Pathophysiology of Mucopolysaccharidosis

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Inborn Errors of Metabolism today

- more than 500 diseases (~10 % of the known genetic diseases)
- all areas of metabolism involved
- vast majority are recessive conditions
- individually rare or very rare
- overall frequency around 1:800 (similar to Down syndrome)

LSDs: 1: 5,000 live births
MPS: 1: 25,000 live births

understanding of pathophysiology and early diagnosis leading to successful therapy for several conditions
The Lysosomal Diseases (LSD)

- Gaucher Disease 14%
- GM1 Gangliosidosis 2%
- Krabbe Disease 5%
- MPSI
- A-Mannosidosis
- Neuronal Ceroid Lipofuscinosis
- Others

- Tay-Sachs Disease 4%
- Wolman Disease
- Aspartylglucosaminuria
- Cystinosis 4%
- Fabry Disease 7%
- Gaucher Disease 14%
- GM1 Gangliosidosis 2%
- Krabbe Disease 5%
- A-Mannosidosis
- Metachromatic Leukodystrophy 8%

- Mucopolysaccharidosis
- Mucolipidosis
- Sphingolipidosis
- Oligosaccharidosis

MPS: 34%
Initial Description of MPS

Charles Hunter, 1917: “A Rare Disease in Two Brothers”

- brothers: 10 and 8 years
- hearing loss
- dwarfism
- macrocephaly
- cardiomegaly
- umbilical hernia
- joint contractures
- skeletal dysplasia

death at the age of 11 and 16 years
Description of the MPS Types...

M. Hunter - MPS II (1917)
M. Hurler - MPS I (1919)
M. Morquio - MPS IV (1929)
M. Sanfilippo - MPS III (1963)
M. Maroteaux-Lamy - MPS IV (1963)
M. Scheie - MPS I (MPS V) (1968)
M. Natowicz - MPS IX (1996)
The Lysosome

Lysosomes are...

- ... cell organelles containing digestive enzymes
- ... surrounded by a membrane composed of phospholipids that separate the inside of the lysosomes from the membrane's external environment
- ... range in size from 0.1 to 1.2 micrometers
- ... like a floating garbage bag that contains enzymes capable of digesting molecules in MPS GAGs
- ... the garbage disposals of the cell
- ... responsible for recycling or excretion of the disposals (damaged or obsolete cell parts as well as invaders such as bacteria)
Deposit Degradation and Recycling

Normal Degradation

Missing Enzyme → Accumulation
Pathophysiology

Dysfunction of at least 1 lysosomal enzyme

multiorgan-involvement
Proposed Model of Cell Death in LSDs

Enzyme deficiency → Lysosomal storage of substrates → Impairment of autophagy

Accumulation of toxic proteins
Accumulation of dysfunctional mitochondria

Cellular distress → Phagocytosis by Microglia → Chronic inflammation → Cytokine release (LATE STAGE)

CELL DEATH

Settembre et al. PNAS 2007
Bone and Joint Disease in MPS

Accumulation of GAGs

Activation TLR 4 pathway

↑ transcription of proinflammatory regulators

Proinflammatory chemokines (MIP-1α)

Proinflammatory cytokines (TNF, IL1)

Nitric oxide products

Prostanoids

Metalloproteinases

Growth factors (TGFβ)

Stimulation of osteoclastogenesis (↑ RANKL gene expression)

↑ apoptosis of chondrocytes

Enhanced cell proliferation (immature chondrocytes, synoviocytes)

Degradation ECM, cartilage, bone, joints destruction, osteopenia

### Classification of MPS

<table>
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<tr>
<th>MPS Type</th>
<th>Eponym(s)</th>
<th>Enzyme Deficiency</th>
<th>GAG Affected</th>
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</tr>
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<td>Sanfilippo C</td>
<td>acetyl CoA:a-glucosaminide acetyltransferase</td>
<td>HS</td>
</tr>
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<td>Sanfilippo D</td>
<td>N-acetylglucosamine-6-sulfatase</td>
<td>HS</td>
</tr>
<tr>
<td>MPS IV</td>
<td>Morquio A</td>
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DS = dermatan sulfate, HS = heparan sulfate, CS = chondroitin sulfate, KS = keratan sulfate, HA= Hyaluronan
Introduction to GAGs
Function of GAGs...

- Ideal as a lubricating fluid in the joints
- Provide structural integrity to the cells
- Attached to proteins... cell and tissue development and physiology
Types of GAGs...

Due to the missing enzyme- missing degradation of different GAGs- different type of MPS
Where the GAGs are...

<table>
<thead>
<tr>
<th>Glycosaminoglycan</th>
<th>Main localization</th>
<th>Sulfated?</th>
<th>Attached to protein?</th>
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<tr>
<td>chondroitin sulfate</td>
<td>cartilage, tendon, ligaments, aorta</td>
<td>Yes</td>
<td>Yes</td>
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<td>dermatan sulfate</td>
<td>skin, blood vessels, heart valves</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>keratan sulfate</td>
<td>cartilage, cornea</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>heparan sulfate</td>
<td>basement membranes, cell surfaces</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>heparin</td>
<td>mast cells (anticoagulant)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>hyaluronic acid</td>
<td>joints, cartilage, umbilical cord, vitreous humor of the eye</td>
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11 known enzyme deficiencies

Storage of GAGs

7 main MPS types
MPS II... a typical case

- Recurrent infections of the upper airways
- Diarrhoea
- Hepatosplenomegaly
- General stiffness
- Inguinal hernia
### MPS II...First Symptoms

<table>
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<th>Feature</th>
<th>Prevalence</th>
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<tr>
<td>Cardiac valve disease</td>
<td>57%</td>
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<tr>
<td>Kyphosis/scoliosis</td>
<td>39%</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>84%</td>
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<tr>
<td>Enlarged tongue</td>
<td>70%</td>
</tr>
<tr>
<td>Enlarged tonsils/adenoids</td>
<td>68%</td>
</tr>
<tr>
<td>Enlarged liver/spleen</td>
<td>89%</td>
</tr>
<tr>
<td>Facial features</td>
<td>95%</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>34%</td>
</tr>
<tr>
<td>Hernia</td>
<td>78%</td>
</tr>
<tr>
<td>Otitis</td>
<td>74%</td>
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**Median Age at Onset (years)**

(10<sup>th</sup> – 90<sup>th</sup> percentile)

MPS ... a Multisystemic Disease

**Respiratory:**
- Upper airway obstruction
- Obstructive sleep apnea/snoring
- Restrictive lung disease
- Frequent infections
- Restrictive airway disease
- Rhinorrhea

**Cardiac:**
- Cardiomyopathy
- Dysplastic valves
- Heart murmur

**Skeletal:**
- Degenerative hip dysplasia
- Kyphosis or Kyphoscoliosis
- Gibbus
- Joint contractures
- Genu valgum deformities

**Gastrointestinal:**
- Hepatosplenomegaly
- Umbilical & inguinal hernia
- Swallowing problems
- Diarrhoea
- Drooling

**Peripheral nervous system:**
- Peripheral nerve entrapment (eg, carpal tunnel syndrome)

MPS ... a Multisystemic Disease

**CNS:**
- Hydrocephalus
- Atlanto-axial instability
- Cervical cord compression
- Myelopathy
- Seizures
  (Severe behaviour problems)
- Sleep disturbance
- Mental retardation
- Developmental delay

**Appearance:**
- Coarse face
- Short stature, short neck

**Eyes:**
- Glaucoma
- Retinal dystrophy
- Corneal clouding

**Ears:**
- Recurrent otitis media
- Hearing loss

**Dental:**
- Caries
- Dental abscesses
- Cysts

Disease Progression

Appearance of children with MPS is normal at birth.

MPS I
- 4 yrs
- 24 yrs
- 31 yrs
- 54 yrs

MPS II
- 6 months
- 5 years
- 9 years
- 30 years
Disease Progression

rasch progrediente Verlaufsform

- ZNS-Symptome
- Hornhauttrübung
- vergröberte Gesichtszüge
- Bewegungsapparat
- Herz- und Gefäßbeteiligung
- Atemwegsbeteiligung
- Hepato- (spleno-) megalie
- Lebensqualität
- Lebenserwartung

attenuierte Verlaufsform

Symptomentwicklung und Verlauf

Lebensalter

Symptomentwicklung und Verlauf
Spectrum of Disease Severity **MPS I** (Scheie, H-S, Hurler)

- **severe**
  - M. Hurler
  - M. Hurler-Scheie
  - With and without CNS involvement
  - ERT available
  - <2 yrs of age: HSCT or BMT
- **attenuated**
  - M. Scheie
Spectrum of Disease Severity **MPS II** (Hunter)

- **severe**
  - neuronopathic
  - X-linked
  - No corneal clouding
  - With and without CNS involvement
  - **ERT available**

- **attenuated**
  - non-neuronopathic
Spectrum of Disease Severity MPS VI (Maroteaux-Lamy)

- Severe
- Fast progressive
- No mental retardation
- ERT available

- Attenuated
- Slowly progressive
Spectrum of Disease Severity **MPS IV** (Morquio)

- **severe**
  - Mainly musculoskeletal disease
  - Hypermobility of joints
  - Atlanto-axial instability
  - ERT available

- **classic**

- **attenuated**

- **non classic**
MPS III (Sanfillippo A-D)

- Mainly progressive mental retardation
- Neurological problems (seizures)
- Behavioural problems (hyperactivity)
  - Clinical trial for intrathecal ERT

MPS VII (Sly)

- Typical: hydrops fetalis
- Mental retardation + clinical symptoms
  - Clinical trial for ERT
Mucopolysaccharidoses are...

genetic, heterogenous, chronic, progressive, multisystemic, and life threatening

...but for some MPSs treatment is available !!!
Different MPS - Types

MPS I, II, VI und VII: Clinical symptoms are very similar

MPS III: Mainly mental retardation

MPS IV: mainly musculo-skeletal (hypermobility of joints)

MPS I
MPS II
MPS VI
MPS Differential Diagnosis

- Mucolipidosis
- Mannosidosis

MSD
Diagnosis of MPS Can Be Challenging

Before confirmation with enzyme or genetic testing...

1. Signs and symptoms often not specific to MPS
   Not all clinical features will be present or manifest themselves in the same way in each patient

2. Diagnosis, and therefore treatment, may be delayed – particularly for those without a known familial history of MPS

3. Delayed treatment leads to irreversible disease manifestations
DIAGNOSIS

1. Preliminary screening:
   - Urine testing of GAG excretion (Cave: can be normal in adult and/or attenuated patients!)

Confirmation of Diagnosis:

2. Biochemical analysis: GOLD STANDARD
   - Enzyme activity testing in leukocytes, fibroblasts, or plasma (alternatively dry blood spot testing)

3. Genetic analysis:
   - Mandatory in X-linked disorder! (MPS II)

4. Prenatal diagnostic possible
Therapies

1. Bone Marrow Transplantation / (HSCT) Hematopoetic Stem Cell Transplantation **MPS I**

2. Enzyme Replacement Therapy (ERT) **MPS I, II, IV, VI**

3. Symptom based Therapy (supportive) all **MPSs**

4. Biotech Based Therapies (in development)

The best therapy is the combination of ERT, regular follow ups to **detect life threatening and quality of life reducing complications** and an adequate supportive therapy!!!!
Let’s make a Quizz....
Quiz Aishe 18 months:

- 18 month old girl height (10.P), weight (3.P)
- Consanguineous Turkish parents
- Healthy older and healthy younger sister
- Normal height (40.P) and weight (60.P) at birth

18 months:
- No free walking, only standing with support
- No speaking, but understanding
- Umbilical hernia
- Thorakolumbar kyphosis, pectus carinatum, hip dysplasia, craniosynostosis, turricephalus
- Muscles hypoton, reflexes normal
- Mital insuff I°, tricuspid insuff II°
- Snoring, adenoidectomy
- No joint stiffness

What type of MPS is it????
Quizz Aishe 18 Months:

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**Quizz Aishe 18 Months:**

**Diagnostics:**

**Urinary GAGs:** Dermatansulfate
- MPS VI: DS
- MPS I: DS, HS
- MPS VII: DS, HS, CS

**Enzyme testing in blood:** Arylsulfatase B deficiency
- MPS I: Iduronidase normal
- MPS VII: β-Glucuronidase normal

**Genetics:** homocygote ARSB gene

**Why is it important to exclude MPS I?**
- BMT is 1st treatment option up to the age of 2 years in MPS I

Start of ERT at the age of 18 months
Mucopolysaccharidosis are...

- rare (1:25,000)
- multisystemic, progressive and extremely heterogeneous
- 70% CNS involvement
- inherited: autosomal-recessive, (Cave: MPS II x-chromosomal)
- one typical symptom: stiffness and contractions of joints (Cave: MPS IV with hypermobility)
- typical is a corneal clouding (not in MPS II)
- therapies are available for MPS I, II, IV and VI (trials for III and VII)

ALL PATIENTS NEED SUPPORTIVE THERAPY

Quality of Life  !!
Thank you very much for your attention!!!
MPS I (Scheie, Hurler-Scheie, Hurler Syndrome)

- 18 month old girl height (10.P), weight (3.P)
- Consanguineous Turkish parents
- Healthy older and healthy younger sister
- Normal height (40.P) and weight (60.P) at birth

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- No joint stiffness

Hurler-Scheie, Hurler Syndrome possible !!
MPS II (Hunter Syndrome)

• 18 month old girl height (10.P), weight (3.P)
• Consanguineous Turkish parents
• Healthy older and healthy younger sister
• Normal height (40.P) and weight (60.P) at birth

**18 months:**
• No free walking, only standing with support
• No speaking, but understanding
• Umbilical hernia
• thorakolumbar kyphosis, pectus carinatum, hip dysplasia, craniosynostosis, turricephalus
• Muscles hypoton, reflexes normal
• Mital insuff I°, tricuspid insuff II°
• Snoring, adenoidectomy
• No joint stiffness

**Hunter syndrome is very unlikely**
MPS III (Sanfilippo Syndrome)

Coarse face

- 18 month old girl height (10.P), weight (3.P)
- Consanguineous Turkish parents
- Healthy older and healthy younger sister
- Normal height (40.P) and weight (60.P) at birth

18 months:
- No free walking, only standing with support
- No speaking, but understanding
- Umbilical hernia
- Thorakolumbar kyphosis, pectus carinatum, hip dysplasia, craniosynostosis, turricephalus
- Muscles hypoton, reflexes normal
- Mital insuff I°, tricuspid insuff II°
- Snoring, adenoidectomy
- No joint stiffness

MPS III (Sanfilippo Syndrome) is unlikely
MPS IV (Morquio Syndrome)

Coarse face

- 18 month old girl height (10.P), weight (3.P)
- Consanguineous Turkish parents
- Healthy older and healthy younger sister
- Normal height (40.P) and weight (60.P) at birth

18 months:
- No free walking, only standing with support
- No speaking, but understanding
- Umbilical hernia
- thorakolumbar kyphosis, pectus carinatum, hip dysplasia, craniosynostosis, turricephalus
- Muscles hypoton, reflexes normal
- Mital insuff I°, tricuspid insuff II°
- Snoring, adenoidectomy
- No joint stiffness

MPS IV (Morquio Syndrome) is unlikely
MPS VI (Maroteaux-Lamy)

- 18 month old girl height (10.P), weight (3.P)
- Consanguineous Turkish parents
- Healthy older and healthy younger sister
- Normal height (40.P) and weight (60.P) at birth

18 months:
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- Muscles hypoton, reflexes normal
- Mital insuff I°, tricuspid insuff II°
- Snoring, adenoidectomy
- No joint stiffness

MPS VI (Maroteaux-Lamy) is possible!!
MPS VII (Sly Syndrome)

- 18 month old girl height (10.P), weight (3.P)
- Consanguineous Turkish parents
- Healthy older and healthy younger sister
- Normal height (40.P) and weight (60.P) at birth

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- Muscles hypoton, reflexes normal
- Mital insuff I°, tricuspid insuff II°
- Snoring, adenoidectomy
- No joint stiffness

MPS VII (Sly Syndrome) is possible
MPS IX

Coarse face

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- Healthy older and healthy younger sister
- Normal height (40.P) and weight (60.P) at birth

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MPS XI is unlikely