Mucopolysaccharidoses FAQs

How common is MPS in our country?

- **Panethnic disorder**
- **Exact incidence in India -?**
- **Estimated total incidence of all types of MPS of approximately 1 in 20,000 live births**

Deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs)

Lysosomal Storage of GAG

- Respiratory
- Connective tissue
- Cardiovascular
- Gastrointestinal
- Ocular
- Neurologic
- Skeletal
- Organomegaly

Multisystem manifestations

Pic source- Internet

What are the major types of mucopolysaccharidoses and their major clinical features?

- I (three subtypes), II, III, IV, VI, VII, and IX
- Differentiated clinically by their clinical features and age of presentation and biochemically by their associated enzyme deficiency
- Coarse facial features, hepatosplenomegaly, and bone disease (dysostosis multiplex) with or without central nervous system (CNS) abnormalities

Multisystem involvement

Facial dysmorphism

Skin and Joints

Cardiac

Neurological

Ophthalmological

Visceral

Dysostosis multiplex

4 broad categories

Soft tissue storage and skeletal disease with or without brain disease (MPS I, II, VII)

Soft tissue and skeletal disease (MPS VI)

Primarily skeletal disorders (MPS IVA, IVB)

Primarily central nervous system disorders (MPS III A-D)

What are the different lab tests to diagnose MPS and its types? What is the sensitivity and specificity of MPS spot test?

- **Measurement of urinary GAG concentration**
- **Fractionation of GAG by electrophoresis or chromatography** (MPS typing) to verify pathologic GAG (heparan, dermatan, keratan) from common normal GAG (other chondroitins)
  - Sensitive but nonspecific screening test
  - False-negative results may occur, especially if the urine is too dilute
- GAG analysis - usually sensitive in MPS I, II, VI, and VII
- **MPS spot** -False positive results (Normal high excretion of GAG in children younger than one year of age)

Based upon the urine MPS typing, can one distinguish between different MPS types? Is it really necessary to do before ordering a specific enzyme assay?

Type	Enzyme deficient	Substrate accumulated
MPS I	α-L-iduronidase	Heparan sulfate Dermatan sulfate
MPS II	Iduronate sulfatase	Heparan sulfate Dermatan sulfate
MPS VII	β-glucoronidase	Heparan sulfate Dermatan sulfate
MPS VI	N-acetylgalacto- samine-4-sulfatase (arylsulfatase B)	Dermatan sulfate
MPS IV	N-acetylgalactosamine-6-sulfatase	Keratan sulfate
MPS III	Sulfamidase, α-N-acetylglucosaminidase, GAC-acetylase, N-acetylglucosamine-6-sulfatase	Heparan sulfate

What are the confirmatory tests?

- **Enzyme assay -** usually in peripheral blood leukocytes/fibroblasts, serum, or blood spots

- **DNA analysis for the specific MPS type**

Development & Behaviour & Neurological issues

Do all children with MPS have Developmental delay/ID?

- **No.** Developmental delay and progressive decline seen in **severe forms of MPS I, II, III, and VII.**
- **MPS IV and VI-normal development**
- **Hurler syndrome-** delay begins during the first year of life but is **often not appreciated until the second year followed by decline slowly (**average IQ is 50 by age three to four years)
- **Severe Hunter and Sanfilippo syndromes**
  - Developmental delay **typical at two to six years of age**
  - Accompanied by **hyperactive and aggressive behavior**

Phenotype evolves over time

What are the other neurological manifestations in different types of MPS?

- Developmental delay, abnormal behaviour **(I,II,III,VII)**
- **Seizures** may occur in Hunter and Sanfilippo syndromes
- **Sleep problems**
- **Communicating hydrocephalus** frequently develops in MPS I, II, III, VI, and VII – Head circumference monitoring

What are the other neurological manifestations in different types of MPS?

- **Spinal cord compression resulting in cervical myelopathy-** pachymeningitis cervicalis (VI) or C1-C2 subluxation(IV A and IV B; MPS I, VI, and VII)
  - **Pachymeningitis cervicalis** — Pachymeningitis cervicalis is the progressive thickening and scarring of the meninges around the cervical spinal cord caused by MPS storage (MPS VI)
  - **C1–C2 subluxation** due to Odontoid dysplasia and ligamentous laxity:Flexion and extension radiographic views of the neck, for evaluation of cervical spine stability. **Repeat every 1 to 2 years and/or before any surgical procedure requiring general anesthesia**
- **Carpel tunnel syndrome**

Is it necessary to do baseline neuroimaging for hydrocephalus and cervical spine instability?

- Yes.
- Neuroimaging (Computed tomographic or MRI scans of brain) **should be performed if hydrocephalus is suspected and in patients with developmental delay**
- MRI scans of spine - **Baseline and then every 1-2year**

Is surgery for hydrocephalus & craniovertebral/cord compression recommended & is safe?

- Yes
- **Communicating hydrocephalus- ventriculoperitoneal shunt**
- **Pachymeningitis cervicalis -Laminectomy with incision and removal of meningeal tissue**
- **Cord compression** -predominantly motor dysfunction with slowly progressive and nonspecific fatigue followed by decreased activity and preference for sedentary play If untreated, the cord compression can result in progressive ascending paresis and paralysis
- **Prophylactic posterior cervical fusion** in MPS IV A and IV B to avoid sudden high cord compression

When should NCV be done in these patients? Do they get any benefit after release?

- **All MPS** patients **should be evaluated for carpal tunnel syndrome** using nerve conduction studies **at baseline and every 1-2year**
  - Insidious onset
  - Symptoms of median nerve compression such as pain, paresthesias, or weakness, occur rarely in affected children, leading to under-recognition of the disorder

Treatment- Carpal tunnel release results in functional improvement
Recurrence common due to accumulation of storage material in soft tissues

What are the different behavioural problems seen in patients with MPS and in which MPS these are more common?) Is there any drug treatment available for hyperactivity? When do you start?

- Hyperactive and aggressive behavior **(II,III)**
- Short attention spans, do not respond to instructions, and have no sense of danger
- Aggressive behavior improves with age, as overall function progressively declines, usually reaching a neurologically devastated and unresponsive state in the early teenage years

Drugs-

Chlorpromazine, haloperidol, atomaoxatine (use limited by their side effects)
Methylphenidate is usually not helpful
Sleep disturbances (III)-Melatonin: 2 to 3 mg and increase if necessary after one to two weeks to 4 to 6 mg

Does early stimulation and behavioural therapy help?

- **Yes**
- Severe MPS I- as much developmental stimulation as possible during the early may support development
- Skills developed early may be retained throughout later stages of deterioration
- Adapting the environment to the child's needs
- **Neurocognitive function testing at diagnosis and then every year**

What are the different ophthalmologic problems seen in patients with MPS?

- loss of peripheral vision
  - Corneal clouding
  - Glaucoma
  - Optic neuropathy
  - Retinal degeneration

Corneal clouding
MPS IHS

No corneal clouding
MPS II

- **Yearly pediatric ophthalmologic evaluations**, including intraocular pressure measurements

Is there any role of corneal transplantation? When should it be considered? What are the chances of recurrence?

- **Penetrating keratoplasty** provides good results with maintainence of clear cornea in types IV, VI, and VII MPS. Types IS, II, and III do not require corneal transplantation.
- **Success of graft is limited by co-existent presence of retinal degeneration, optic atrophy, glaucoma and cortical visual impairment. Important to weigh the visual benefits against systemic problems and anaesthetic risks.**
- **Corneal grafts may remain clear for months. BMT and ERT may even cause partial clearing of host cornea.** Usually the visual impairment is not long lived due to reopacification of the graft with the original pathology.

How frequently should visual acuity testing, retinal examination and corneal examination be done?

- Patients need regular ophthalmic assessment to detect, monitor, and treat ocular complications
- **Visual acuity testing and refraction, corneal exam to look for degree of corneal opacification should be done yearly**.
- Regular glaucoma assessment including IOP, fundus exam should be done wherever possible
- ERG : helpful in assessment of prognosis after corneal transplantation. **Serial ERG** allows diagnosis and monitoring of retinopathy.
- **Regular fundus exam** to look for optic disc swelling and atrophy. Ophthalmologist may help to pick up signs of raised ICT early

ENT / Pulmonary/Cardiac

What are the common respiratory problems in these children?

- Severe respiratory insufficiency due to restrictive lung disease, obstructive sleep apnea, and/or asthma.
- **Upper airway obstruction**
- **Central apnea from cord compression** — MPS IV A and IV B
- **Lower airway obstructions** due to malformed and floppy tracheal cartilage, redundant respiratory epithelium, or pedunculated nodules

What is the cause of upper airway obstructions and what are its consequences?

- Snoring and obstructive upper airway disease by 2 or 3 years of age
- Due to enlarged tongue, tonsils, and adenoids; narrowed trachea; redundant airway tissue; and thickened vocal cords
- **Progressive respiratory insufficiency with severe hypoxemia , severe sleep apnea, right heart failure and sudden death**

How frequently should sleep study be done in these children?

- Sleep disturbances reported in 80-90% patients with MPS
- In severe MPS I after the age of 2 to 3 years and for patients with attenuated MPS I at diagnosis and every year thereafter, if respiratory insufficiency is detected
- Decision for polysomnography should be symptom based….

  - simple history taking about snoring, apneas, hyperactivity or excessive daytime sleepiness should determine need
- Several sleep disturbances described
- Most frequent and primary disorder is Sleep disordered breathing

What is the best possible management?

Positive airway pressure treatment

Continuous positive airway pressure

Bilevel positive airway pressure therapy, with or without supplemental oxygen

Tracheostomy in severe cases

When should pulmonary function studies be done in these children?

- **Severe restrictive lung disease** (due to a combination of skeletal abnormalities of the chest and spine and hepatosplenomegaly, limiting diaphragmatic excursion)
- Aggravation of developing obstructive sleep apnea

- **Baseline and then every 6 months**

What are the common ENT issues? How to manage them

Chronic recurrent rhinitis accompanied by persistent nasal discharge and frequent ear infections, chronic sinusitis

Routine ear, nose, and throat examinations performed at least annually

- **Tonsillectomy and adenoidectomy for all patients who develop airway compromise- Temporarily reduce airway obstruction and sleep apnea (recurrences possible)**
- **T-tube placement**
- **Influenza vaccine**

When should audiometry be done in these children?

Conductive and neurosensory deafness attributable to frequent ear infections, defective ossification in the middle ear, scarring of the tympanic membrane, or nerve damage

Annual audiologic examinations are warranted for all patients

Hearing aids

Do they have additional cardiac problems like cardiac valve disease and coronary insufficiency & how frequently should echocardiography and ECG be done in these children.

- Valvular disease, arrhythmia, cardiomyopathy, congestive heart failure, coronary artery disease
- Left-sided valvular disease with primary mitral and aortic valve dysplasia, causing regurgitation or stenosis (types I, II, and VI, and less commonly in MPS III)
- Patients with obstructive airway disease also may develop pulmonary hypertension and/or cor pulmonale
- **ECG and ECHO at diagnosis and every 1 to 2 years thereafter**

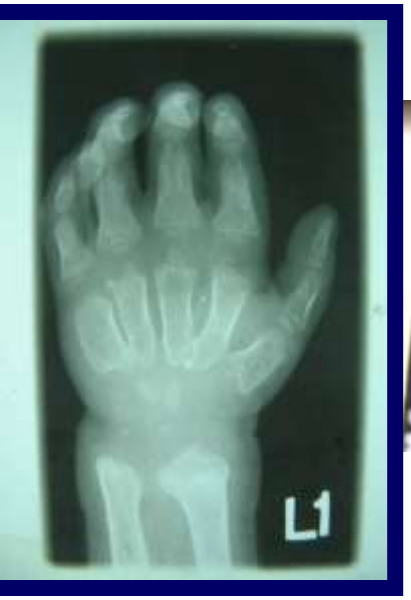
Medical treatment of hypertension and congestive heart failure
Valve replacement
Bacterial endocarditis prophylaxis

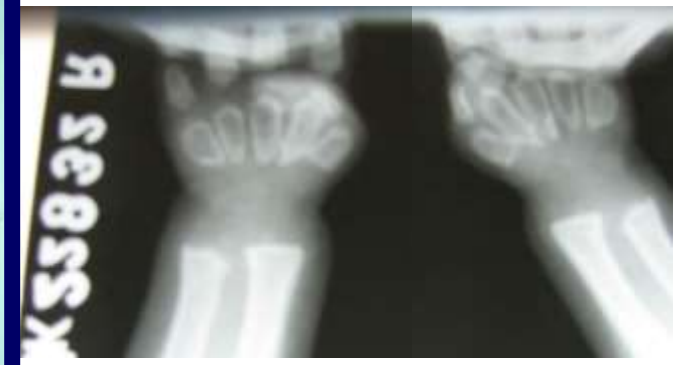
Skeletal and connective tissue

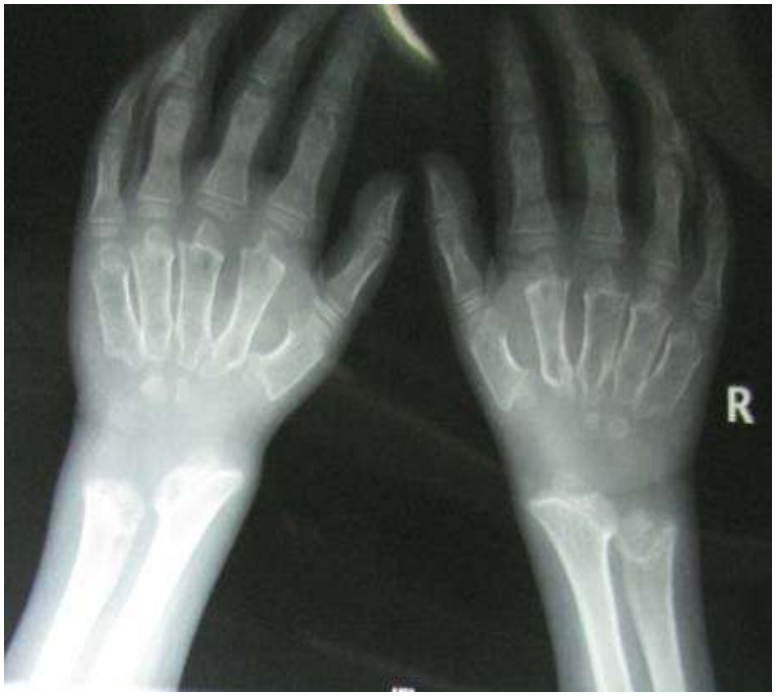
What are the radiographic findings in patients with MPS ? Can we differentiate between the different types based upon the X Ray findings?

Dysostosis multiplex

(the constellation of characteristic bony abnormalities)

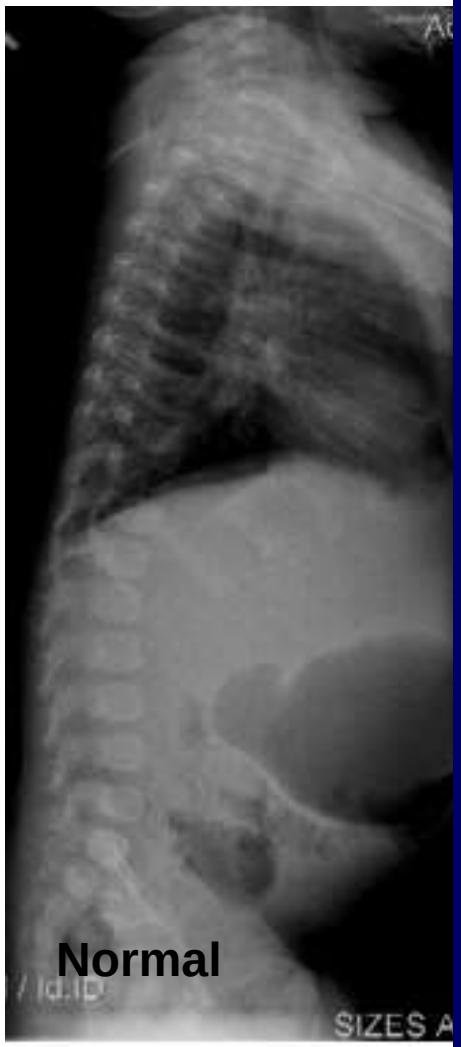


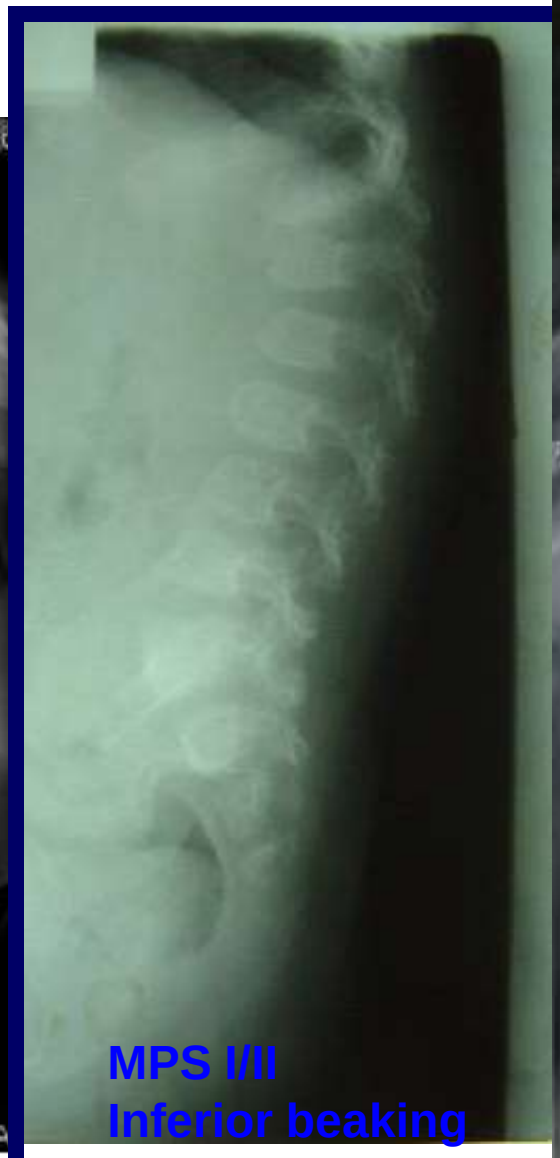


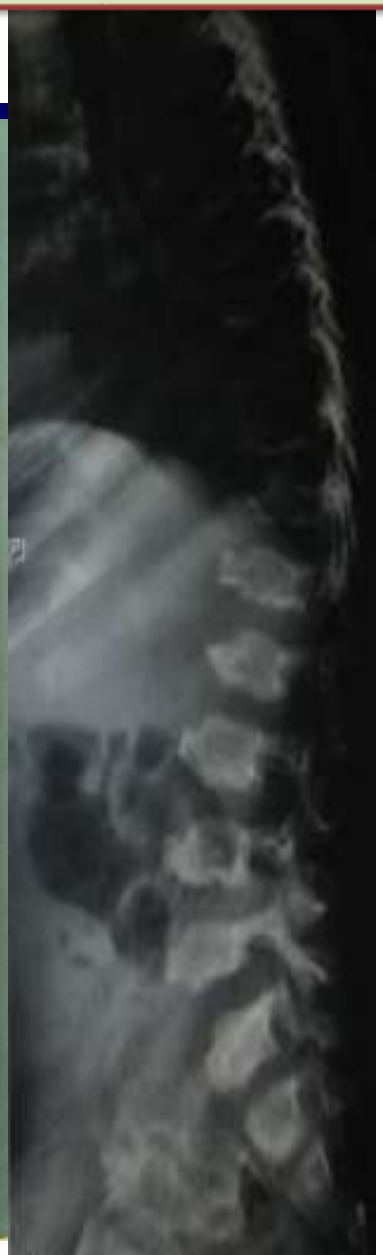


Variable degree of proximal pointing, wide (expanded) short metacarpals and phalanges, thin cortices, ulnar hypoplasia

Dysostosis multiplex

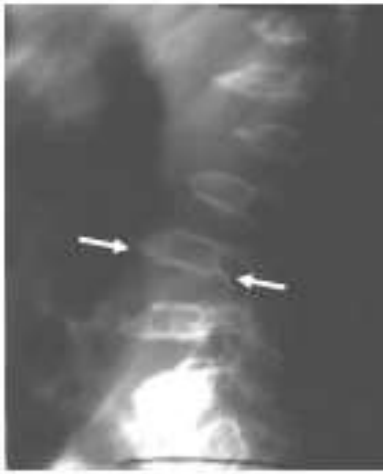




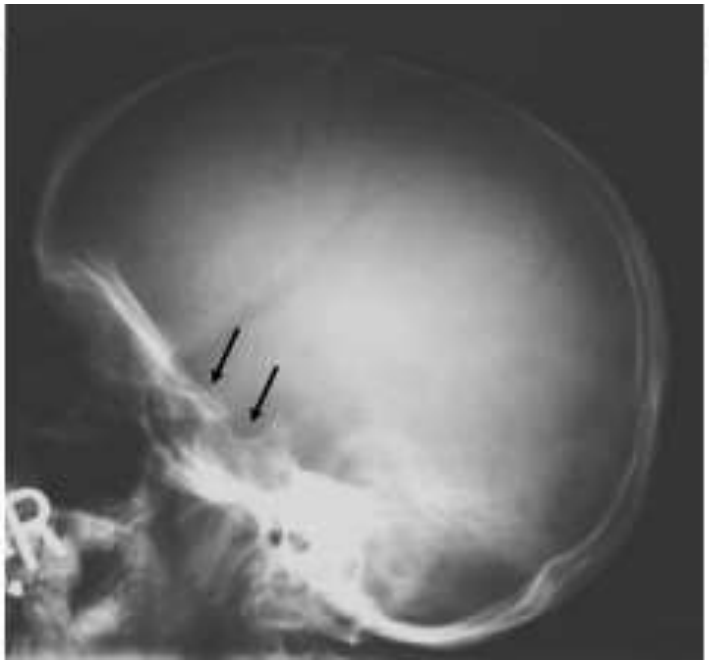


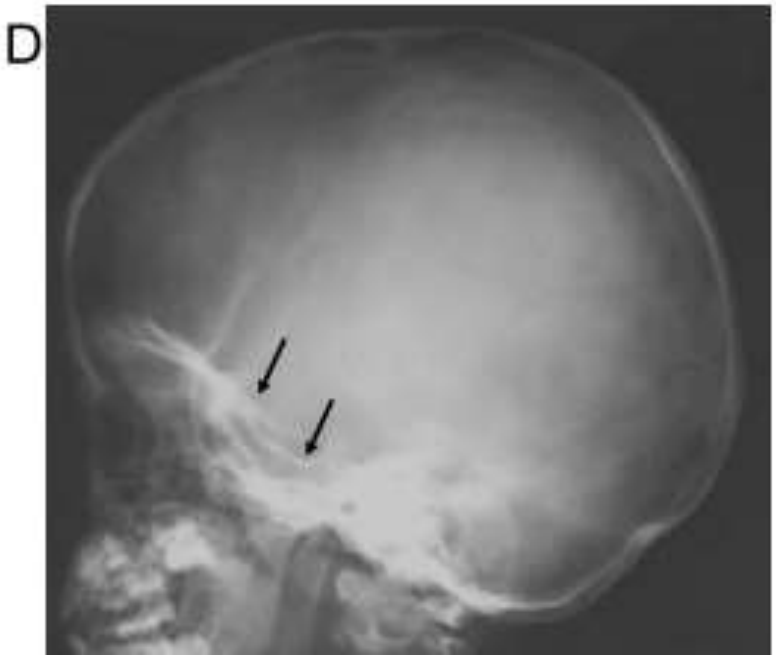
Characteristic gibbus deformity of the lumbar spine is apparent at 6 to 14 months of age

MPS IV
Central beaking



Dysostosis multiplex





J shaped sella

Do these patient need surgical repair for hernia, atlantoaxial dislocation/genu valgum?

- Spine deformities require fusion
- Acetabular hip dysplasia : osteotomy
- Genu valgum : epiphyseal stapling
- Surgical repair of inguinal hernias often fails and needs to be repeated/truss
- Large umbilical hernias –Repair

Preferably local or regional anesthesia
If GA- Bronchoscopic intubation using an endotracheal tube smaller than indicated by the patient's age or weight may help with airway management

What should be done for Joint stiffness in these patients? What are the pattern of exercises that should be done and how regularly?

- **Assessment of the degree of joint restriction**
- **Interventions to maintain joint function and muscle strength**

What exercises should be recommended to prevent respiratory complications

Which activities should be avoided in these patients?

- **Activities involving sudden jerky movements of neck**

- **Encourage passive and active range-of-motion exercises that may decrease joint restriction and pain**

What are the treatment modalities available to alter the severity of these disorders?

- **Hematopoietic stem cell transplantation**
  - **MPS I and some mild cases of MPS II and MPS VI**
  - **Most effective when initiated**
    - **before two years of age and before the onset of significant mental regression**
    - **Related donor with homozygous normal enzyme activity**
  - **Preprocedure counseling**
  - **Advantage of cord blood transplants - Ease of finding a donor**
  - **Engraftment and survival rates are similar with cord blood, bone marrow, and peripheral blood transplantation**
  - **Cord blood achieve full donor chimerism (93 versus 66 percent) and normal enzyme levels (100 versus 60 percent)**
- **Enzyme replacement**
- **Combination of ERT and HSCT**

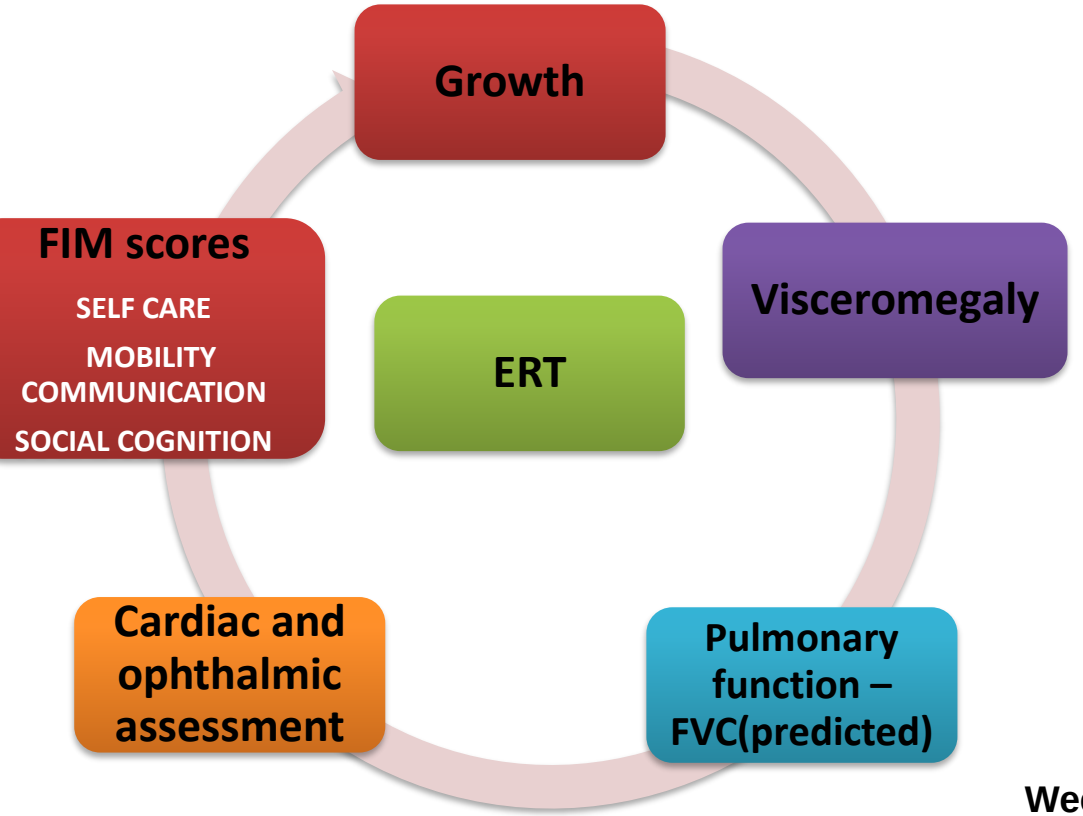
For which MPS ERT is available?
Status of ERT for MPS in India

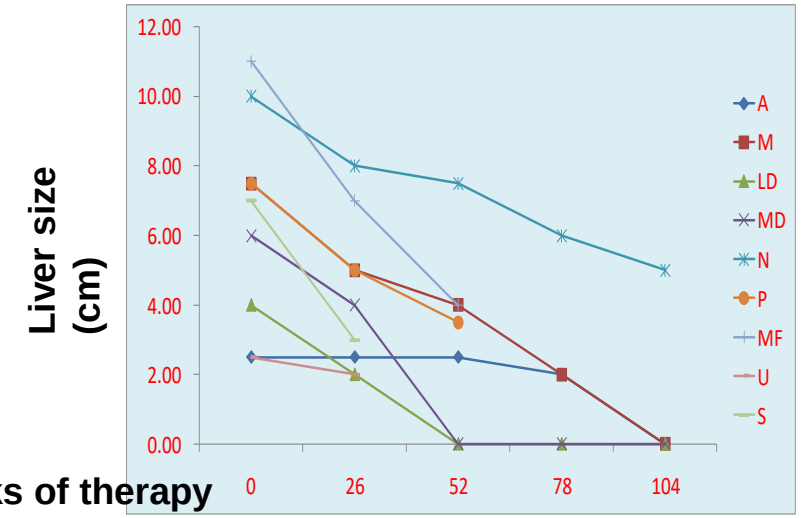
- Mucopolysaccharidosis (MPS) I - 2003
- MPS II - 2006
- MPS VI - 2005
- Morquio type A Biomarin phase 2
- Sanfillipo

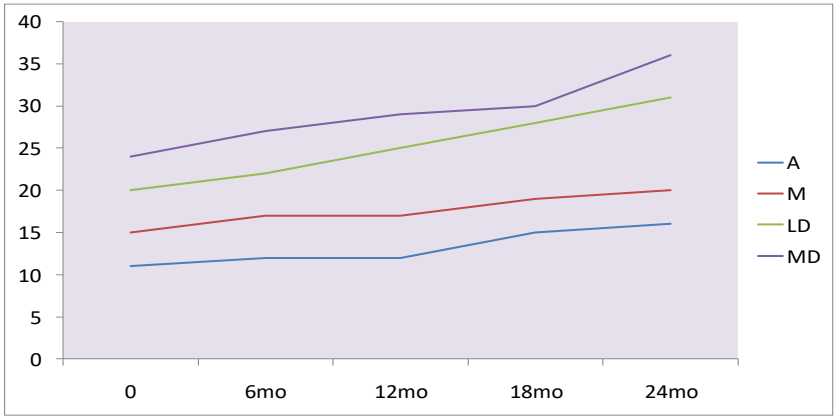
Compassionate Program (Genzyme, Shire)
Reimbursement for govt employees
Efforts of the parent group

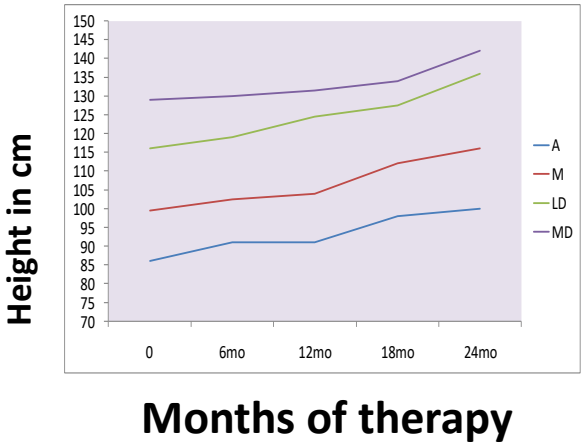
What is the effect of ERT on visceral, pulmonary and skeletal manifestations of MPS?

Liver size reduces rapidly (Week 26)

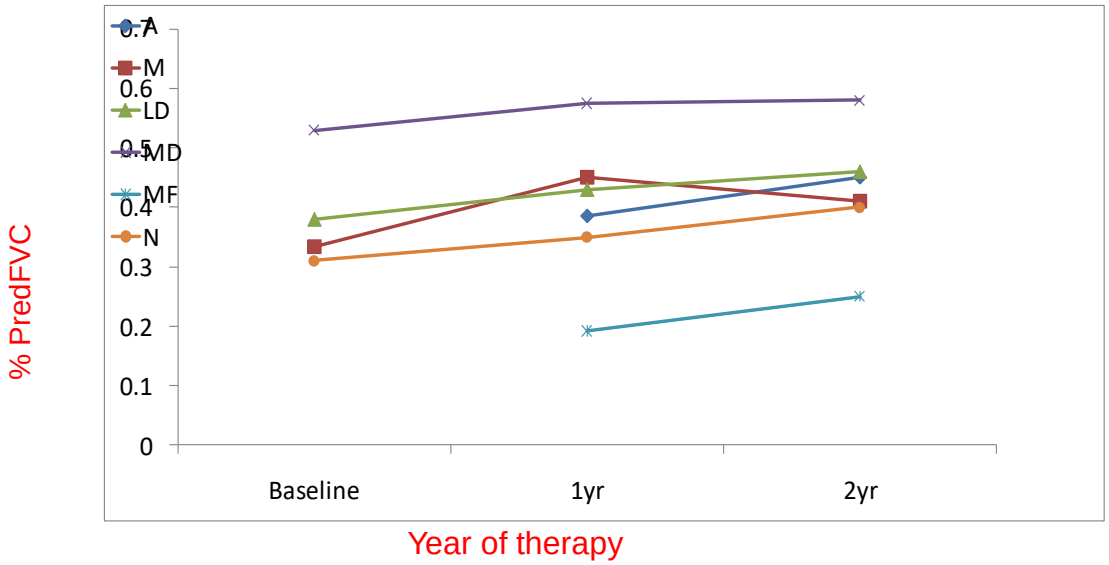








Improved height and weight



Forced vital capacity

Improvement in pulmonary function and functional capacity

Urine biomarker

GAG excretion reduces rapidly (Week 6) ;
Normal by Week 152

Improvements in sleep apnoea

Effect on FIM score(>7 years)

Pt	Pre therapy Total	Motor	Cognitive	Post therapy Total	Motor	Cognitive
MD	118	85	32	125	91	34
LD	100	72	28	116	85	31
M	67	43	24	111	81	30

SELF CARE
MOBILITY
COMMUNICATION
SOCIAL COGNITION

Total score=Min 18 Max=126
Motor-Min=13 Max=91
Cognitive-Min=5 Max=35

Improvement in FIM scores especially in the motor component

Kato et al .Brain dev 2007;298-305

What is the effect of ERT on neurological, cardiac and ocular manifestations of MPS ?

- ERT does not cross the blood-brain barrier : Unlikely to improve cognitive or central nervous system function
- May not correct preexisting cardiac valvular disease or skeletal abnormalities
- Stablity in ocular manifestations (including visual acuity)

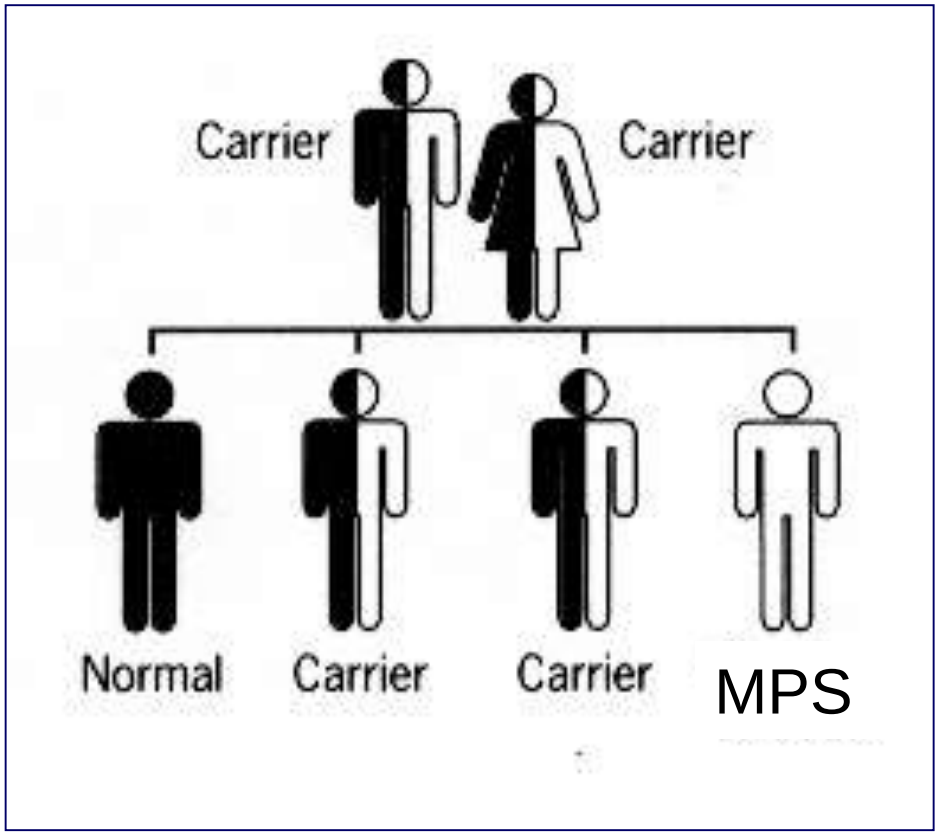
Effect on Cardiac status

	Pre therapy ECHO	Post therapy(12-18months) ECHO
MD	Normal	Mild MS(MVA2.3)
LD	Mild AR	Thick MV, mild MS(MVA1.8), mild MR
MF	Slight thickening of mitral valve	Mild MS,MR,TR
N	mod PS/PAH/TR, RV dysfunction	Severe MS(MVA-0.5),NO MR,PAH,Severe RV dysfunction

The cardiac valves appear unresponsive

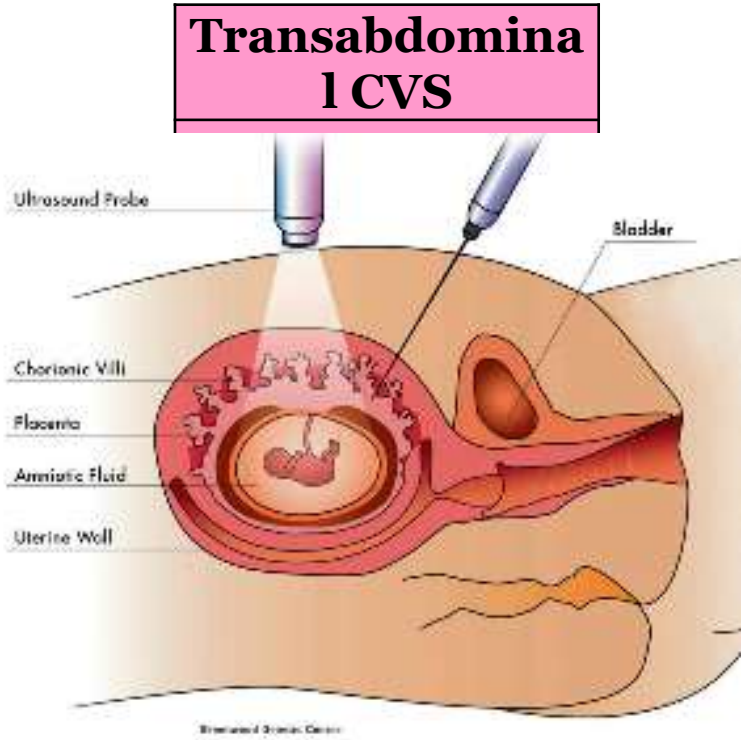
What is the chance that my other child will have MPS?

- **Autosomal Recessive/X linked**
- **ROR**



How and what gestation prenatal diagnosis can be done?

- Analysis of enzymatic activity of fetal cells by chorionic villus sampling (CVS) after 10 weeks
- Mutation analysis on fetal DNA obtained by CVS or amniocentesis

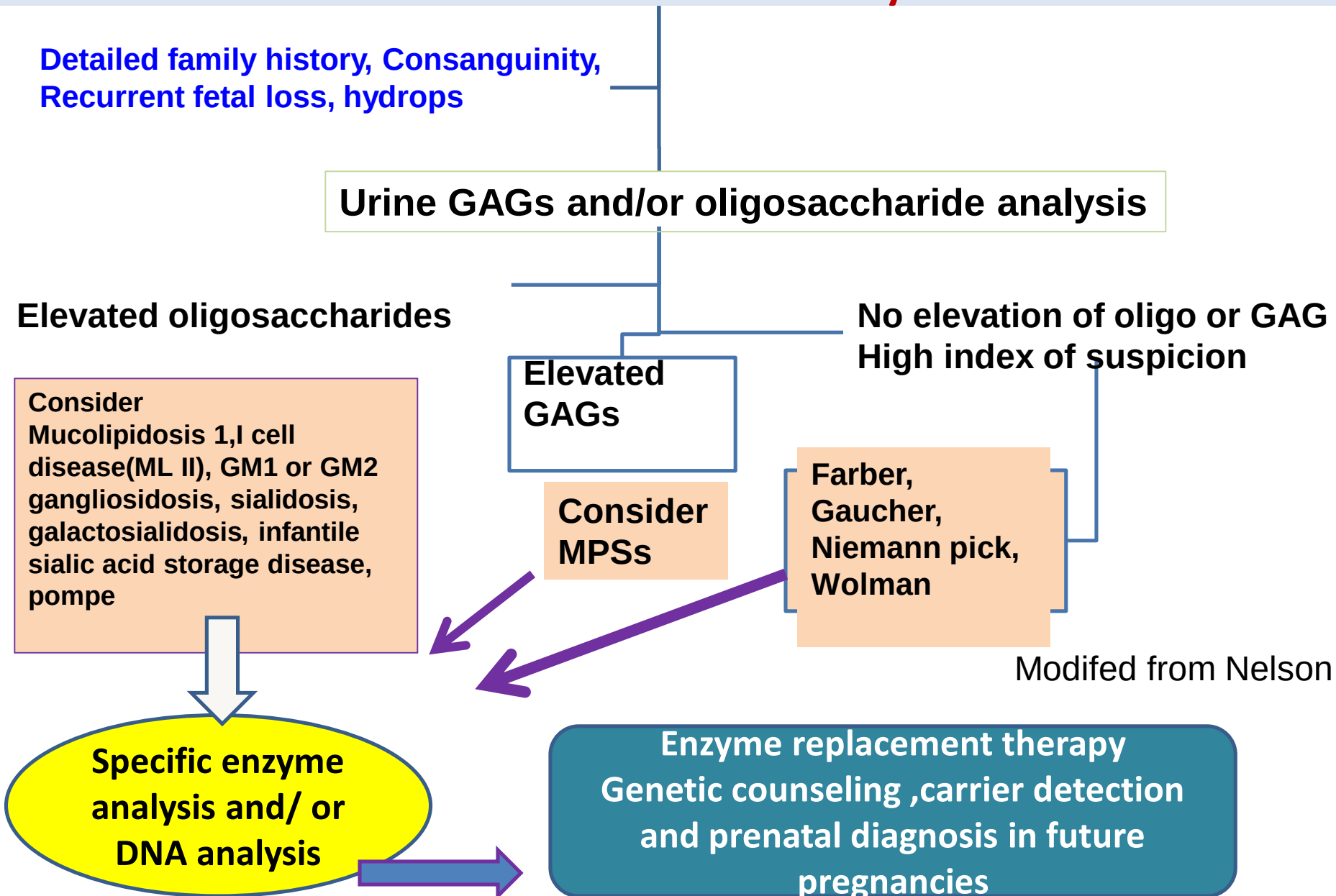


How reliable is PND?

- **CVS enzyme is reliable, however DNA testing is the gold standard.**

Wrap up

Coarse facial features, organomegaly, skeletal dysplasia, skin changes with or without dev delay



Modifed from Nelson

Summary

- The mucopolysaccharidoses (MPS) are differentiated by their clinical features and age of presentation
- Panethnic, multisystem manifestations
- Early diagnosis
- Specific therapies
  - hematopoietic cell transplantation
  - enzyme replacement therapy (for MPS I [Hurler, Hurler-Scheie, and Scheie syndromes], MPS II [Hunter syndrome], MPS VI [Maroteaux-Lamy syndrome])
  - Available in India for type I and probably for II in near future
- Multidisciplinary and supportive
- Early stimulation &Rehabilitation
- Treatment of complications
- Parent Support groups

Take home messages - 5As

- **A**ccurate diagnosis
- **A**ppropriate sample to **a**ppropriate lab
- **A**sk a geneticist (Phone a friend)
- **A**vailability of treatment, counseling, prenatal diagnosis