) without AMN	Dementia, psychoses, paralysis, epilepsy, loss of vision loss of speech , bulbar palsy	5 to adulthood	VLCFA, brain MRI	Adrenal HRT, general support
Pure AMN	Paraparesis, Sphincter disturbances Sensory changes Incoordination pain, impotence	28	VLCFA	Adrenal HRT, possibly Lorenzo's oil, physical therapy
Cerebral AMN	Like pure AMN plus dementia, behavioral disturbances, psychosis, epilepsy aphasia, visual loss, bulbar palsy	28	VLCFA, brain MRI	Adrenal HRT, general support, possibly HSCT

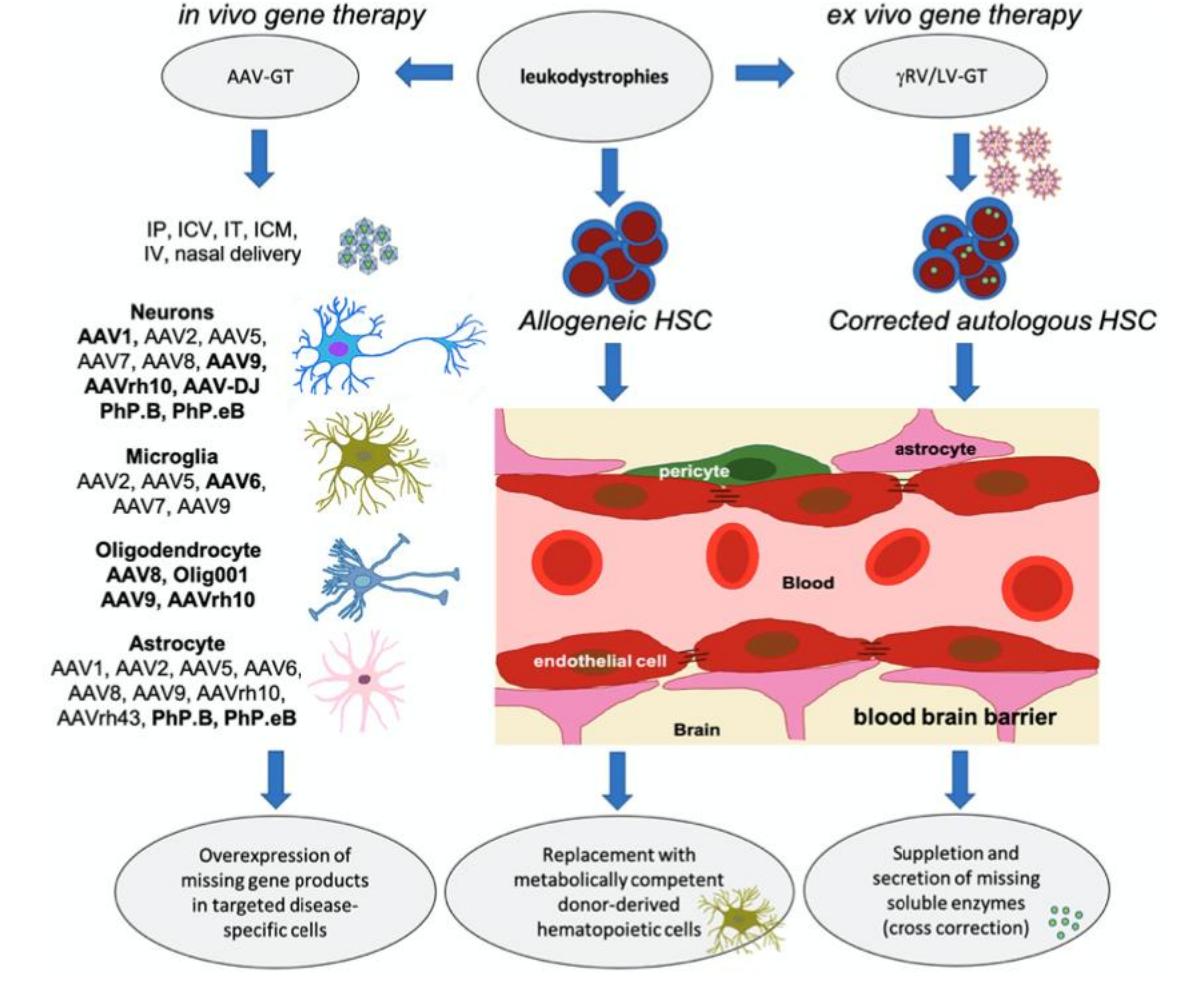
JAMA, 2005.Vol 294:3131-34 , www.UpToDate.com

THERAPEUTIC APPROACHS

- **Pharmacological Treatment Strategies :**
  - **Treatment of Adrenal & Gonadal Insufficiency**
  - **Lorenzo's Oil**
  - **Immunomodulators & Immunosuppresive Drugs**
  - **Statins**
  - **Pharmacological Induction of The Redundant Gene ABCD2**
  - **Antioxidant**
- **Hematopoietic Stem Cell Transplantation (HSCT)**
- **Gene Therapy**

,Brain Pathology 2010.vol 20: 845–856

GENE THERAPY IN ALD



STEM CELL GENE THERAPY

FIRST IN 2009 IN 2 PATIENTS

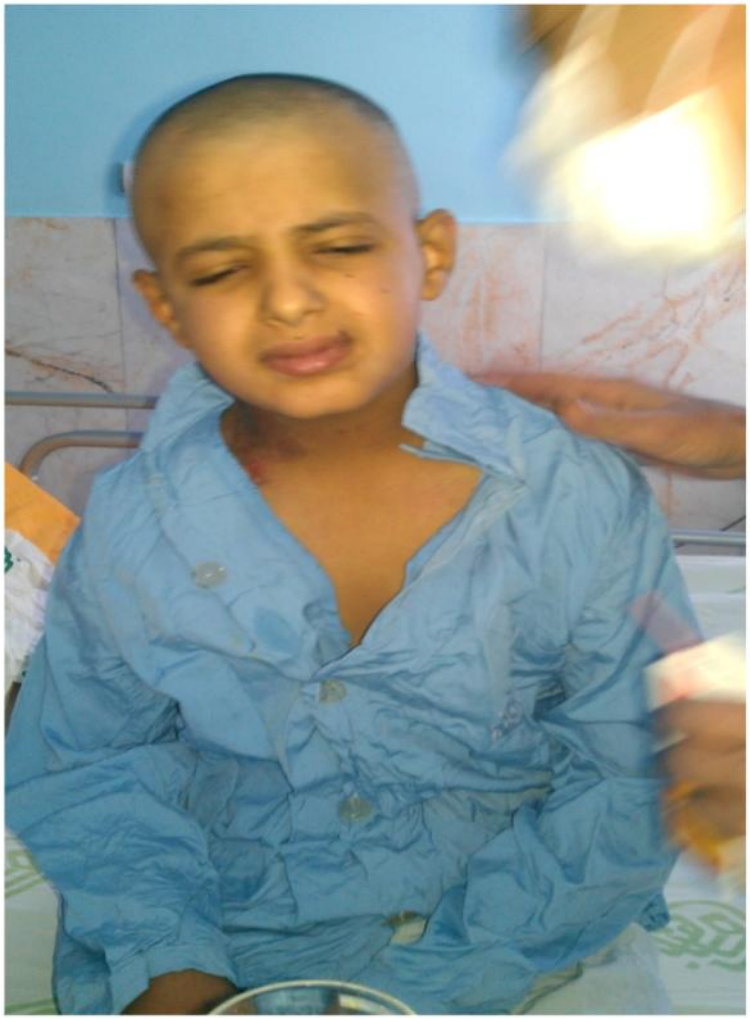
The US clinical trials for elivaldogene autotemcel (eli-cel) enrolled boys less than17 years who presented with early symptomatic CALD, defined as radiologic Loes score 0.5 to nine [and clinical neurologic functional scale (NFS) score 1.

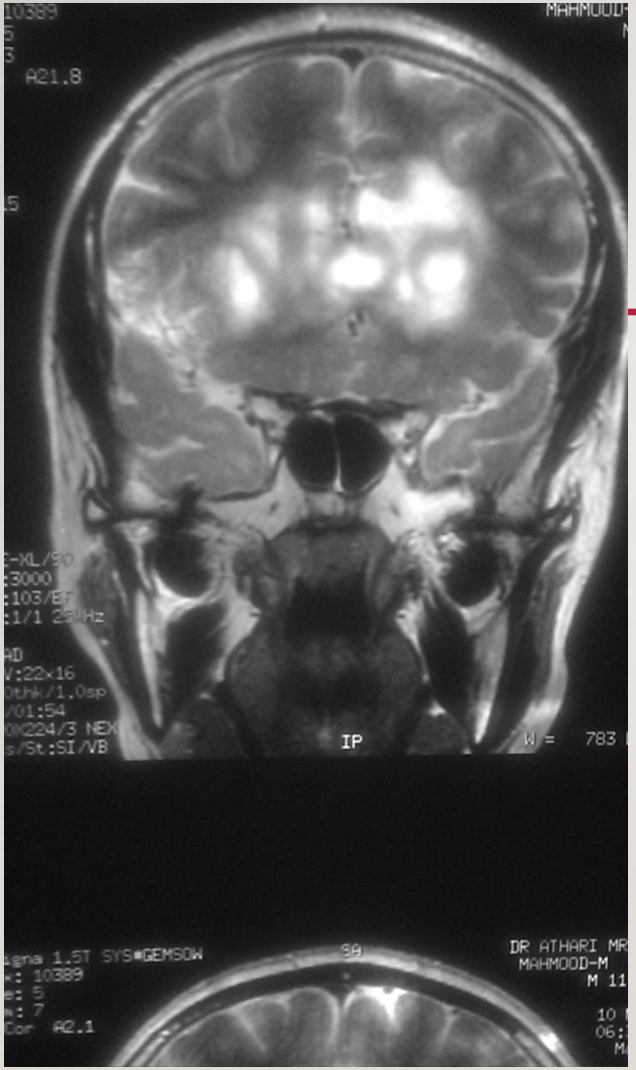
Presymptomatic X-ALD boys were excluded as it is impossible to predict which patients will develop the CALD pheno- type

Fifteen of the 17 patients included in the interim analysis were alive without major functional disabilities or clinical symptoms with a median follow-up time of 29.4 months.

Twelve treated patients had stable MRI findings without progression and two had increasing Loes scores with relative preservation of the NFS score.

The results of this initial interim analysis were largely confirmed in a subsequent interim analysis with 32 treated CALD patients .

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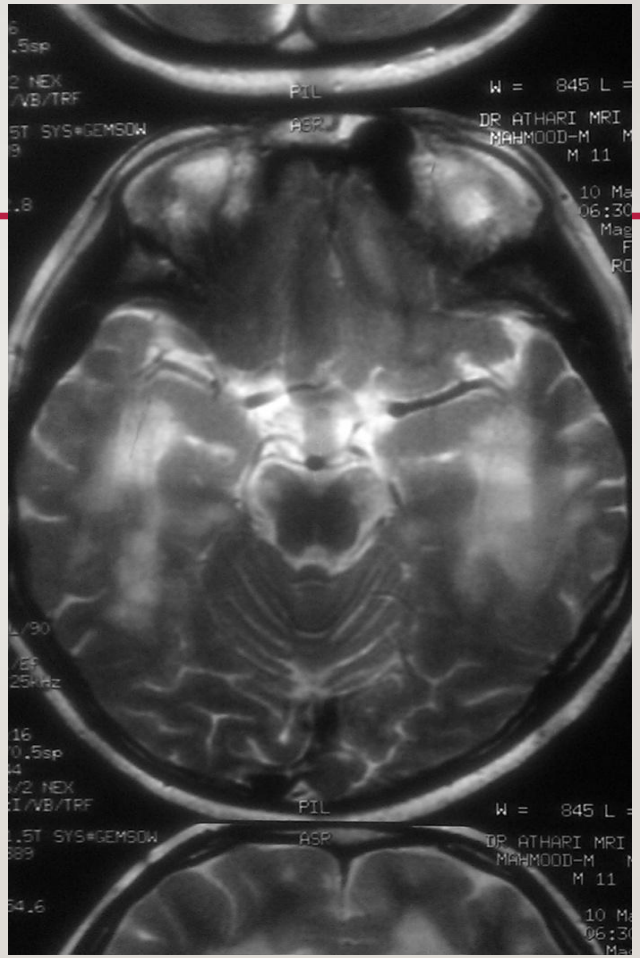
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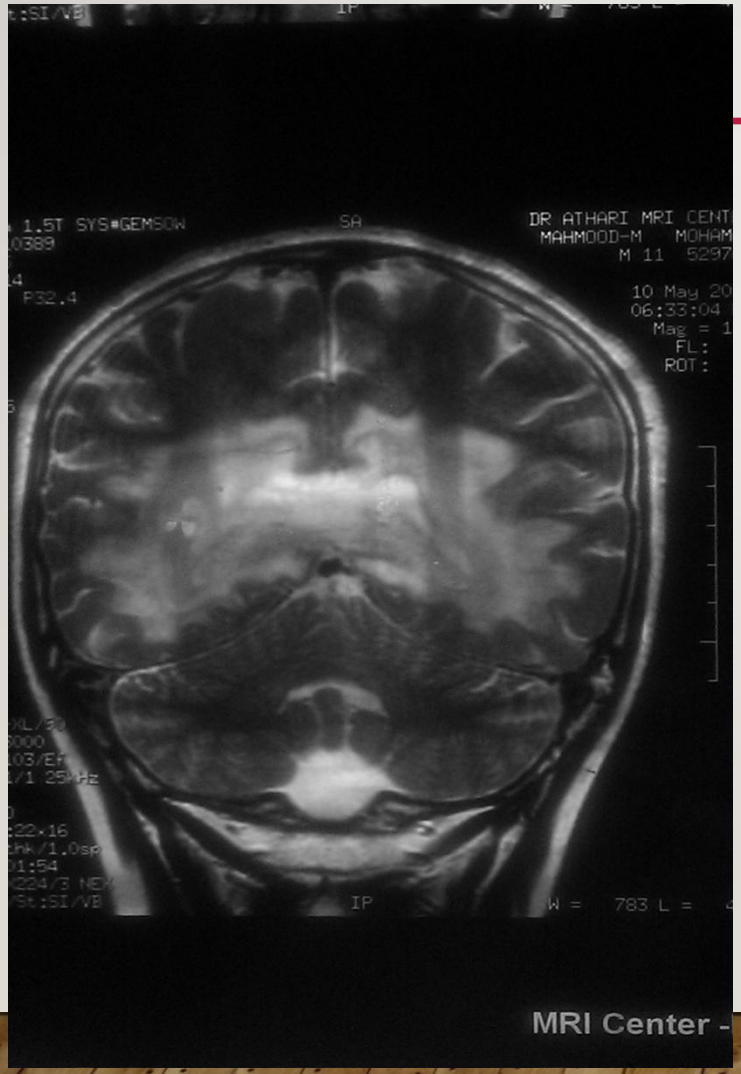
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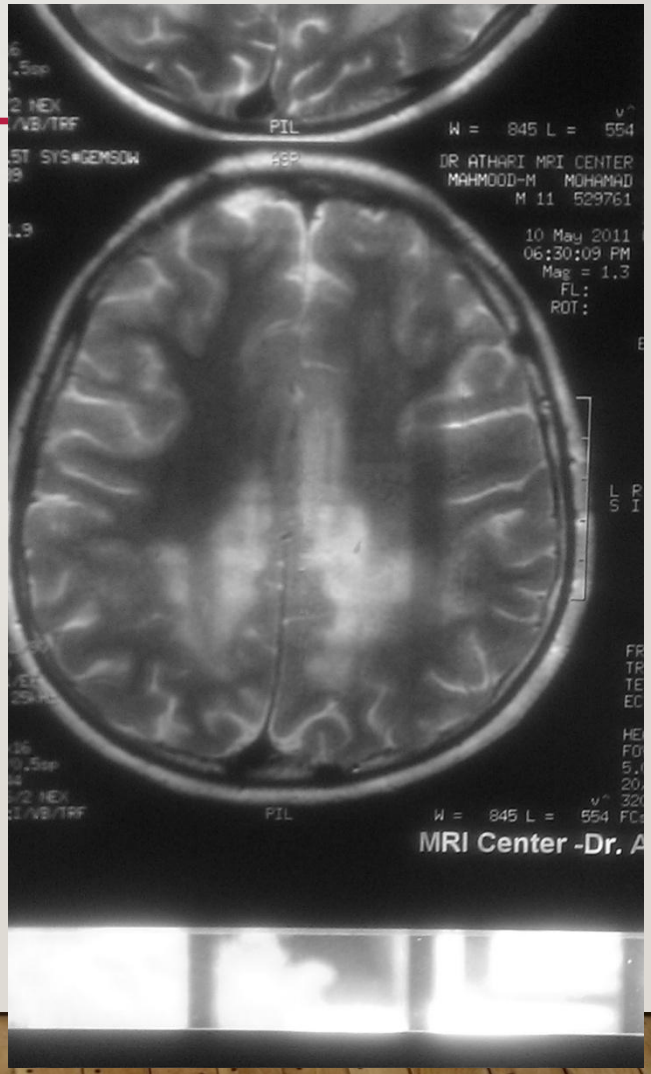
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GLOBOID LEUKODYSTROPHY "KRABBE DISEASE"

- Caussed by deficiency of galactocerebrosidase
- Spasity,mentalretardation,blindness,deafness

,sizure and early death are natural history of the disease

- Prenatal diagnosis is possible by gene defect 14q31
- HSCT is the only available therapy

GLOBOID LEUKODYSTROPHY "KRABBE DISEASE"

- First report in 1998 by Krivit in 5 late onset affected boy who responded to HSCT
- Report of successful neonatal cord blood transplantation in 25 neonates by
- Escolar in 2005 but transplantation in
- symptomatic infants are less effective

METACHROMIC LEUKODYSTROPHY

- A lysosoma disorder due to deficiency of Arylsulfatase A and increased urinary sulfatides(very important to rule out psudodeficiency)
- Clinical phenotypes:early infantile,late infantile,early juvenile,late juvenile,adult form
- The first report of HSCT about 20 years ago and more than 100 transplantation later but long term data are not available

METACHROMIC LEUKODYSTROPHY

- Usually children who were transplanted for symptomatic or asymptomatic late infantile MLD perfoemed poorly in all aspects
- In late onset juvenile MLD and adult forms ,CNS disease was stabilized after HSCT
- Current preferred practice is to transplant only presymptomatic or minimally affected chidren

Metachromatic Leukodystrophy

MLD is a lysosomal storage disease caused by mutations in the arylsulfatase A gene (ARSA), leading to deficiency of arylsulfatase, accumulation of sulfatides, and subsequent demyelination in the CNS and peripheral nervous system. There are 3 subtypes of MLD based on age at onset of clinical symptoms. All subtypes present most commonly with gait abnormalities or weakness.

MLD.AND ALLOGENEIC MESENCHYMAL STROMAL/STEM CELLS (MSC)

- allogeneic HSC transplantation slows disease progression, but local ARSA expression by donor cells is not sufficient for metabolic correction of MLD
- In addition to HSC transplantation, the use of allogeneic mesenchymal stromal/stem cells (MSC) has also been proposed, since MSCs have been shown to be able to migrate and engraft in the brain, differentiate into astrocytes, and express high levels of ARSA
- . When MSCs were infused in patients who had persistent progressive neurologic and skeletal defects despite achieving 100% donor chimerism after HLA-identical allogeneic bone marrow transplantation, patients displayed increased bone mineral density and improved nerve conduction velocity, but no clinical improvement in overall health, or mental and physical development .
- Similarly, when patients were treated with MSC infusions shortly after allogeneic HSC transplantation, they showed improved hematopoietic reconstitution and increased *ARSA* expression, but no overall improvement in clinical outcome and gross motor function

STEM CELL GENE THERAPY

- Following two open-label, non-randomized phase 1/2 human clinical trials with expanded access for arsa gene autotemcel (arsa-cel) (NCT01560182, NCT03392987), this approach received FDA approval in 2024. Arsa-cel is an ex vivo HSC-directed LV-mediated gene therapy for pre-symptomatic late-infantile
- . At a median follow-up of 6.76 years, 25/26 treated patients continued to have preserved ambulation . In contrast, 50% of untreated late infantile MLD patients lose their ability to walk a year after symptom onset . Arsa-cel is now being evaluated in a clinical trial for late-juvenile MLD patients (NCT04283227).
- the presence of pre-treatment neurologic symptoms is a predictor of poor treatment outcomes

STEM CELL GENE THERAPY

- A similar ex vivo HSC-directed LV-mediated gene therapy is being conducted in China for all MLD patients with disease onset 16 years (NCT02559830). Unlike the clinical trials presented above, this clinical trial targets symptomatic MLD patients, and presymptomatic disease is an exclusion criterion. No published data are available for this trial.


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