Mucopolysaccharidosis type IVA: Morquio A syndrome

The 1st International Morquio family meeting in LA, USA (Oct. 2003)

Producers:
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These educational CD slides were kindly co-produced by Morquio families, International Morquio Organization (IMO), and Dr. Shunji Tomatsu (Department of Pediatrics, Saint Louis University) to increase the awareness of mucopolysaccharidosis IVA (MPS IVA; Morquio A syndrome). It provides a short introduction about lysosomal storage disorders (LSD) and MPS in general, before going into more detail about MPS IVA. We have tried to cover the whole spectrum of disease, ranging from the most severe MPS IVA patients to the attenuated form of the disease. The slides included the update basic research and clinical research. The slides can be used for education to physicians, families, patients, and local communities.

We would like to thank individual Morquio families for providing the pictures and acknowledge Dr. Tadao Orii (Department of Pediatrics, Gifu University) and Dr. William Mackenzie (Department of Pediatric Orthopedics, Alfred I. duPont Hospital for Children) for contributing the slides and proofreading the slides.

Please contact Mary Smith (President of IMO; www.morquio.com) if you have any question on this educational CD. IMO has been founded in 1997 by Mary Smith.

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Morquio A Disease
MPS IVA

- Introduction to LSDs
- Introduction to MPSs
- Introduction to MPS IVA
- Clinical overview
- Clinical presentation - General
- Clinical presentation – Organ specific
- Genetics of MPS IVA (Morquio A Disease)
- Diagnosis and misdiagnoses
- Management and treatment
- Summary
MPS IVA

Mucopolysaccharidosis type IVA

Introduction to LSDs
Lysosomal Storage Disorders (LSDs)

- A group of over 40 genetic disorders
- Due to a deficiency of a lysosomal enzyme resulting in the accumulation of substrate in the cells
- Jointly affect an estimated 1:7,700 newborns
- Usually displaying progressive disease pattern, with wide spectrum of symptoms, signs and severity.
# LSD subdivision

<table>
<thead>
<tr>
<th><strong>Sphingolipidoses</strong></th>
<th><strong>Mucopolysaccharidoses</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to degrade glycosphingolipids containing three or less carbohydrate residues. Fabry, Gaucher, ASM deficiency (Niemann Pick A,B), Metachromatic Leukodystrophy, Krabbe,….</td>
<td>Failure to degrade glycosaminoglycans Hurler, Hunter, Sanfilippo, Morquio, Maroteaux-Lamy, Sly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Oligosaccharidoses</strong></th>
<th><strong>Others</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to degrade oligosaccharides Fucosidosis, Mannosidosis, Sialidosis, Galactosialidosis,….</td>
<td>Pompe, Mucolipidosis, Ceroid lipofuscinosis, …</td>
</tr>
</tbody>
</table>
Relative diagnostic frequency (Portugal, 1982-2001)
- Sphingolipidosis: 60.2%
- MPS: 26.3%
- Oligosaccharidosis: 9.9%
- Others: 9%

Relative birth prevalence (Netherlands, 1970-1996)
- Sphingolipidosis: 45.0%
- MPS: 33.1%
- Others: 19.0%
Incidence of lysosomal storage disorders (LSDs) in Australia (1980-1996)

- Gaucher: 14%
- MPS I: 9%
- Metachromatic Leukodystrophy: 8%
- MPS IIIA: 7%
- MPS II: 6%
- MPS III B: 4%
- MPS VI: 3%
- Niemann Pick A/B: 3%
- Niemann Pick C: 4%
- MPS II: 6%
- Pompe: 5%
- Krabbe: 5%
- Fabry: 7%
- MPS I: 9%
- MPS IIIA: 7%
- MPS II: 6%
- MPS III B: 4%
- MPS VI: 3%
- Niemann Pick A/B: 3%
- Niemann Pick C: 4%
- MPS III B: 4%
- Tay-Sachs: 4%
- Cystinosis: 4%
- GM1 Gangliosidosis: 2%
- Mucolipidosis II/III: 2%
- Sandhoff: 2%
- MPS IV (Morquio): 5%
Incidence of each type of MPS
(number of patients in each bar)

- MPS I
- MPS II
- MPS III
- MPS IVA
- MPS IVB
- MPS VI
- MPS VII

<table>
<thead>
<tr>
<th>Country</th>
<th>MPS I</th>
<th>MPS II</th>
<th>MPS III</th>
<th>MPS IVA</th>
<th>MPS IVB</th>
<th>MPS VI</th>
<th>MPS VII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>44</td>
<td>6</td>
<td>11</td>
<td>22</td>
<td>15</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>North Ireland</td>
<td>75</td>
<td>3</td>
<td>6</td>
<td>156</td>
<td>23</td>
<td>64</td>
<td>5</td>
</tr>
<tr>
<td>Netherlands</td>
<td>205</td>
<td>14</td>
<td>52</td>
<td>22</td>
<td>31</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Portugal</td>
<td>51</td>
<td>82</td>
<td>20</td>
<td>48</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>British</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colombia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Japan: 205 patients
North Ireland: 75 patients
Netherlands: 205 patients
Portugal: 51 patients
Australia: 48 patients
British Colombia: 3 patients
Poland: 12 patients
Introduction to MPSs
Common features among MPS

- 7 different types divided in subtypes
- Progressive, life threatening, multi-systemic diseases
- Heterogeneous clinical presentation
- Accumulated substrates are glycosaminoglycans (GAG):
  - Dermatan sulfate
  - Heparan sulfate
  - Keratan sulfate
  - Chondroitine sulfate

Pattern of accumulation dependent on the type of MPS

- Detected by measuring GAGs in the urine
- To be confirmed by analysis of specific deficient enzyme
## MPS current status

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Deficient Enzyme</th>
<th>Trait</th>
<th>Chromosome</th>
<th>Storage material</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I (Hurler)</td>
<td>α-L-Iduronidase</td>
<td>AR</td>
<td>4p16.3</td>
<td>HS, DS</td>
</tr>
<tr>
<td>MPS II (Hunter)</td>
<td>Iduronate-2-sulfatase</td>
<td>XR</td>
<td>Xq28</td>
<td>HS, DS</td>
</tr>
<tr>
<td>MPS IIIA (Sanfillipo A)</td>
<td>Heparan-N-sulfatase</td>
<td>AR</td>
<td>17q25.3</td>
<td>HS</td>
</tr>
<tr>
<td>MPS IIIB (Sanfillipo B)</td>
<td>α-N-Acetylgalactosaminidase</td>
<td>AR</td>
<td>17q21</td>
<td>HS</td>
</tr>
<tr>
<td>MPS IIIC (Sanfillipo C)</td>
<td>α-Glucosaminidase acetyltransferase</td>
<td>AR</td>
<td>-</td>
<td>HS</td>
</tr>
<tr>
<td>MPS IIID (Sanfillipo D)</td>
<td>N-Acetylgalactosamine 6-sulfatase</td>
<td>AR</td>
<td>12q14</td>
<td>HS</td>
</tr>
<tr>
<td>MPS IVA (Morquio A)</td>
<td>N-acetylgalactosamine-6-sulfate sulfatase</td>
<td>AR</td>
<td>16q24.3</td>
<td>KS, C6S</td>
</tr>
<tr>
<td>MPS IVB (Morquio B)</td>
<td>β-Galactosidase</td>
<td>AR</td>
<td>3p21.33</td>
<td>KS</td>
</tr>
<tr>
<td>MPS VI (Maroteaux-Lamy)</td>
<td>N-Acetylgalactosamine-4-sulfatase</td>
<td>AR</td>
<td>5q13.3</td>
<td>DS, C4S</td>
</tr>
<tr>
<td>MPS VII (Sly)</td>
<td>β-D-Glucuronidase</td>
<td>AR</td>
<td>7q21-q22</td>
<td>HS, DS, C4, 6S</td>
</tr>
</tbody>
</table>
GAGs

- Glycosaminoglycans (GAGs) were previously named mucopolysaccharides

- Biological macromolecules as a proteoglycan
  - Present in every tissue and organ
  - Present both extracellular and intracellular
  - Important component of the connective tissue and bone matrix
  - Regulate several cellular events (e.g. cell adhesion)
N-Acetyl glucosamine 6-sulfatase

β-Galactosidase

N-Acetyl glucosamine 6-sulfatase

β-Hexosaminidase A,B

Stepwise degradation of KS

1: MPS IVA
2: MPS IVB
3: MPS IIID
4: Sandhoff
MPS IVA

Introduction to MPS IVA
A disease with many faces and variations
History for study of MPS IVA
(Morquio syndrome)

- **1929** - First description of Morquio patients in Uruguay (Morquio L)
- **1974** – Identification of defective enzyme in Morquio syndrome (Matalon R et al.)
- **1976** – Assay of N-acetylgalactosamine-6-sulfate sulfatase (GALNS) in Morquio syndrome (Singh J et al)
- **1991** – Purification of enzyme (Masue M et al., Bielicki J et al.)
- **1991** - cDNA cloning of GALNS (Tomatsu et al.)
- **2003** – Establishment of model mouse with Morquio A disease (Tomatsu et al)
- **2004** - Development of keratan sulfate assay in Morquio (Tomatsu et al)
Keratan sulfate (KS)

- Inability to degrade KS gives rise to **MPS IV, Morquio syndrome**.

- KS is present as a style of proteoglycan mainly in cornea (KS 1 = N-linked) (lumican) and cartilage aggregated with chondroitin sulfates (KS 2 = O-linked) (aggrecan).

- The unique clinical manifestations of this disorder are attributable to the restricted tissue distribution of **corneas and cartilage**, in contrast to the much wider distribution of dermatan sulfate and heparan sulfate.
Mucopolysaccharidosis type IV (MPS IVA)

- Historically known as Morquio Syndrome
- Rare (1/200,000 - British Columbia, 1/76,000 - Northern Ireland, 1/500,000 - Japan)
- Progressive accumulation of glycosaminoglycans (GAGs), mainly Keratan Sulfate (KS) and Chondroitin-6-sulfate (C6S)
- Two forms are recognized, type A and type B - MPS IVA; N-acetylgalactosamine 6-sulfate sulfatase (GALNS), MPS IVB; β-galactosidase.
- Autosomal recessive disorder
Aggrecan

- Major component of extracellular matrix including KS (KS 2) and CS.
- Large aggregates (molecular size up to 800 MDa) with hyaluronan and so-called link-protein
- Provide a hydrated gel structure of cartilagenous tissues.
- Provide a function to resist compression in cartilage.
- Extreme content of negatively charged polysaccharide chains creating an osmotic environment that is responsible for the extremely high osmotic swelling pressure of cartilage.
- Prominent feature in joint disease (such as rheumatoid arthritis and osteoarthritis) by loss of aggrecan.
Structure of aggrecan

G1  IGD  G2  **KS rich**  CS1  CS2  G3

**N-Linked oligosaccharides**

Link protein  **KS 2**  O-Linked oligosaccharides  CS
Aggrecan

Link Protein

Aggrecan

Hyaluronan

Collagen Fibril

Collagen Tension

Proteoglycan

Swelling

Pressure $H_2O$
LUMICAN

• Lumican is a KS (KS 1) proteoglycan most closely resembling fibromodulin.

• Besides cornea, it can be found from muscle, cartilaginous tissues, kidney, lung, and intestine.

• In the cornea, an exact spacing and thickness of the collagen fibers can be suggested to be critical for the transparency.
Structure of Lumican

- **Keratan sulfate**
- **Disulfide bonds**
- **Putative β sheet in leucine rich repeat**

**MOTIFS**
- LPXXLXXLYLXNNXI
- LQXLXLXHNXL
- LXXLDLSFNQL

Potential N linked oligo site (Keratan sulfate 1)

Potential N linked oligo site (High mannose oligosaccharide)
Keratan sulfate proteoglycan

KS 1 (Cornea)
GALNS deficiency disrupts the sequential breakdown of KS.
The deficient diseases corresponding to the numbered reactions are 1 = MPS IVA; 2 = MPS IVB. In Morquio syndrome, the degradation of KS is defective because of the deficiency of either GALNS in MPS IVA or β-galactosidase in MPS IVB. KS consists of galactose-6-sulfate + GlcNAc-6-sulfate.
MPS IVA

Clinical overview
Cervical myelopathy can develop early in patients with the severe form of Morquio syndrome. Patients with the severe form may not survive beyond their twenties or thirties. Paralysis from the myelopathy, restrictive chest wall movement, and valvular heart disease all contribute to their shortened life span. Length of survival may improve with the improved comprehensive care available to these patients today.
MPS IVA – Clinical summary

- Systematic bone dysplasia
- Wide spectrum of disease severity
- Progressive and debilitating
- Severe morbidity and early mortality
Clinical features of MPS IVA

Deficiency of GALNS

Storage of GAGs in tissues, especially cartilage cells

- Short neck and trunk dwarfism
- Fine corneal clouding
- Skeletal dysplasia (cervical spinal cord compression, pectus carinatum, genu valgus, kyphoscoliosis)
- Waddling gait with a tendency to fall
- Ligamentous laxity
- Small teeth with thin enamel and frequent caries formation
- Facial features (coarsening of facies)
- Hearing loss
- Easy fatigue
- Sleep apnea
- Restriction of breathing
- Recurrent infection

Short neck and trunk dwarfism
Fine corneal clouding
Skeletal dysplasia (cervical spinal cord compression, pectus carinatum, genu valgus, kyphoscoliosis)
Waddling gait with a tendency to fall
Ligamentous laxity
Small teeth with thin enamel and frequent caries formation
Facial features (coarsening of facies)
Hearing loss
Easy fatigue
Sleep apnea
Restriction of breathing
Recurrent infection
Disease progression: severe to attenuated

3 months
12 months
2 years
7 years
Disease progression: severe

1-2 months 1 year 2 years 3 years 6 years
Disease progression: severe

- 7 years
- 8 years
- 11 years
- 16 years
- 16 years
Disease progression: after operation of osteotomy

MPS IVA (10 years old)
<table>
<thead>
<tr>
<th>Clinical severity</th>
<th>Most severe</th>
<th>Attenuated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (valvular) disease</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Corneal clouding</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Obstructive airway disease</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Hyperlaxity of joints</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Dysostosis multiplex</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Skeletal malalignment</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Walking disturbance</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Short stature</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Walking disturbance</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Attenuated Most severe</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Most severe</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Morbidity</td>
<td>Symptoms</td>
<td>Treatment</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>Bone Dysplasia Severe</td>
<td>short stature, abnormal gait, joint pain, bone</td>
<td>orthopedic surgeries; realignment osteotomy,</td>
</tr>
<tr>
<td></td>
<td>defomities</td>
<td>corrective knee surgery, hip replacement etc.</td>
</tr>
<tr>
<td>Spinal Cord Compression</td>
<td>cervical myelopathy, bowel and bladder</td>
<td>spinal bracing, cervical decompression, cervical</td>
</tr>
<tr>
<td>Severe</td>
<td>dysfunction, apnea</td>
<td>spinal spinal fusion</td>
</tr>
<tr>
<td>Joint Disease Severe</td>
<td>ligamentous laxity</td>
<td>weight control, physical therapy, wrist splint,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bracing</td>
</tr>
<tr>
<td>Obstructive Airways</td>
<td>sleep apnea, pneumonia, tracheostomy, high risk</td>
<td>tonsillectomy and adenoidectomy, tracheostomy, CPAP</td>
</tr>
<tr>
<td>Severe</td>
<td>in anesthesia</td>
<td></td>
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## Morbidity & management - 2

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear problem</td>
<td>Mixed hearing loss; frequent middle ear infections, deformity of the ossicles, abnormalities of the inner ear</td>
<td>ventilating tube, hearing aid</td>
</tr>
<tr>
<td>Mild to moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye problem</td>
<td>corneal clouding; visual disturbance, photophobia</td>
<td>no definitive treatment, darkened glasses</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental problem</td>
<td>dental caries and tooth fractures and; abnormally thin enamel</td>
<td>daily oral hygiene, professional dental cleaning, sealants</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart problem</td>
<td>cardiac dysfunction; coronary heart disease and valve thickening</td>
<td>endocarditis prophylaxis, valve replacement</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MPS IVA

Clinical symptom in MPS IVA

General
Physical appearance

- Short trunk dwarfism
- Genu valgum (knocked knee)
- Pectus carinatum (pigeon chest)
- Kyphoscoliosis
- Hypermobile joints
- Fine corneal clouding
- Facial dysmorphisms
- Coarse thick hair
- Flat nose bridge
- Short nose
- Prominent forehead
Possible initial symptoms during infancy (0 - 24 months)

**Signs and Symptoms**

- **Signs and symptoms not apparent at birth**
- Skeletal deformities; pectus carinatum, genu valgus, kyphoscoliosis
- Waddling gait with a tendency to fall
- Delayed onset of standing and walking
- Growth delay
- Large head circumference
INITIAL SYMPTOMS (n=259)

International Morquio Registry (2005)

- Bone Deformity: 64.1%
- Growth Retardation: 54.1%
- Kyphosis: 48.6%
- Abnormal Gait: 45.9%
- Difficulty of Joint Movement: 48.6%
- Cervical Spine: 54.1%
- Hearing Loss: 17.4%
- Incresased Cranial Circumference: 12.7%
- Lower Leg Pain: 12.4%
- Chronic Ear Infections: 12.4%
- Corneal Clouding: 9.4%
- Knees Slightly Bent: 5.4%
- Others: 5.4%

Percentage (%)
Possible current symptoms from early childhood to adolescence

**Signs and Symptoms**
- Skeletal deformities; pectus carinatum, genu valgus, kyphoscoliosis, coxa valga, hip and knee pain
- **Cervical spine instability**
- **Cervical myelopathy (spinal cord compression)**
- Abnormal gait with a tendency to fall
- Growth retardation with short trunk and neck
- **Restriction of efficient breathing**
- Fine corneal clouding
- **Hypermobile joints**
- Limited endurance
- Coarse facial features
- **Hearing loss**
- Hepatomegaly
- Abnormally thin enamel and frequent caries formation
- Recurrent infection; chronic otitis, upper respiratory infection
CURRENT SYMPTOMS
(n=263; Average, 16 years)

International Morquio Registry (2005)
Possible clinical symptoms from adolescence to adulthood

**Signs and Symptoms**

- Skeletal deformities; pectus carinatum, genu valgus, kyphoscoliosis, gibbus, coxa valga, hip and knee pain
- **Inability of walking (wheel-chaired)**
- Growth retardation with short trunk and neck
- Hypermobile joints
- Cervical spinal myelopathy
- Restriction of efficient breathing
- Fine corneal clouding
- **Aortic/mitral valve disease**
- Limited endurance
- Coarse facial features
- Hearing loss
- Abnormally thin enamel and frequent caries formation
- Recurrent infection; chronic otitis, upper respiratory infection
Surgical operation
(total number = 156, average; 17.5 years)

No (22%)

Yes (78%)

International Morquio Registry (2005)
Location of surgical operations (number; 156 patients)

- Neck
- Knee
- Ear tube
- Hip
- Leg
- Tonsil
- Adenoid
- Hernia
- BMT

International Morquio Registry (2005)
Clinical presentation in MPS IVA

Organ specific
Multi-systemic manifestations

- Atlantoaxial instability
- Cervical myelopathy
- Ears/Nose/Throat
- Eye
- Dental
- Cardiovascular
- Gastrointestinal
- Airway disease
- Skeletal/joints
Spinal cord pathophysiology

GAG (KS) accumulation.

- Metaphyseal and epiphyseal bone dysplasia
- Degradation of connective tissues near the joint

- Odontoid hypoplasia
- Ligamentous laxity
- Anterior extradural GAG deposition
- Atlantoaxial subluxation
- Spinal cord compression

Cervical myelopathy - bowel and bladder dysfunction, decreased endurance, apnea, hyperreflexia, and clonus
Consequential quadripareisis or even death

Degradation of connective tissues near the joint
MRI (magnetic resonance imaging)

- 4 year-old patient
- Normal

- Spinal cord compression
- Hypoplasia of odontoid process
CT scan (Computer tomography)

Absence of odontoid process

MPS IVA patient (6.6 years)
X-ray picture on the neck

Extension

Flexion

2.3 years

Atlantoaxial subluxation

Hypoplasia of odontoid
Ears, Nose, and Throat

- Chronic recurrent ENT infections
- Thick and copious secretions
- Loud breathing, sleep apnea
- Hearing loss
- Flattened nose bridge
- Enlarged tonsils and adenoids, narrowed trachea, thickened vocal cords
- Large tongue
Ear problem

- **Mild to moderate conductive deafness, sensorineural deafness, mixed deafness**, especially of higher frequencies: mostly by the end of the first decade

- **Resulting from frequent ear infections, inner ear and middle ear abnormalities**
Hearing loss – pathophysiology

GAG storage

Mucosal linings
Connective tissue
Cartilage and bone

Recurrent loops, leading to progression of symptoms

Airway narrowing

Thick and copious secretions

Chronic middle ear infections

Abnormalities or damage in the inner ear

Deformity of the ossicles (middle ear)

Hearing loss
• Fine stromal corneal clouding
• Photophobia
• Strabismus
• Impaired visual field
• Decreased visual acuity
• Cataracts in adulthood
• Blindness in adulthood (rare)
• Glaucoma in adulthood (rare)
• Retinal degeneration in adulthood (rare)
Corneal clouding-pathophysiology

**GAG storage**

- Stroma in cornea
  - Non-uniform fibril diameter
  - Increased fibril number density
  - Inhomogeneities such as expanded cells and collagen-free lakes in stroma
  - Increased light scattering: corneal clouding

**Normal**

- Ed
- St
- Ep

**Affected**

- Ed
- St
- Ep
Dental problem

- Defective thin enamel of baby & permanent teeth with sharp pointed cusps
- Small and widely spaced teeth
- Spade-shaped incisors
- Concave buccal and occlusal surfaces and pitting
- Tendency to fracture and flake off
- Frequent caries formation

39 year-old patient

3D diagram of tooth structure:
- Enamel
- Dentine
- Pulp Chamber
- Cementum
- Root Canal
- Periodontal Ligament
- End of root
- Nerves & Blood Vessels
- Bone
- Crown
- Root
widely spaced teeth and spade-shaped incisors:
24 year-old patient

Normal

MPS IVA

Spade-shaped incisors

Concave occlusal surfaces
Cardiovascular disease

Signs and symptoms

- Valvular thickening /deformity leading to insufficiency:
  - Aortic, mitral or other regurgitation
  - Mitral or other narrowing
  - Heart murmur
- Congestive heart failure
- Pulmonary hypertension (rare)
- Coronary artery disease (rare)
- Myocardial infarction (rare)
- Cardiomyopathy (rare)

Generally, mild heart disease!
Gastrointestinal tract

- Mild hepatosplenomegaly, caused by excessive storage in liver and spleen, leading to:
  - Hernias

- Loose stools, diarrhea, constipation, abdominal pain
  - Episodic, chronic
  - Unknown etiology, may be connected with cervical myelopathy

**Generally, mild gastrointestinal disease!**
<table>
<thead>
<tr>
<th>Airway problem</th>
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<tbody>
<tr>
<td>The most important and difficult aspect in MPS IVA is the management of restrictive lung disease and obstructive airway!</td>
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<tr>
<td>Frequent respiratory infections</td>
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<tr>
<td>Limited endurance</td>
</tr>
<tr>
<td>Superficial and rapid breathing</td>
</tr>
<tr>
<td>Snoring</td>
</tr>
<tr>
<td>Abnormally shaped thoracic cage: restrictive</td>
</tr>
<tr>
<td>Respiratory collapse</td>
</tr>
</tbody>
</table>
Airway – pathophysiology

- **GAG storage**
  - Mucosal membrane
  - Connective tissue
  - Cartilage and bone
  - Restrictive

- **Recurrent loop**
  - Large tongue
  - Adenoid, tonsil, and vocal cord hypertrophy
  - Tracheobronchial abnormalities, short neck, large mandible

- **Obstructive**
  - Airway narrowing
  - Thick and copious secretions
  - Chronic respiratory infections

- **Sleep apnea**
  - Noisy breathing
  - Shortness of breath
Airway problem

- Obstructive airways disease
- Restrictive lung disease
  - Sleep apnea
  - High rate of anesthesia complications
- Cor pulmonale
- Respiratory insufficiency

Need for adenoidectomy/tonsillectomy/C-PAP/ Bi-PAP/ Tracheostomy.

Abnormal oar-shaped ribs, curved clavicles and scoliosis
Pathophysiology of skeletal joint and muscle disease

Bones
- Dysostosis multiplex: all bones can be affected
  - Ossification centers:
    - abnormal modeling (delayed, incomplete)
    - dysplasia may induce dislocation and osteoarthritis
  - Storage in growth plates: destruction of cartilage layer

Joints
- GAG storage in and around (potentially all) joints and ligaments: hyperlaxity
Joint problem

- **Ligamentous laxity** unlike other MPS
- Small joints, most severely, the wrists with a very weak grip
- Difficulties with dressing, personal hygiene, and writing
- **Subluxation** in neck and hip joints
- Decreased joint mobility in large joints such as hips, knees, and elbows

Range-of-motion exercises, swimming, and computer typing appear to offer some benefits in preserving joint function fine motor skills and should be started early in the clinical course.
Degradation near the joint

Hyperlaxity of joints

GAG storage

Connective tissue

Cartilage and bone

Degradation near the joint

Metaphyseal deformities, hypoplasia of the bones

Hyperlaxity of joints

Floppy wrists and fingers

Knocked knee

Subluxation of hip and neck joints

Cervical instability
Skeletal/joint problem

10 year-old patient

Knocked knee

Floppy wrist restriction and contracture

Metatarsal abnormalities and flat foot

Protrusion of the chest and deformity of the ribs

Sandal gap
Skeletal/joint problem; 3 year-old patient (Severe)

Genu valgum
Pectus carinatum
Kyphoscoliosis
Prominent Forehead
Skeletal/joint problem; 3 year-old patient (Severe)

Genu valgum
Pectus carinatum
Kyphoscoliosis
Prominent bone deformity
Skeletal/joint disease - Thorax

Flat, oar shaped ribs

5 year-old patient
Skeletal/joint disease - spine

- Hyperkyphosis
- Flared ribs
- Platyspondyly
- Ovoid vertebrae
- Compressed vertebrae
- Hyperlordosis
- Anterior central beaking

Incomplete ossification!
<table>
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<th>Description</th>
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<td>1 day</td>
<td>Beaking</td>
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<tr>
<td>2 mo</td>
<td>Ovoid vertebrae, Gibbus, Platyspondyly</td>
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<tr>
<td>15 mo</td>
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<td>32 mo</td>
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</table>
Skeletal/joint disease - hip

- Wide flared iliac
- Underdeveloped acetabula
- Flattered capital femoral epiphyses
- Coxa valgus

8 year-old patient
Cartilage

Function: To decrease friction in joints

Mature articular cartilage is **avascular**, aneural, and alymphatic.

Comprises:

1. **Chondrocytes (5%)**
2. Extracellular matrix (95%)
   a. Water (75%)
   b. Collagen 2 (5%)
   c. Proteoglycans (20%)
   d. Enzymes
   e. Growth factors (PDGF, TGF beta, FGF, IGF-1)
   f. Lipids
   g. Adhesives (fibronectin, chondronectin)
Other bone deformities

- **Ulnar** deviation of the wrist
- **Valgus** deformity of the elbow
- Inclinations of distal ends of radium and ulna toward each other
- Deformities of **metacarpals and short phalanges**, epiphyseal deformities of the tubular bones, widened metaphyses
No Vessels in Cartilage Layers!
Zones of articular cartilage and growth plate

**ARTICULAR CARTILAGE**
- Superficial
- Intermediate
- Deep
- Tidemark
- Calcified cartilage
- Bone

**GROWTH PLATE**
- Resting
- Proliferating
- Hypertrophic
- Bone

**MATRIX COMPARTMENTALIZATION**
- Interterritorial
- Territorial
- Pericellular

**Zones of Articular Cartilage and Growth Plate**
- Articular cartilage
- Growth plate
- Resting
- Proliferating
- Hypertrophic
- Bone
Extracellular matrix of cartilage

- Collagen II/XI
- PRELP
- HS-PG
- Biglycan
- Collagen VI
- Aggrecan
- KS
- CS
- Fibulin
- COMP
- CILP
- Decorin
- NC4 domain
- Collagen IX
- Collagen II/XI
- Chondroadherin
- Integrin
- Chondrocyte

CILP: cartilage intermediate layer protein
COMP: cartilage oligomeric matrix protein
CS: chondroitin sulfate
HA: hyaluronic acid
HS-PG: heparan sulfate-proteoglycan
KS: keratan sulfate
PRELP: proline/arginine-rich end leucine-rich repeat protein
Skeletal/joint disease - Long bones

- Tilted radial epiphysis
- Abnormal curvature and tubulation of the radial bone
- Bones are **osteopenic** with cortical thinning

10 year-old patient
Skeletal/joint disease – Hands

Signs, symptoms

- Tapering of the proximal portion of metacarpals
- **Small irregular carpal bones**
- Distal portion of the radius tilted toward the ulna (both bones laterally bowed)
- Joint laxity
- Significant loss of mobility

6 year-old patient

Floppy hand deformity in a 24 year-old patient
Growth

- At birth, the length and weight are within normal ranges.
- Patients grow normally at first but growth may start to slow down around 18 to 24 months.
- Those who are severely affected stop growing very early between 4 and 8 years old.
- The average final height is 127 cm for male patients and 117 cm for female patients in the registry from International Morquio Organization.
- Patients with an attenuated type continue to growing into their teens and reach over 150 cm.
Bone pathology in MPS IVA mouse

A Growth Plate

B Storage in cartilage cells

C Bone marrow

cortical bone
osteoblasts
sinus lining cells

D Storage in the ligament
Weight and height at birth

BIRTH WEIGHT (n=237) Average=3.5 Kg ,
1SD=0.64

BIRTH HEIGHT (n=201) Average=52 cm ,
1SD=4.5

International Morquio Registry (2005)
Growth Curve in MPS IVA

Boys Growth Curve (cm)
Average: 127.6 cm SD: 22.6 (over 18 years)

Girls Growth Curve (cm)
Average: 117.3 cm SD: 20.9 (over 18 years)
Weight Curve in MPS IVA

**Boys Weight Curve (kg)**
Average: 46.7 kg, SD: 18.6 (over 18 years)

**Girls Weight Curve (kg)**
Average: 37.1 kg, SD: 14.3 (over 18 years)
MPS IVA

Genetics of MPS IVA
(Morquio A Disease)
Genetics of MPS IVA
(Morquio A Disease)

1. Why does Morquio A Disease Occur?
Why does Morquio A Disease Occur?

- Each cell contains instructions that tell our bodies how to function and grow.
- These instructions are contained in DNA.
- DNA is organized into units called chromosomes in nucleus.

Chromosomal material (chromatin) made of DNA strands
Why does Morquio A Disease Occur?

- **MPS IVA is inherited**

  People inherited two copies of everyone gene – one from each parent. Genes contain information about our genetic makeup – for example, physical characteristics such as eye color and height. All genes that an individual inherits are organized on 23 pairs of chromosomes. Each chromosome contains thousands genes.
Why does Morquio A Disease Occur?

Each cell contains 46 chromosomes, except sperm and eggs, which contain half that number. We all inherit one set of chromosomes from each parent. They can be organized into 22 pairs of numbered chromosomes and one pair of sex chromosomes, called X and Y. Men have one X and one Y. Women have the same 22 pairs of numbered chromosomes as men, plus two X chromosomes.
Every human being carries an estimated 8 to 10 genes that are mutated (“changed”). Some genes changes do not have much impact, but other changes may cause disease in the affected individuals. Just like normal genes, mutated genes are passed from one generation to another.

The genes for production of the enzyme **N-acetyl-galactosamine-6-sulfatase (GALNS)** are passed from parent to child. In MPS IVA disease, the blueprint for this enzyme is defective; thus, the GALNS is unable to function normally.
The gene that makes GALNS is found on the chromosome 16.

MPS IVA disease is an autosomal recessive disorder; “recessive” indicates that in order to develop the disease, an individual must inherit two mutated copies of the gene, one from each parent.

If she or he has one faulty gene, there is a second gene that may produce 50% of the normal amount of GALNS.
Why does Morquio A Disease Occur?

- Males and females share the risk

Copies of the gene for GALNS are carried on chromosome 16 that not involved in determining an individual’s sex. Humans normally have 46 chromosomes, including the two that determine gender (either 2 “X” chromosomes in females, or one “X” and one “Y” chromosomes in males). The other 22 pairs of chromosomes are called autosomes. The gene for GALNS enzyme is carried on one of the autosomal chromosome pairs. Thus, MPS IVA disease is an autosomal recessive disorder; “recessive” indicates that in order to develop the disease, an individual must inherit two mutated copies of the gene, one from each parent.
Genetics of MPS IVA
(Morquio A Disease)

2. Inheriting Morquio A Disease
Who is a MPS IVA carrier?

A person with just one defective gene and one normal gene for GALNS is a carrier of MPS IVA disease. Carriers do not develop the disease because one of the two genes for GALNS is normal, so enough enzyme is produced to prevent GALNS from accumulating. Although MPS IVA carriers will not have symptoms of the disease, the odds are 50:50 that the “MPS IVA gene” will be passed on to each of their children.
Inheriting Morquio A Disease

When both parents have normal genes for GALNS, their children inherit two normal genes, one from each parent.

If both parents have MPS IVA disease, all of their children inherit the two “MPS IVA gene” and therefore the disease.
Inheriting Morquio A Disease

A child with only one parent who is a carrier has a 50% chance becoming a carrier.

If both parents are carriers of MPS IVA disease, with each pregnancy there is a 50% chance the child will inherit one MPS IVA gene from each parent and be a carrier, or a 25% risk of actually having MPS IVA disease. That means, with each pregnancy, carrier parents have a 3 in 4 (75%) chance of having an unaffected child.
Inheriting Morquio A Disease

- If only one parent has MPS IVA and the other parent neither has the disease nor is a carrier, all children will inherit the MPS IVA gene from the parent with the disorder and become carriers. None of the children, however, will have the disease.

- If one parent has MPS IVA and the other parent is a MPS IVA carrier, there is a 50% chance of having a child who inherits “MPS IVA gene” from each parent and thus has the disease. There is also a 50% chance of having a child who inherits the “MPS IVA gene” from one parent only, and becomes a carrier.
For each pregnancy, the odds of inheriting MPS IVA disease are totally independent of whether or not a previous child has the disease. Having one child with MPS IVA disease does not mean that the next child cannot inherit the disease. Likewise, it also not mean that the next child will have the disease.
MPS IVA

Diagnosis and misdiagnosis
Diagnosis

Symptoms cause suspicion of MPS IVA

Test urinary GAG and KS levels & pattern

- Elevated levels
- Normal levels & pattern
- Abnormal pattern
- Low activity ($\leq 5\%$)

Perform enzyme testing

Confirmed diagnosis of MPS IVA

Genotyping

Keep the difference in urinary GAG and KS levels between children and adults in mind!!

Normal or Other MPS?
Clinical tests

1. A full skeletal survey by radiographic studies
   a. X-rays: standing anteroposterior (AP) and lateral views of flexion and extension radiographs of the cervical spine and the odontoid process, the chest, entire spine, pelvis view with visualization of the femoral heads articulating with the acetabulum, the lower extremities including the entire femur, articulation with tibia, and ankles, AP views of both hands, forearms, elbows in extension, humerus, and shoulder.
   b. MRI of the brain stem and cervical: evaluation of odontoid hypoplasia and cord compression.

3. Ophthalmology examination with slit lamp

4. Hearing assessment

5. Echocardiogram

6. Lab tests: urine GAG, blood and urine KS, enzyme assay, and DNA test

7. Growth chart
Urinary GAG and KS testing

Qualitative and quantitative analysis

- 10 ml of morning portion of urine should be collected in a polypropylene tube
- Sample can be kept at room temperature if analyzed within 24 hours
- If the sample will not be analyzed within 24 hours, the sample should be frozen at -20 °C
- Sample can be sipped at an ambient temperature.
Assay for blood and urine KS

- Sandwich ELISA

This method are based on a sandwich immunoassay method using monoclonal antibodies specific for GAGs and to permit measurement specific GAGs in body fluids, culture medium, and extract from tissue.
Methods to measure KS

*Sandwich ELISA Assay for Quantitation of KS*

**Materials**
- Standards (CS of Shark cartilage)
- Primary Antibody coating the plate: monoclonal anti-KS Ab
- Samples: Blood or urine containing specific GAG
- Secondary Antibody: Biotinylated anti-KS conjugate with Streptavidin-Horse Radish Peroxidase
- Substrate: Tetramethylbenzidine (TMB)
Urinary GAG and KS in MPS IVA with age

Left Panel: GAG

Right Panel: KS
Blood KS with age in MPS IVA

1. Age-dependency

2. Correlation between Phenotype and KS level
Testing for Morquio A Disease
Is there a test to determine MPS IVA disease inheritance?

Because MPS IVA disease is a genetic disorder, all close relatives of people with MPS IVA disease are at risk of having the disease, or are potential carriers of the “MPS IVA gene”. Families with a history of MPS IVA disease may want to discuss the possibility of a genetic testing with their physicians. A blood test (enzyme assay and DNA test) can determine if a person has a MPS IVA disease or is a carrier. Prenatal testing for MPS IVA disease is also available early in pregnancy. Genetic counseling is available to couples who are found to be carriers or who have a family history of MPS IVA disease.
Testing for Morquio A Disease

- Morquio A disease can be diagnosed if there is little or no GALNS in the blood (enzyme assay and DNA test)
- Carriers can have nearly normal IDS levels and still carry the faulty gene
- For a precise carrier diagnosis, a genetic test that analyzes DNA is needed for diagnosis

Affected: blood test (enzyme assay and DNA test)

Carrier: Genetic test that analyzes DNA
Testing for Morquio A Disease

Test results can:

- Confirm or rule out the presence of the faulty gene
- Relieve uncertainty
- Enable informed decision-making regarding medical care
- Help other family members understand their risks
Testing for Morquio A Disease

Psychological considerations:

- Depression or despair may occur after a positive test
- Changes in family dynamics may also occur
  - Anger over a positive test
  - Guilt over escaping a disease that affects other family members
Enzyme activity

- **N-acetylgalactosamine 6-sulfatase** activity in patients ranges from 0 - 5% of normal
Measurement of blood KS and enzyme activity

Whole blood sample
- Fill an EDTA tube with 8 ml blood (4 ml in children)
- Sample should be kept at room temperature
- Needs to arrive at the lab for analysis within 24 hours

Leukocyte sample
- Spin blood at 3000 rpm
- Store plasma at -20°C to -80°C
- Isolate leukocytes from the pellet
- The dry leukocyte pellet can be stored at -80°C until shipment
- Leukocytes and plasma sample should be sent together for analysis
Genotyping

Testing

- Fill an EDTA tube with the patients blood (5 ml)
- Keep samples at room temperature
- Samples should arrive at a lab for analysis within 48-72 hours
Summary of Mutations

- To date, about 130 different mutations and seven polymorphisms causing an amino acid change
- Genotype/phenotype correlation for some of these mutations
- GALNS structural modeling: Severe mutations located at the core of the structure leading to destruction of the hydrophobic domain, modification of the packing, or modification of the active site, and attenuated mutations located on the surface of the GALNS protein
- Common mutations in Irish (pI113F, pT312S), Italian (pM1V, pW10X), Japanese (pN204K, double gene deletion), and pan-ethnic (pR386C)
- A large proportion (over 70%) of known lesions by missense mutations
Incidence of Frequent Mutation
(Individual Mutation n=314)

- R386C: 4 times, 13%
- H113F: 3 times, 11%
- G301C: 2 times, 11%
- M1V: 2 times, 18%
- W10X: 2 times, 18%
- P125L*: single, 21%
- M391V: double gene deletion, 2%
- T312S: 2%
- A291T*: 2%
- G301C: 2%

* Denotes deletion
Variety of Mutation (n=129)

- Splicing: 7%
- Insertion: 1%
- Deletion: 9%
- Nonsense: 6%
- Missense: 73%
- Large rearrangements: 2%
- Others: 2%
### a.

- **F1**
- **F2**
- **F3**
- **F4**
- **F5**

### b.

- **M1**
- **F1**
- **F2**
- **F3**
- **F4**
- **F5**
- **M2**
- **C**

#### Fragment Sizes and Primer Names:

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<td>F5 (exons 13-14)</td>
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Misdiagnoses

- Other bone dysplasias
- Other MPSs
- Obstructive airways disease
MPS IVA

Management and treatment
General management issues

- Inter- and multidisciplinary input necessary
- Centers of expertise exist in most countries
- Regular monitoring and evaluation advised
- No “one-size-fits-all” approach available
- Special care around anaesthetic procedures
- Special orthopaedic and respiratory care
Treatment options

- Bone Marrow Transplant/ Hematopoietic Stem Cell Transplantation (BMT/HSCT); limited effectiveness
- Palliative Care; orthopedic surgeries
- Physiotherapy
- Enzyme Replacement Therapy (ERT); under development
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Treatment and management

- **Cervical cord compression**: Surgery to decompress compression and stabilize the upper cervical spine, usually by, can be lifesaving.

- **Corneal clouding**: corneal transplantation - not always successful

- **Deafness**: Ventilating tubes minimize episodes of acute otitis media and chronic middle ear effusions
Treatment and management

- **Joint laxity**: physical therapy, bracing

- **Airway disease (obstructive and restrictive):**
  - **Obstructive Airway Disease.** A narrowed trachea, thickened vocal cords, redundant tissue, and an enlarged tongue all contribute to airway obstruction.
  - **Sleep apnea** - Loud snoring and daytime sleepiness.
    - a. Tracheostomy
    - b. High pressure nasal continuous positive airway pressure and supplemental oxygen
    - c. Tonsillectomy and adenoidectomy
Cervical cord compression

- Cervical decompression or fusion surgery is recommended if there is some evidence for instability or compression at any age (generally, it may happen after 4 years). Prophylactic fusion surgery is controversial without a proof of spinal cord compression.
- C1-C2 fusion (or if necessary, posterior occipito-cervical fusion) in asymptomatic or mild symptomatic patients
- Posterior occipito-cervical fusion with anterior decompression in symptomatic patients with a severe compression
- Complications: instability below the level of the fused segment and thoracic spinal cord compression
After operation of cervical fusion

5 year-old patient
Anesthesia

- Patients with MPS IVA: major anesthesia risks.
- Risk factors: chest wall deformities, hypoplasia of odontoid process, anterior dislocation of the vertebral axis with resultant spinal cord compression.
- Manual in-line stabilization of the head and neck: difficult direct laryngoscopic intubation because of inability to maintain an adequate airway and limitation of visualization during intubation.
- Angulated video-intubation laryngoscope (AVIL): a new helpful device to aid endotracheal intubation in patients when cervical spine immobilization impairs direct laryngoscopy.
- Recovery from anesthesia: slow and postoperative airway obstruction in common.
- Death: reported as a result of anesthesia complication.
BMT/HSCT

- Performed in children with MPS IVA
- Outcomes improved: joint mobility
- Bone disease is usually not beneficially affected and requires careful orthopedic management
- May get some growth unless the patient stops growing
- The detailed assessment is still required for a long-term effectiveness.
MPS IVA – specific follow-up assessments

At least annually:
- GALNS level, urinary GAGs, urinary and blood KS, health assessment questionnaire
- ENT exam and audiology
- Eyes – vision, pressure, split lamp, fundoscopy, ERG for suspected retinal disease
- Respiratory function: FVC/FEV +/- sleep study
- Skeletal survey - hips, spine, knees (pediatric patients)
- MRI – neck (pediatric patients)

Every other year:
- Heart: ultrasound and ECG
- Spleen and liver volume
MPS IVA Registry

- Help to increase disease awareness, and enhance the understanding of the variability, progression, and natural history of MPS IV.
- Evaluate the long-term effectiveness and safety of available treatment options.
- Provide patient reports to help physicians assess value of therapeutic interventions in individuals.
- Generate reports on aggregate patient data to help develop guidelines for monitoring and managing of patients.
Quality of life in each patient will be better.

- Identifying patients at an early stage
- Educating peers
- Supporting families
- Good education to families, doctors, and local community
- Treating patients in an early stage and in a proper manner