Gaucher Disease
FAQs

What is Gaucher disease? How common is Gaucher disease in India?

- **Inherited chronic, progressive lysosomal storage disorder (LSD)**

- **Deficiency of an enzyme called glucocerebrosidase that breaks fatty material, or lipid, present in our body cells**

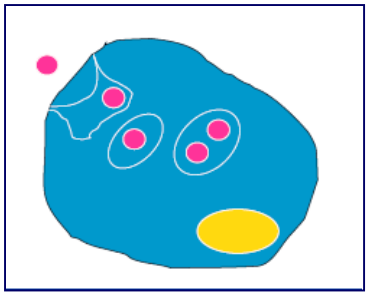
SK

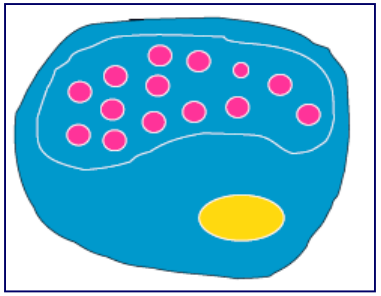
How common is Gaucher disease in India?

- **No Indian data on prevalance**
- **Panethnic disorder**
- **Commonly seen in Clinical practice**

What is the Pathogenesis of LSDs

- LSD -group of Genetic disorders share a common pathogenesis resulting from the accumulation of substrates in cell lysosomes due to deficiency of Lysosomal enzymes
- Most AR,some X-linked





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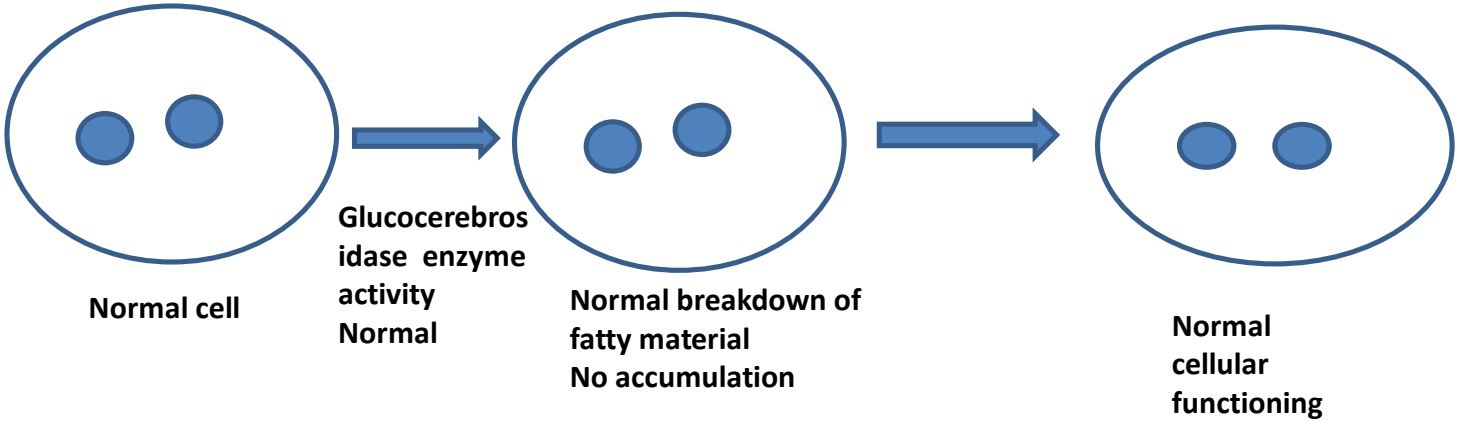
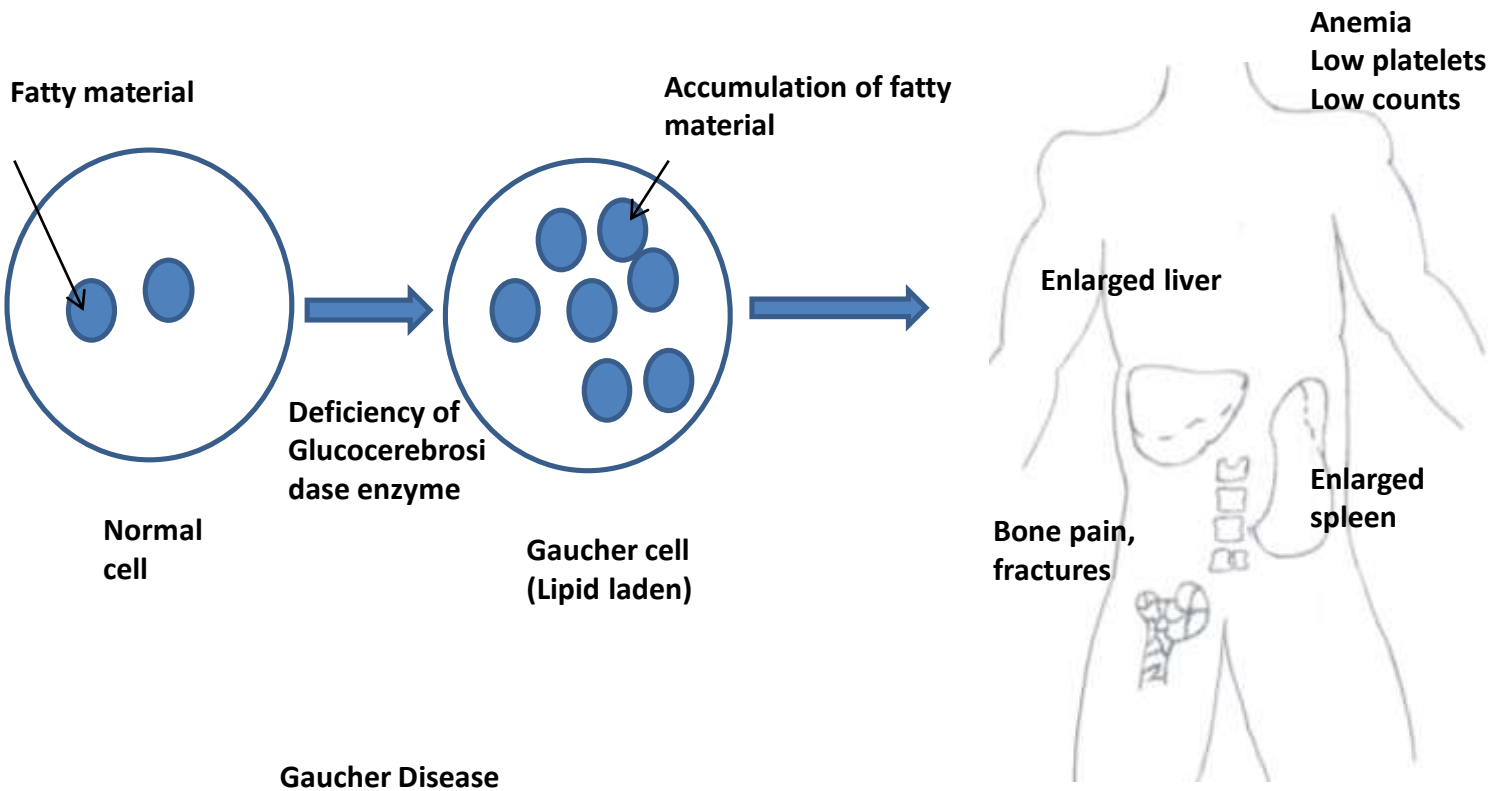
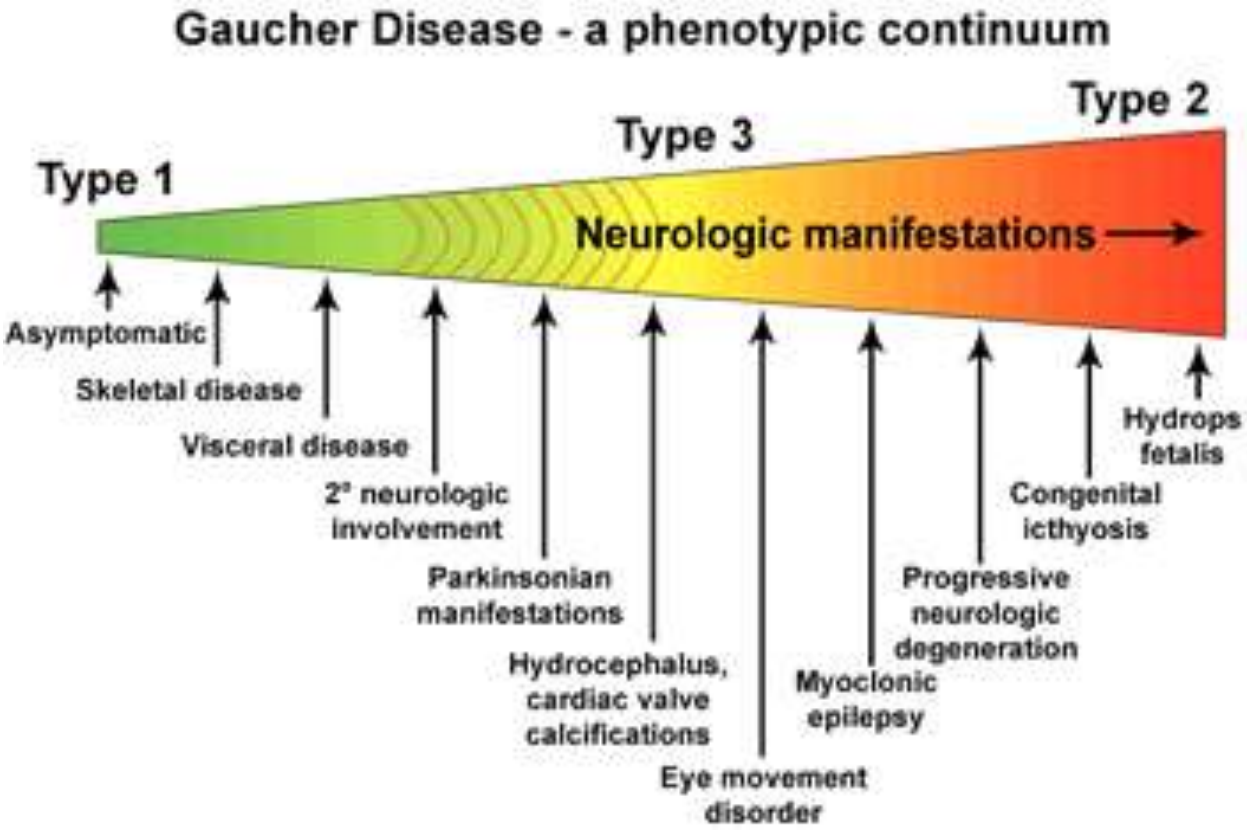




Gaucher Disease

What are the different types of GD?



Patients with Gaucher disease can have a spectrum of symptoms, ranging from mild to severe neurological effects. The classic categories of types 1, 2 and 3 have blurry edges along this continuum.

Pic source- Internet

Classification of Gaucher Disease

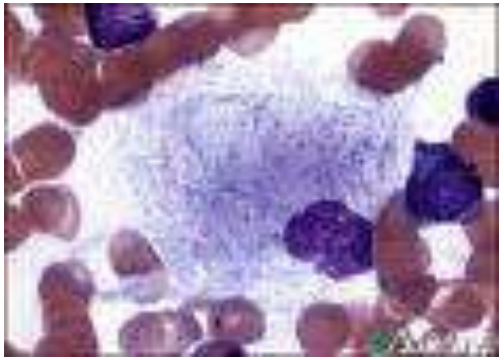
Clinical features	Non-neuronopathic (type 1)	Acute neuronopathic (type 2)	Chronic neuronopathic (type 3)
Onset	Any	Infancy	Any
Visceral involvement	+++	+	+
Hematologic abnormalities	+	+	+
Bone disease	+	-	+
Neurodegenerative course	-	+++	++ (progressive)
Survival (y)	Normal to slightly reduced	< 2	2-60y
Frequency	Extrapolated 1,20,000 (india) 1/40.000-60.000 Ashkenazi Jewish	< 1/100.000	< 1/100.000

What is Non-neuronopathic GD? How does it present?

Gaucher Disease

Can manifest at any age

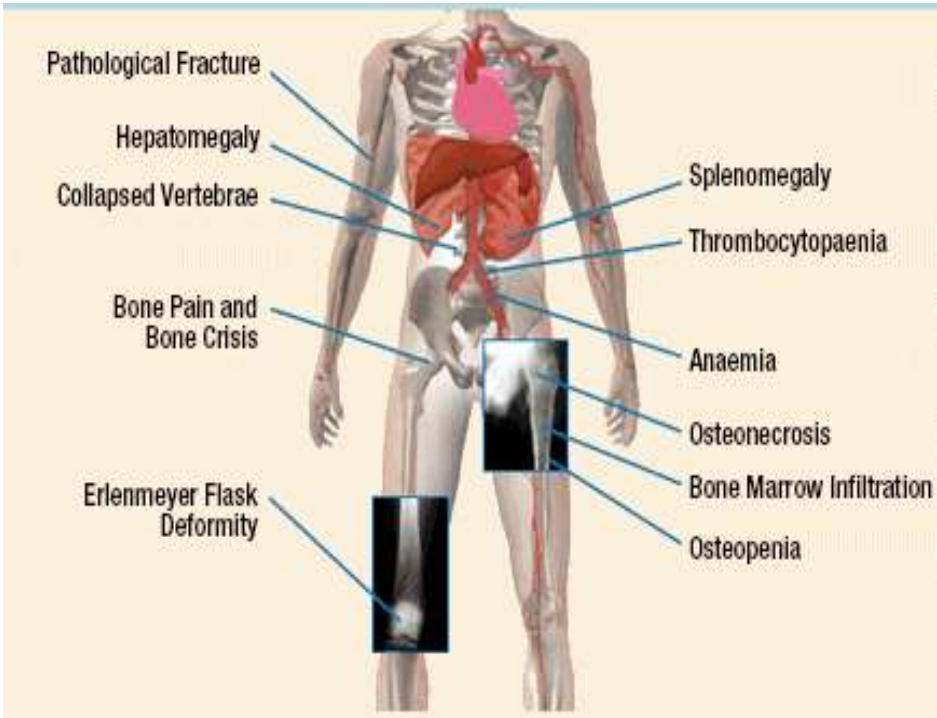
- **Multisystem Involvement**



Gaucher Cell

Four main manifestations

Hematological
Visceral
Skeletal
Neurological

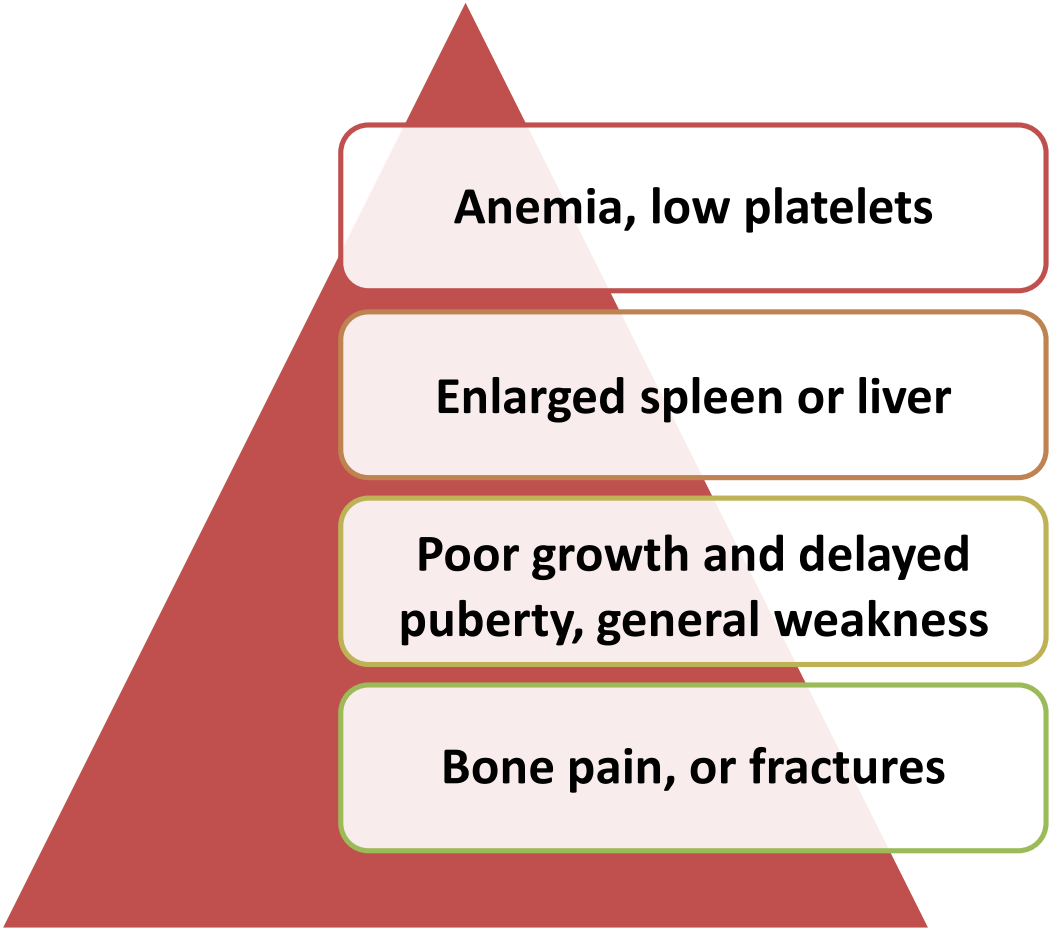


Pic source- Internet

What are the Differential Diagnosis ?

- Infections – Kala Azar, Chronic Malaria
- Hemolytic anemias
- Portal Hypertension
- Hemophagocytic syndromes
- Chronic Leukemias
- Storage other than Gaucher's – NPD B…..
- Important :History/ Exam/Investigations for D/D

Indications for testing for GD?



Close family members such as brother/sister of an individual with GD or siblings of parents of GD for carrier status

What is the age of onset for the neuronopathic GD? How do these patients usually present?

Type II – Infancy , Early Death
Type III – Any age

Neuronopathic Gaucher

Acute Neuronopathic Gaucher

Developmental Delay, Visceromegaly

Cachexia

Neck retroflexion

Bulbar involvement

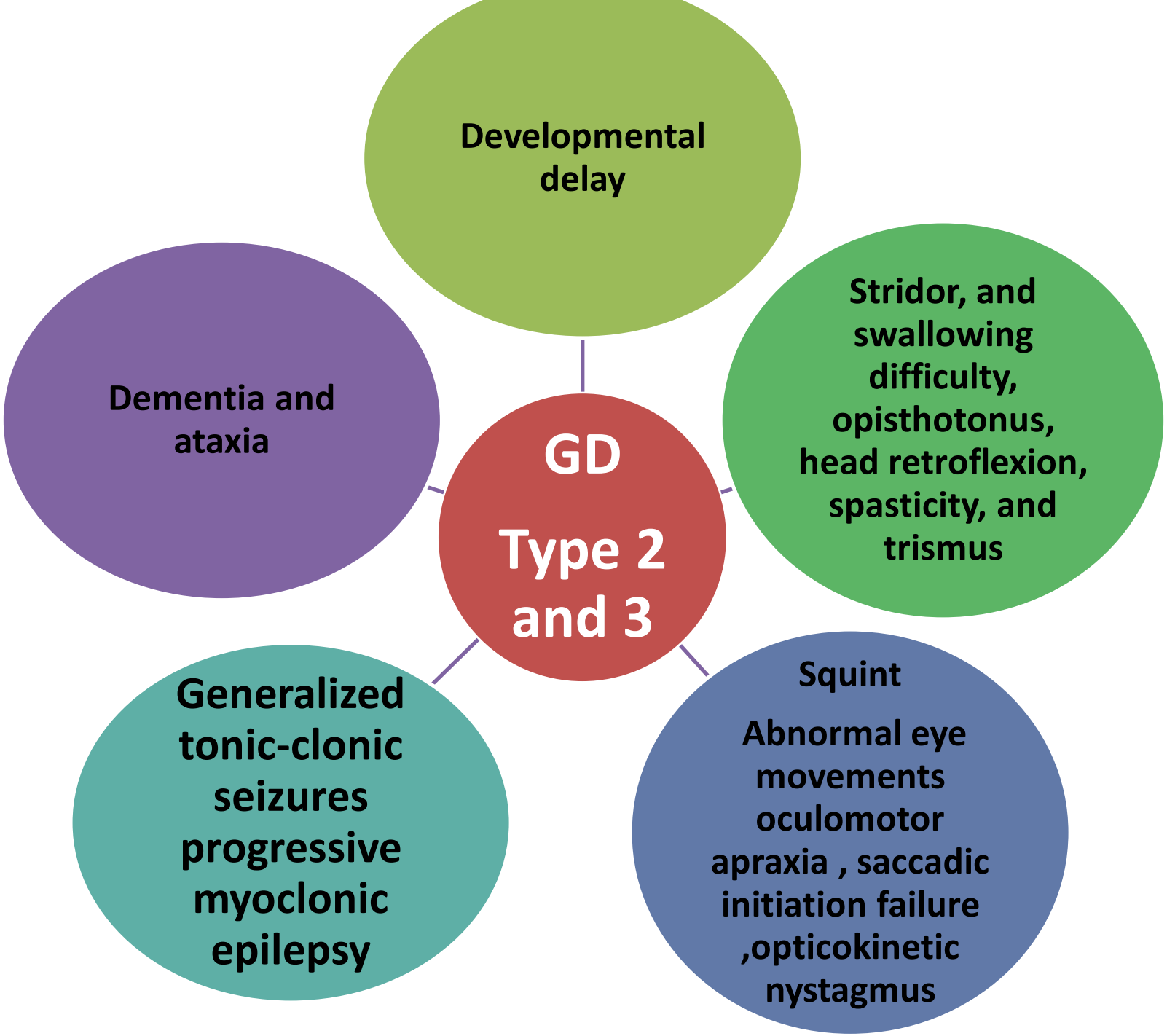
Chronic Neuronopathic Gaucher

Myoclonus

Ataxia

Supranuclear ophthalmoplegia

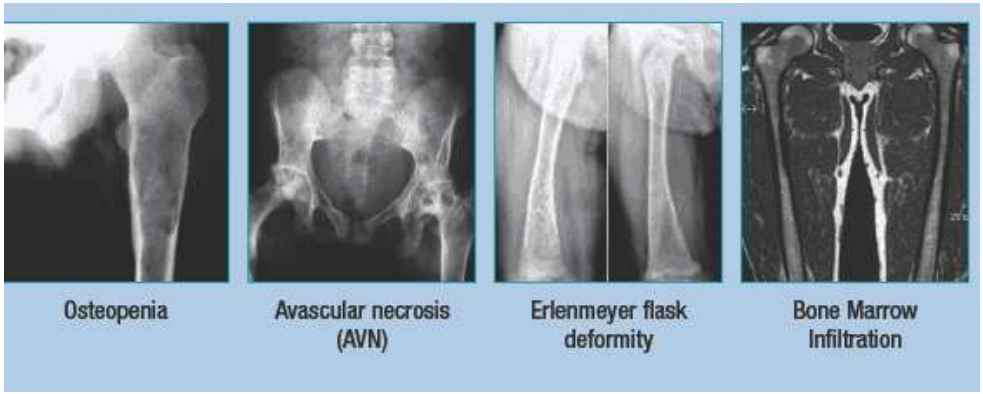
What are different neurological symptoms/signs that should be looked for in a child suspected with GD?


Developmental delay
Dementia and ataxia
GD
Type 2 and 3
Stridor, and swallowing difficulty, opisthotonus, head retroflexion, spasticity, and trismus
Generalized tonic-clonic seizures progressive myoclonic epilepsy
Squint
Abnormal eye movements oculomotor apraxia , saccadic initiation failure ,opticokinetic nystagmus

What are the Skeletal manifestation in GD?

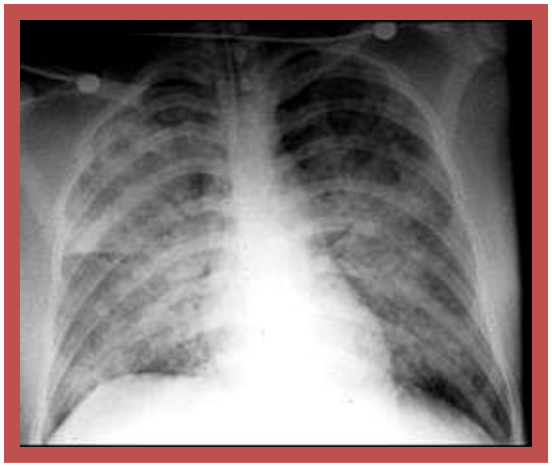
Skeletal -Very common

- Chronic bone pain and/or bone crises
- Bone crises - acute-onset, prolonged episodes of pain that are dull initially but become excruciating, and usually precede osteonecrosis and fractures



Do GD patients have lung involvement?

- **Lung-** Interstitial lung disease, pneumonia, and Pulmonary hypertension especially individuals with liver disease



How can one confirm the diagnosis of Gaucher disease?

- Measuring activity of glucocerebrosidase enzyme (Healthy individuals-normal enzyme activity; GD-lower enzyme activity
- Molecular assay of the gene

What are the precautions to be taken while collecting and transporting and testing sample?

- Patient details
- Collection in EDTA/ Heparin
- Transport precautions – Room temperature/ Ice pack depending on temperatures & transport time
- Preferably Isolate Leukocyte ands transport on ice

How important is Molecular testing
Are there any common mutations in India?

- Most Reliable
- Prenatal Diagnosis
- Genotype Phenotype Correlation
- L444P commonest

What are the initial lab evaluation for monitoring & additional work up ?

Hematology	**Hemoglobin,Platelet count** **PT, aPTT(in case of bleeding)**
Biochemistry	**Liver function tests, Renal function tests** **S. cal, phosphate, alkaline phosphatase** **S. iron, Vit B12, ferritin** **Biomarkers (Serum chitotriosidase, CCL18, tartrate-resistant acid phosphatase (TRAP), and angiotensin converting enzyme(ACE)** **Serum for antibodies**
Cardiac	**Electrocardiogram (ECG) or ECHO or other tests to assess for Cardiac involvement**

Additional work up

- **Hearing assessment by brain evoked response audiometry**
- **EEG**
- **Neuro-psychometry assessment**

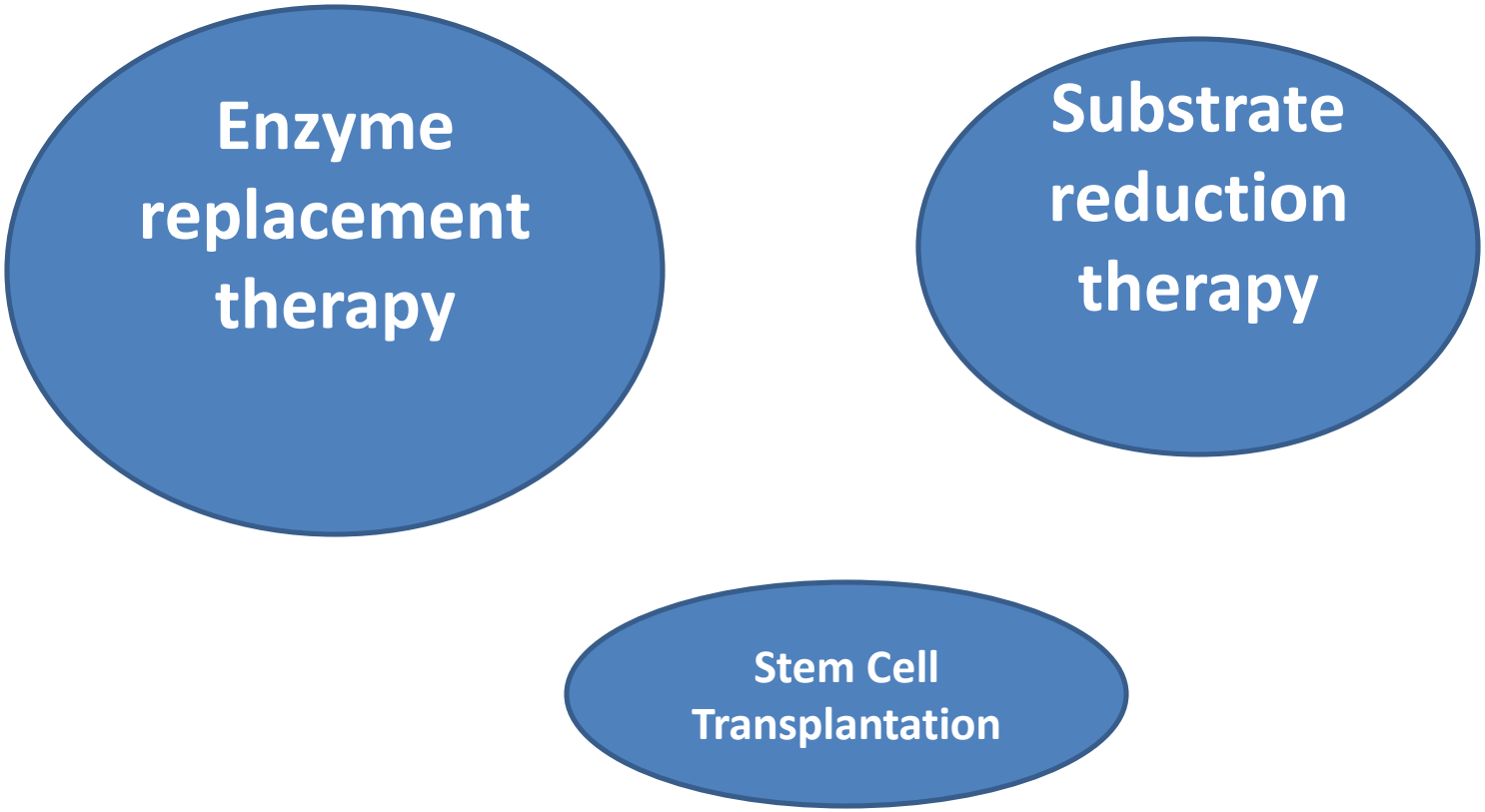
What are the Biomarkers for diagnosis & Follow up?

- Biomarkers: Routine Chitotriosidase- also important in follow up for patients on therapy
- Other Biomarkers CCL18, tartrate-resistant acid phosphatase (TRAP), and angiotensin converting enzyme(ACE)

What is the recommended initial radiologic assessment?

- Bone mineral density (BMD) with dual-energy X-ray absorption (DEXA) of the total body, lumbar spine and/or hips
- MRI of lumbar spine and femur
- Visceral assessment -Volumetric spleen and liver MRI/USG(less accurate)
- X- Ray Chest
- MRI Brain (Neuronopathic)

Is there any cure? What are the treatment options available for GD-Type 1 patients ?



What is Enzyme replacement therapy? Who should be given ERT?

- To provide deficient enzyme externally through intravenous route to allow the removal of the fatty material laden cells by its breakdown
- Cells function in a normal manner resulting in gradual restoration of normal size of spleen and liver, improved growth and quality of life

Who should be given ERT?

- Symptomatic GD Type I & Type III
- The usual dose of ERT is 60 units/kg/every 2 weeks
- Lower doses tried in Type I
- Dose individualized depending upon the clinical status of the patient
- Not recommended in Type II

ERT in TYPE III GD

- Cannot prevent or slow neurological progression in patients with type 2 or type 3 GD
- Not recommended for type 2 GD
- The recommended dose is 60 U/kg per 2 weeks for patients with clinically significant anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly

What is the effect of ERT ?

- **Reduction in**

  Spleen and liver size

  Improvement in

  hemoglobin and platelet count

  Growth and general well being

  Reductions in bone crises

  Prevents bone pain and serious skeletal complications such as joint and vertebral collapse, and fractures

Gaucher's-Response to ERT

Weinreb NJ et al (AJMG, 2002)

- 1028 pts; Effects of 2 to 5 years of treatment
- Hb ↑ to normal or near normal within 6 to 12 months, with a sustained response through 5 years
- Thrombocytopenic patients with intact spleens
  - the most rapid response in first 2 years
- Hepatomegaly ↓ 30% to 40%
- Splenomegaly ↓ 50% to 60%
- Bone pain or bone crises, 52% (67/128) were pain free after 2 years and 94% (48/51) reported no additional crises.

How do you give ERT? Are there any side effects of ERT?

- A recombinant enzyme
- It is available in powder form and has to be reconstituted
- Slow intravenous as an infusion over a period of 3-4 hours

Are there any side effects of ERT?

- Allergic reactions such as difficulty in breathing, choking, hives, swelling of lips, tongue, face, flushing, dizziness or fainting
- Pretreatment with antihistamines or corticosteroids, can prevent these reactions

What is the approximate cost of ERT? Why is the drug so expensive?

- Approx. Rs. 30,00,000 per year for a child weighing 10 kg
- Not manufactured in India
- Recombinant DNA technique

What is the Experience of ERT in India

Many Patients on ERT across India under INCAP Genzyme Humanitarian Initiative

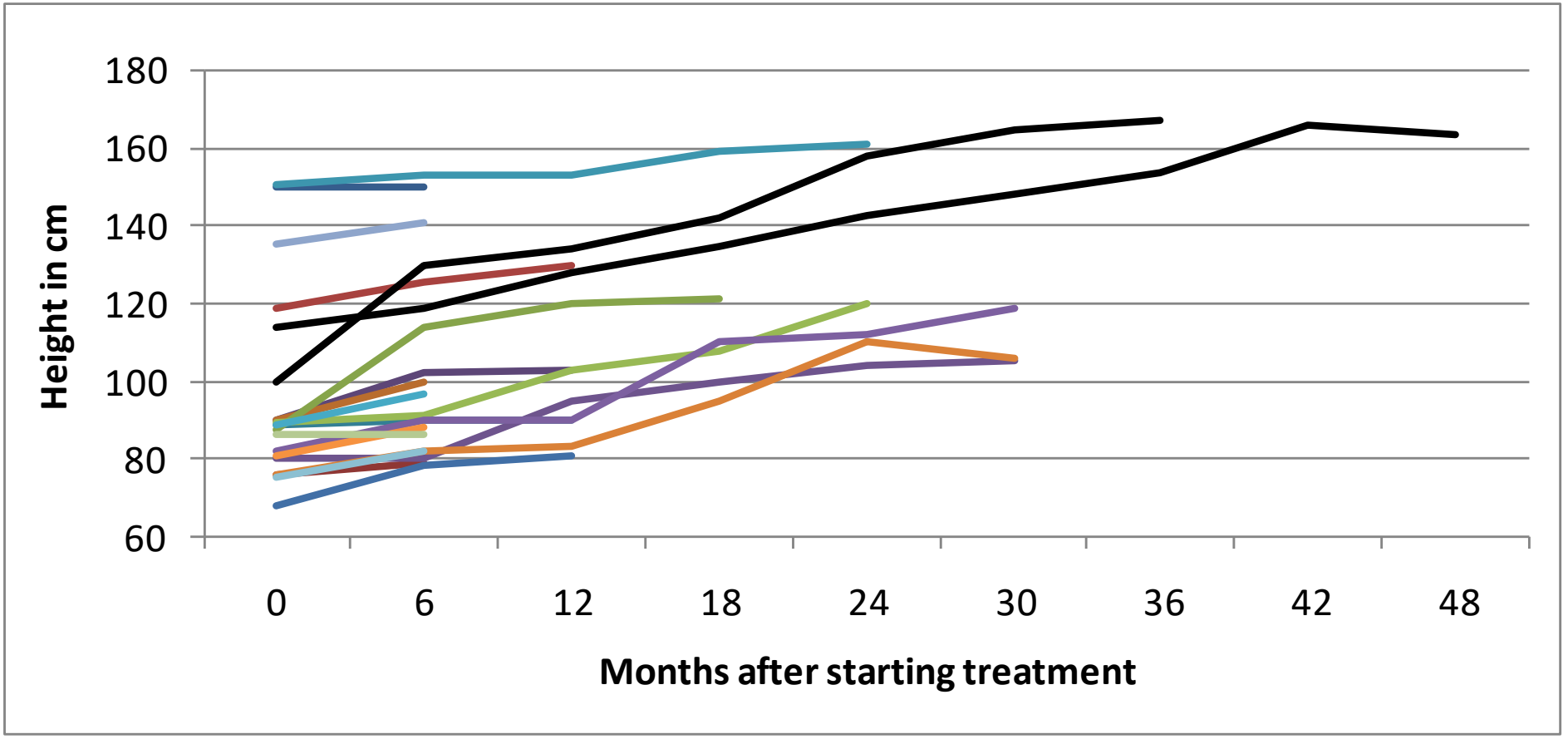
- 5 centers across India
- 22 patients on ERT for ≥ 6 months
- Data (compiled by Dr A Nagral) across all 5 centres
- *Indian Pediatr2011 Oct;48(10):779-84*

Hemoglobin and Platelets - ERT

	Haemoglobin (g/dl) mean ± SD	Platelets (per cmm) mean ± SD
6 months post ERT	1.5 ± 2.3 (p=0.01)	32,095 ± 59,538 (p=0.023)
1 year post ER	2.2 ± 1.8 (p=0.002)	1,32,833 ± 1,20,592 (p=0.003)

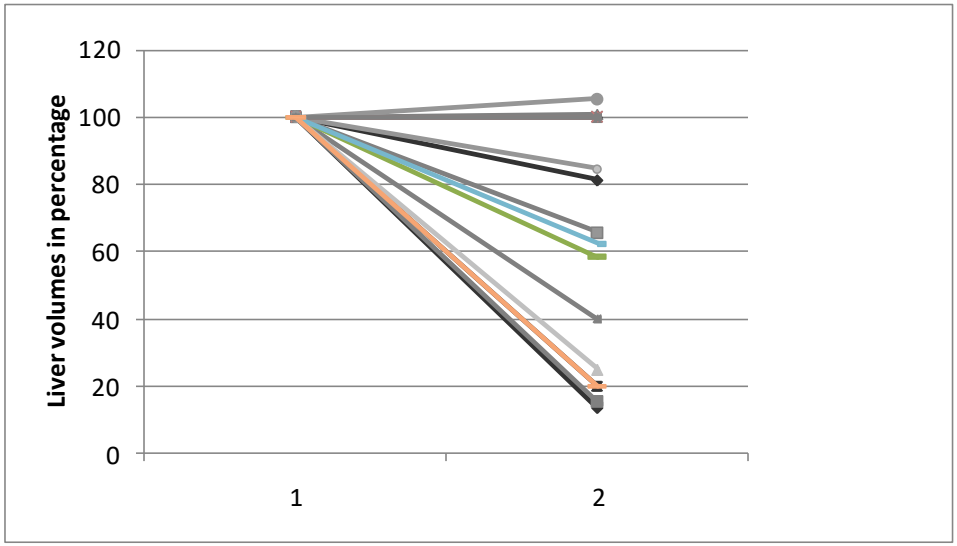
Data compiled by Dr A Nagral

Acceleration of growth on enzyme replacement therapy

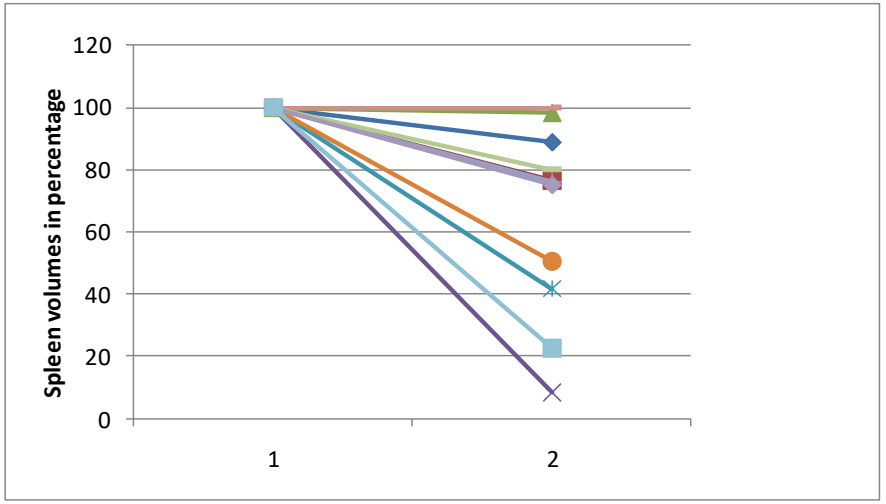


Reduction in Organ volumes

Liver



Spleen



What is Substrate reduction therapy (SRT)? Is it effective for all pts.?

- **Substrate reduction therapy (SRT) means reducing the production of the fatty material in the cells thereby avoiding accumulation in the cells**
- **SRT is useful for GD patients for whom ERT is not suitable**

Substrate ReductionTherapy

- **Miglustat (Zavesca®) is an oral treatment for adult patients with GD type 1 with mild to moderate manifestations for whom enzyme therapy is not an option**
- **Not yet approved to treat children with GD**

What is Enzyme Enhancement therapy ?

Chemical Chaperone Therapy

- Specific small molecules act as a chaperone to increase the residual activity of the lysosomal enzyme

(Sawkar AR , Cell Mol Life Sci 2006)

- AT2101 (oral agent) under trial

What is the role of Splenectomy ?

Splenectomy

- **Generally not recommended**
- **May be an option for patients (partial splenectomy preferred to total)with very low red blood cell or platelet count requiring repeated blood transfusions or massive splenomegaly**
- **Caution-severe bacterial infections and may lead to increased liver and skeletal symptoms**

Role of Stem Cell Transplantation ?

- To decrease the substrate overload of macrophages
  Ringdén et al; Transplantation1995
- Successful engraftment can correct the metabolic defect, improve blood counts, and reduce increased liver volume & improved QOL
- Severe GD (type 3), with chronic neurologic involvement
- Individuals with chronic neurologic GD & progressive disease despite ERT (BMT or combined ERT and BMT)
- **High morbidity and mortality**
- **ERT Preferred presently**

How to manage convulsions in GD ?

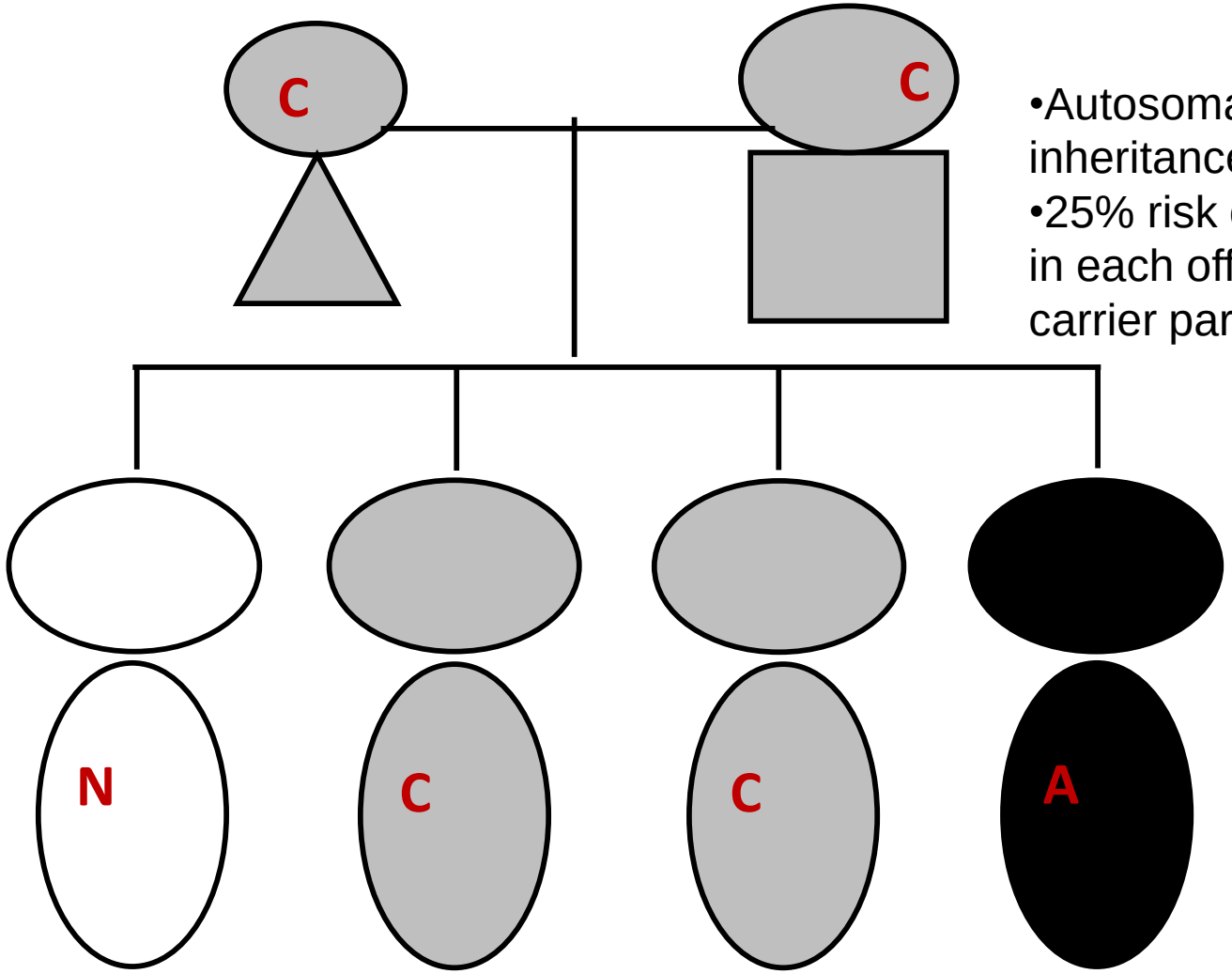
- **Convulsions can be difficult to control**
- **Routine anconvulsants can be used with dose adjustment**
- **May evolve into progressive myoclonic epilepsy phenotype**
- **ERT Cannot prevent or slow neurological progression in patients with type 2 or type 3 GD**

How to manage Bone Crises & Bone pains in GD ?

- **Bone crises and bone pains-** High-dose oral prednisone 1 gm/m^2 for 2 days followed by smaller doses of prednisone is useful to alleviate the pain within several hours
- **For nonspecific pains**, non-steroidal anti-inflammatory drugs (such as paracetamol)
- Oral bisphosphonates and **calcium/vitamin D** -low bone density
- Patient should receive **Iron and vitamin B12 supplements** in the presence of deficiency

What is the genetic basis of Gaucher disease? What is the Inheritance & risk of recurrence?

What is the Inheritance and risk of recurrence ?



- Autosomal recessive inheritance
- 25% risk of recurrence in each offspring of carrier parents

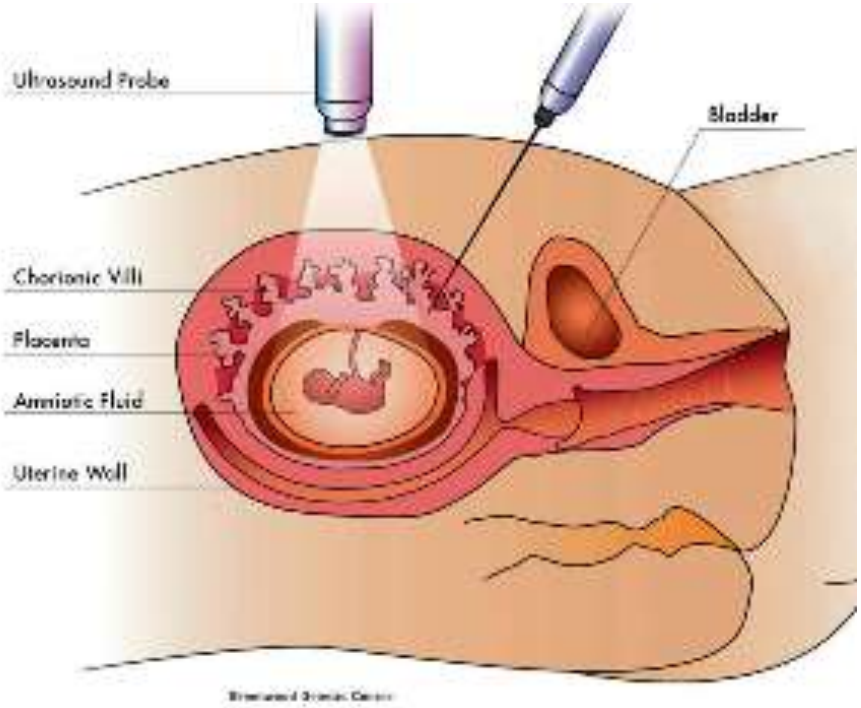
C=**C**arriers
N=**N**ormal
A=**A**ffected

Is prenatal diagnosis possible for Gaucher disease?

- Yes !!
- By chorionic villi sampling at 11-12 weeks of gestation
- Sample is tested for enzyme levels or gene defects if identified in the previous affected child

How is it done?

Transabdominal CVS



- **In this procedure a small amount of fetal tissue is biopsied from the placenta under ultrasound guidance and**
- **This procedure carries a small risk of fetal loss (around 1-2%)**

Pic source- Internet