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# Mucopolysaccharidoses and spinal deformities

R. Stücker

Department of Pediatric Orthopedics

The Children‘s Hospital Hamburg-Altona and
University Clinic  Hamburg

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# Confict of interest disclosure

- Travel expenses and speaker fees
  - Nuvasive
  - Depuy / Synthes

# Mucopolysacccharidoses

- Lysosomal enzyme deficiencies result in progressive accumulation of natural (macro-) molecules
- Macromolecules which cannot be degraded are mucopolysaccharides = glykosaminoglycans = GAG‘s
- GAG‘s are biological active molecules in the cell membrane and extracellular matrix

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# MPS (from Wikipedia)

**Main mucopolysaccharidoses**

| Type[1] | Common name<br>Other names | OMIM | Gene | Locus | Deficient enzyme | Accumulated products | Symptoms | Incidence |
|---|---|---|---|---|---|---|---|---|
| **MPS IH** | Hurler syndrome | 607014 | *IDUA* | 4p16.3 | α-L-iduronidase | Heparan sulfate<br>Dermatan sulfate | Intellectual disability, micrognathia, coarse facial features, macroglossia, retinal degeneration, corneal clouding, cardiomyopathy, hepatosplenomegaly | 1:100,000[2] |
| **MPS IH/S** | Hurler–Scheie syndrome | 607015 | | | | | | |
| **MPS IS** | Scheie syndrome<br>*Formerly:* Mucopolysaccharidosis type V | 607016 | | | | | | |
| **MPS II** | Hunter syndrome | 309900 | *IDS* | Xq28 | Iduronate sulfatase | Heparan sulfate<br>Dermatan sulfate | Intellectual disability (similar, but milder, symptoms to MPS I). This type exceptionally has X-linked recessive inheritance | 1:250,000[3] |
| **MPS IIIA** | Sanfilippo syndrome A<br>Sulfamidase deficiency | 252900 | *SGSH* | 17q25.3 | Heparan sulfamidase | Heparan sulfate | Developmental delay, severe hyperactivity, spasticity, motor dysfunction, death by the second decade | 1:280,000[4] – 1:50,000[5] |
| **MPS IIIB** | Sanfilippo syndrome B<br>NAGLU deficiency | 252920 | *NAGLU* | 17q21.2 | N-acetylglucosaminidase | | | |
| **MPS IIIC** | Sanfilippo syndrome C | 252930 | *HGSNAT* | 8p11.21 | Heparan-α-glucosaminide N-acetyltransferase | | | |
| **MPS IIID** | Sanfilippo syndrome D | 252940 | *GNS* | 12q14.3 | N-acetylglucosamine 6-sulfatase | | | |
| **MPS IVA** | Morquio syndrome A | 253000 | *GALNS* | 16q24.3 | Galactose-6-sulfate sulfatase | Keratan sulfate<br>Chondroitin 6-sulfate | Severe skeletal dysplasia, short stature, motor dysfunction | 1 in 75,000[4] |
| **MPS IVB** | Morquio syndrome B | 253010 | *GLB1* | 3p22.3 | β-galactosidase | Keratan sulfate | | |
| **MPS V** | *See MPS IS (Scheie syndrome) above* | | | | | | | |
| **MPS VI** | Maroteaux–Lamy syndrome<br>ARSB deficiency | 253200 | *ARSB* | 5q14.1 | N-acetylgalactosamine-4-sulfatase | Dermatan sulfate | Severe skeletal dysplasia, short stature, motor dysfunction, kyphosis, heart defects | |
| **MPS VII** | Sly syndrome<br>GUSB deficiency | 253220 | *GUSB* | 7q11.21 | β-glucuronidase | Heparan sulfate<br>Dermatan sulfate<br>Chondroitin 4,6-sulfate | Hepatomegaly, skeletal dysplasia, short stature, corneal clouding, developmental delay | <1:250,000[6] |
| **MPS IX** | Natowicz syndrome<br>Hyaluronidase deficiency | 601492 | *HYAL1* | 3p21.31 | Hyaluronidase | Hyaluronic acid | Nodular soft-tissue masses around joints, episodes of painful swelling of the masses, short-term pain, mild facial changes, short stature, normal joint movement, normal intelligence | |

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# MPS – clinical presentation

- All have normal development initially
- Central nervous disease
  - Hydrocephalus, Myelopathy
- Cardiovascular disease
  - Valvular dysfunction, hypertension
- Pulmonary disease
  - Obstructive airway disease
- Ophthalmologic disease
  - Corneal clouding, glaucoma
- Hearing impairment
- Musculoskeletal disease
  - Short statue, contractures, spinal deformations
  - Dysostosis multiplex in I,II, VI, VII

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# Overview orthopaedic manifestations

**Table 2**

**Orthopaedic Manifestations of Mucopolysaccharidosis**

| Type | Cervical Stenosis | Occipito-cervical Instability | Thora-columbar Kyphosis | Scoliosis | Hip Dysplasia | Proximal Femoral Epiphyseal Dysplasia | Genu Valgum | Carpal Tunnel Syndrome |
|---|---|---|---|---|---|---|---|---|
| MPS I (severe)[a] | 2+ | 1+ | 3+ | 2+ | 3+ | 1+ | 2+ | 2+ |
| MPS I (attenu-ated) | 2+ | 0 | 0 | 0 | 0 | 0 | 0 | 3+ |
| MPS II | 1+ | 0 | 1+ | 1+ | 1+ | 1+ | 0 | 2+ |
| MPS III | 0 | 0 | 0 | 1+ | 0 | 2+ | 1+ | 0 |
| MPS IV | 2+ | 3+ | 2+ | 0 | 1+ | 3+ | 3+ | 0 |
| MPS VI | 3+ | 3+ | 1+ | 0 | 2+ | 2+ | 0 | 1+ |
| MPS VII | ? | ? | ? | ? | ? | ? | ? | ? |

0 = not reported, 1+ = rare, 2+ = common, 3+ = frequent, ? = unknown, MPS = mucopolysaccharidosis

[a] Following hematopoietic stem cell transplantation

Adapted with permission from White KK, Harmatz P: Orthopedic management of mucopolysaccharide disease. *J Pediatr Rehabil Med* 2010; 3(1):47-56.

**White, K. K., Sousa T.; Mucopolysaccharide Disorders in Orthopaedic Surgery, J Am Acad Orthop Surg 2013;21: 12-22**

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# Kyphosis in MPS1 severity and natural history

- 33 patients
- Treated by BMT and/or ERT
- Mean kyphosis at 17 mo was 38°
- 15/33 had progression > 10°
- Magnitude of initial deformity was predictive for progression
- Initial curves of >45° are more likely to progress

Yasin et al, Spine 2014

# MPS 1 and HSCT

- Musculoskeletal manifestations in mucopolysaccharidosis type I following hematopoietic stem cell transplantation
  Schmidt, M., Breyer, S., Löbel U., Yarar S., Stücker R., Ullrich K., Müller I., Muschol N
  Orphanet Journal of rare Diseases, 2016

  - N= 19 patients
  - Stable or improved diameter of craniocervical junction in 67%
  - Correction or stabilization of odontoid hypoplasia in 64%
  - Thoracolumbar kyphosis, scoliosis, genu valgum and hip dysplasia were progressive

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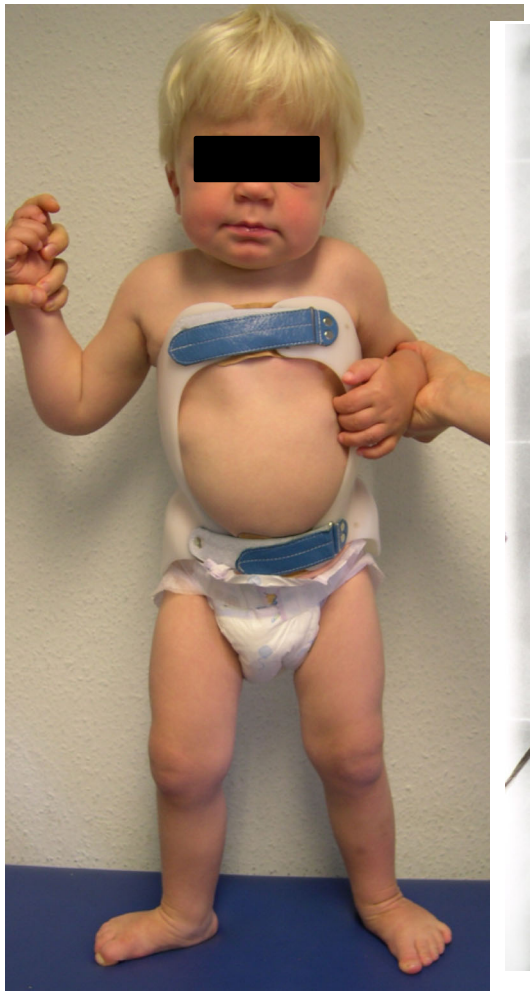
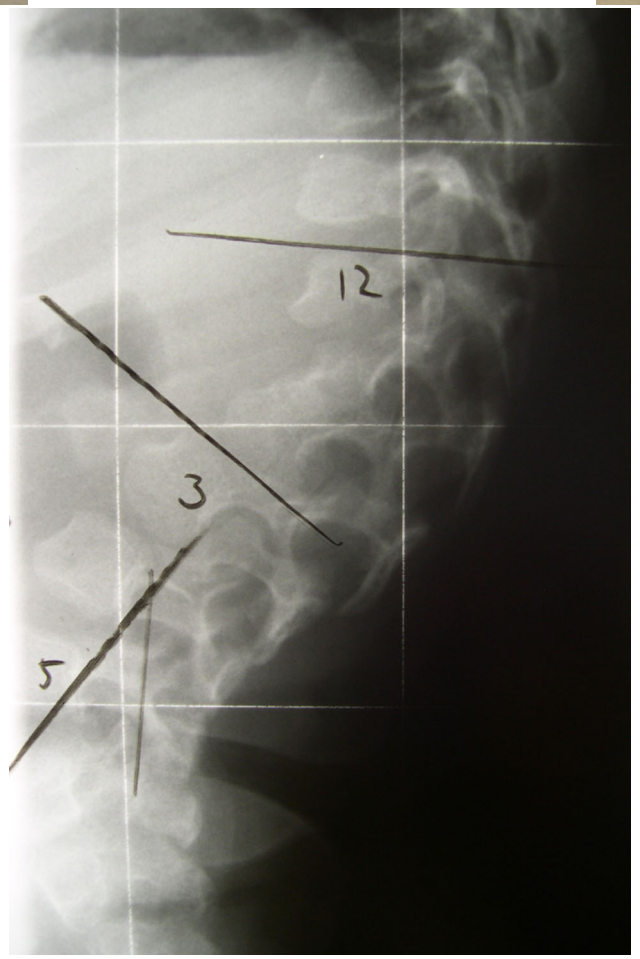
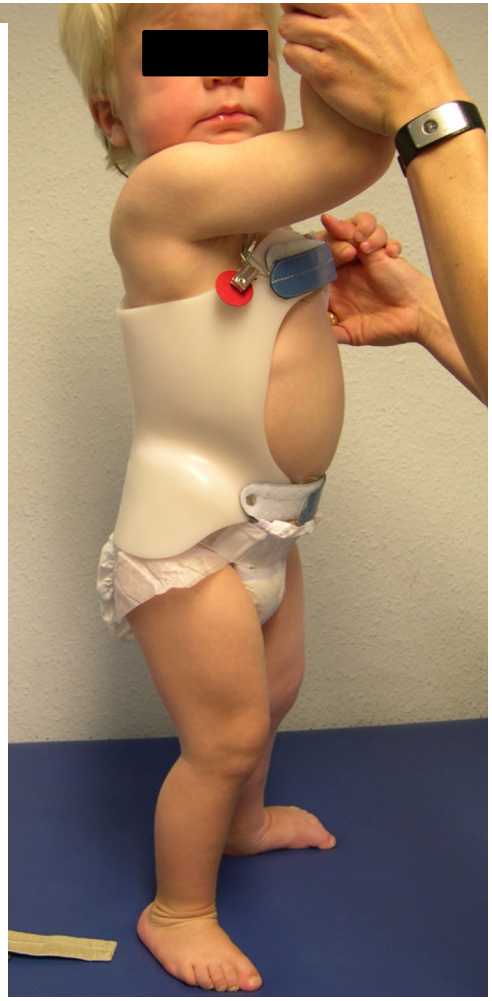
# Bracing for thoracolumbar kyphosis





# Role of bracing

- There is no evidence to support bracing
  - Tandon et al, 1996
- However, there is also no evidence that bracing is not helpful
- Recommendations to brace when kyphosis is still flexible (Blaw, Langer; 1969)
- May have negative effects on pulmonary function and may increase breathing efforts

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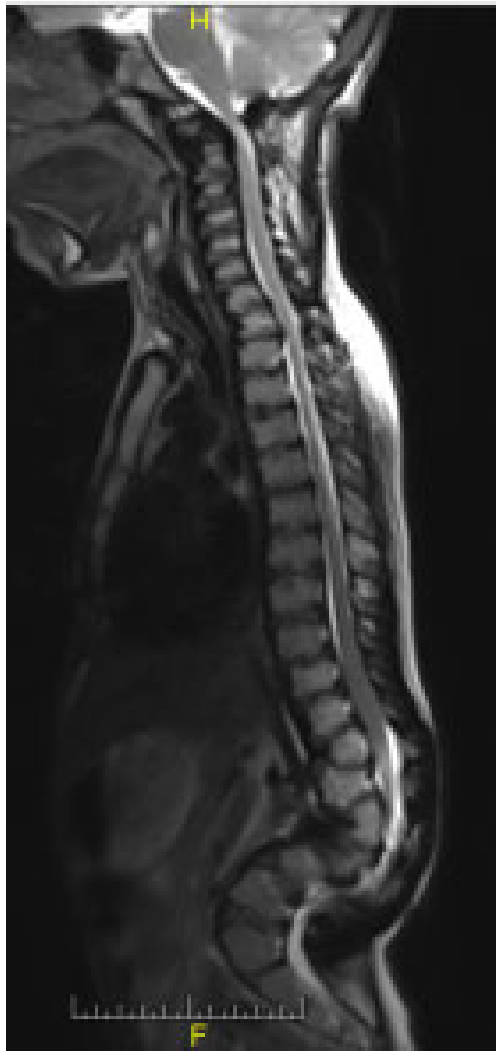
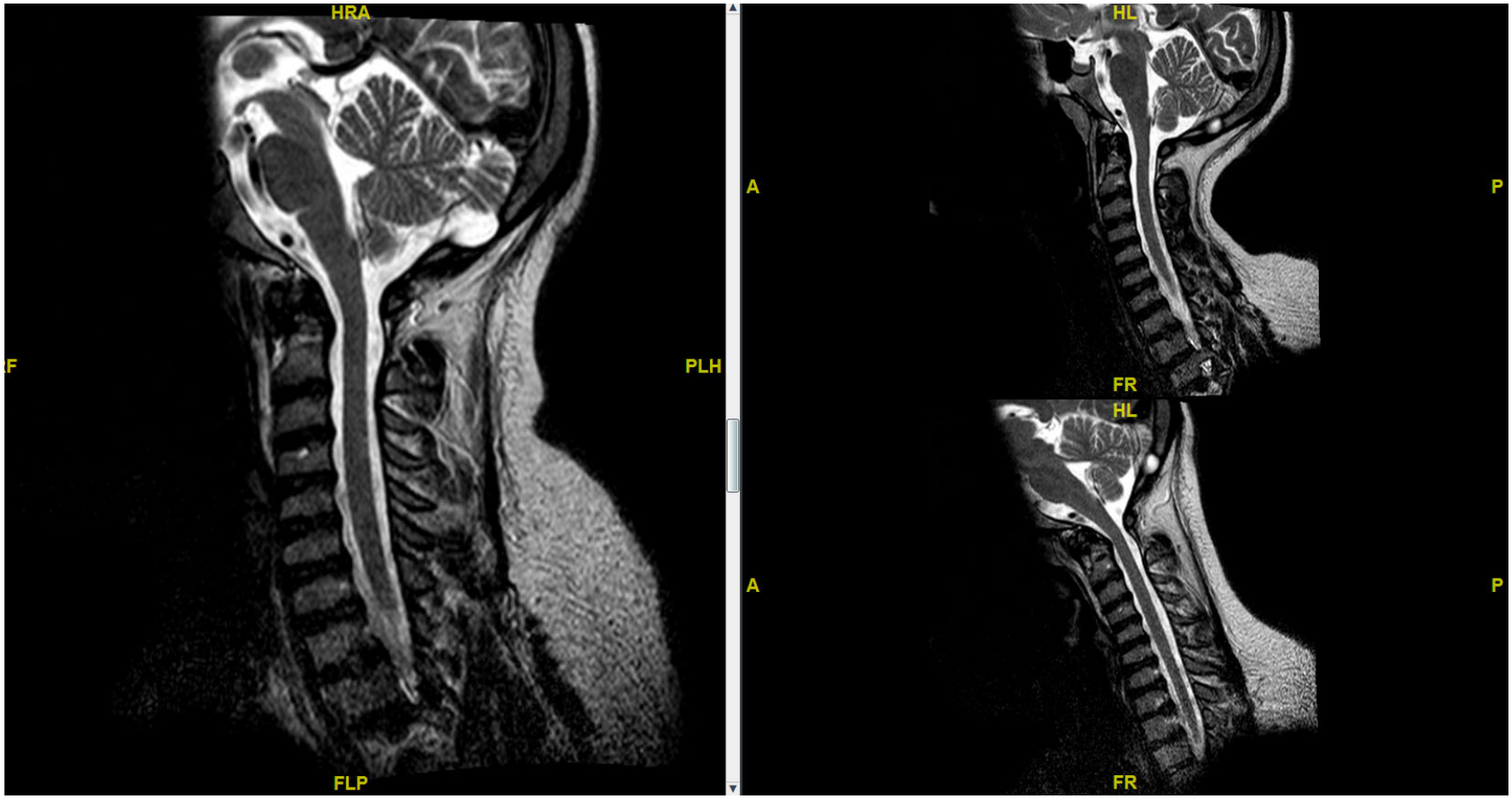
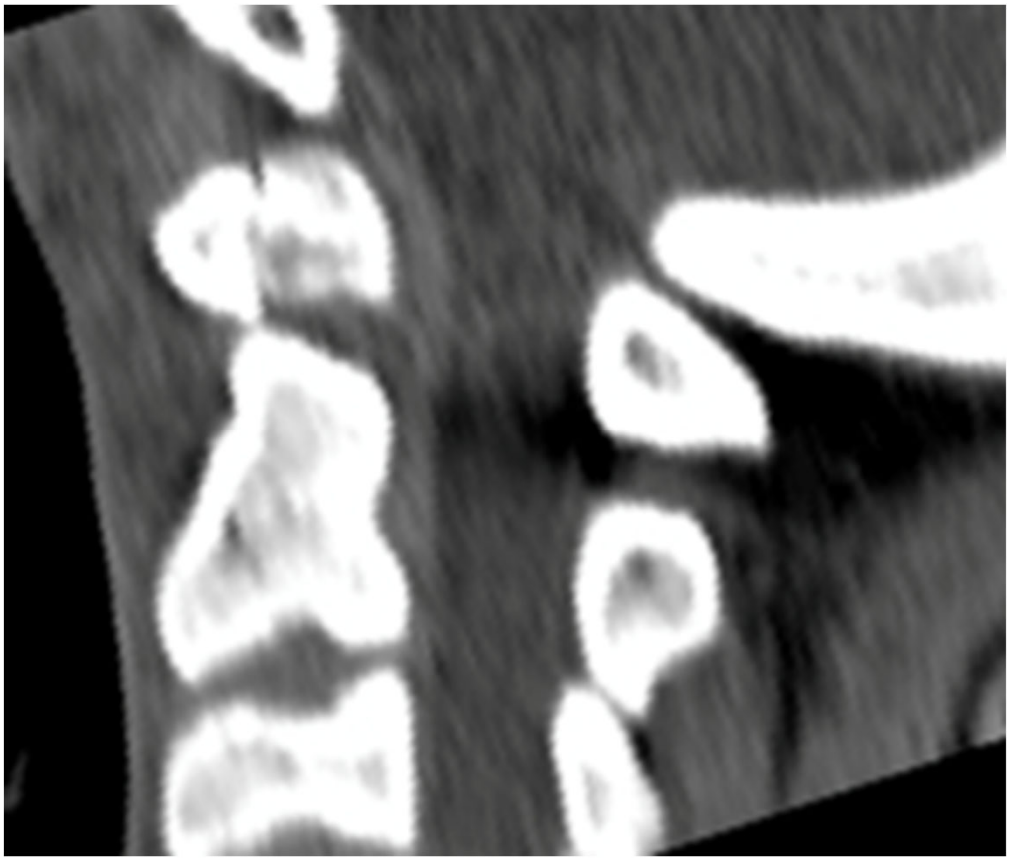
# Cervical spine abnormalities and deformities

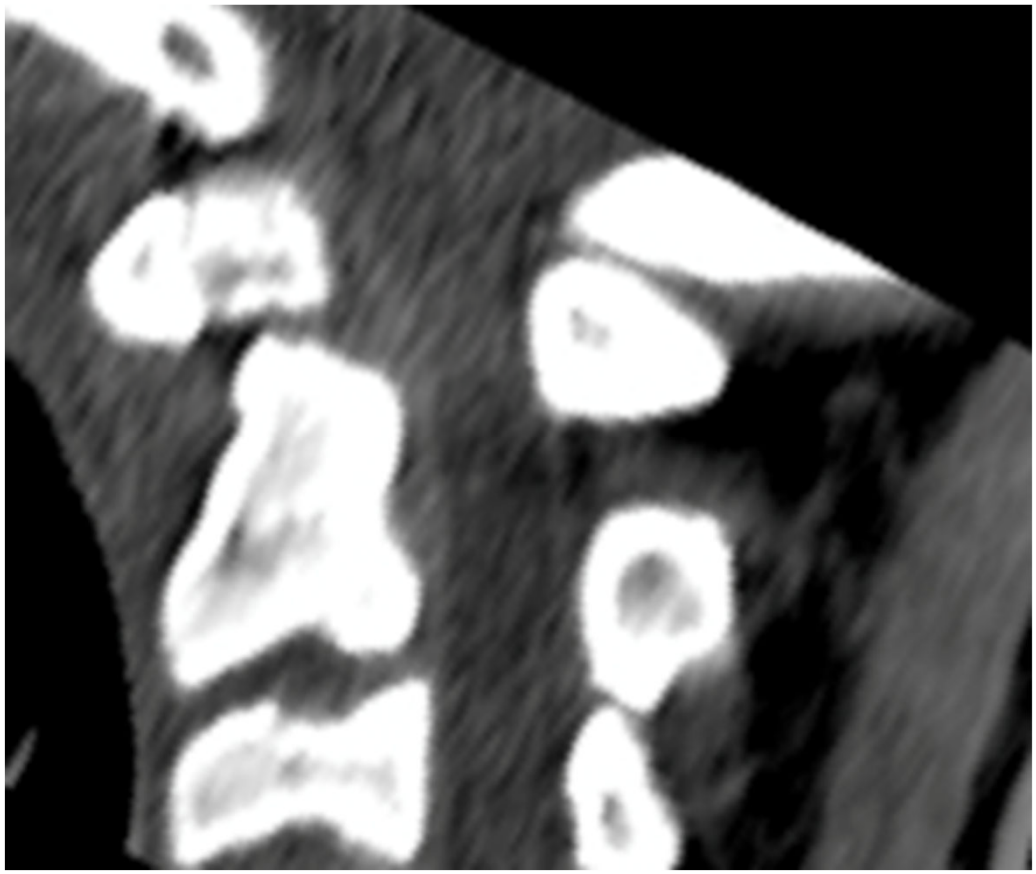
- Cervical spine
  - Spinal stenosis and cord compression
  - Odontoid hypoplysia
  - Atlantoaxial instability
- Thoracolumbar gibbus
  - Bullet shaped vertebra
  - Wedge shaped vertebra



# Dynamic testing in MRI







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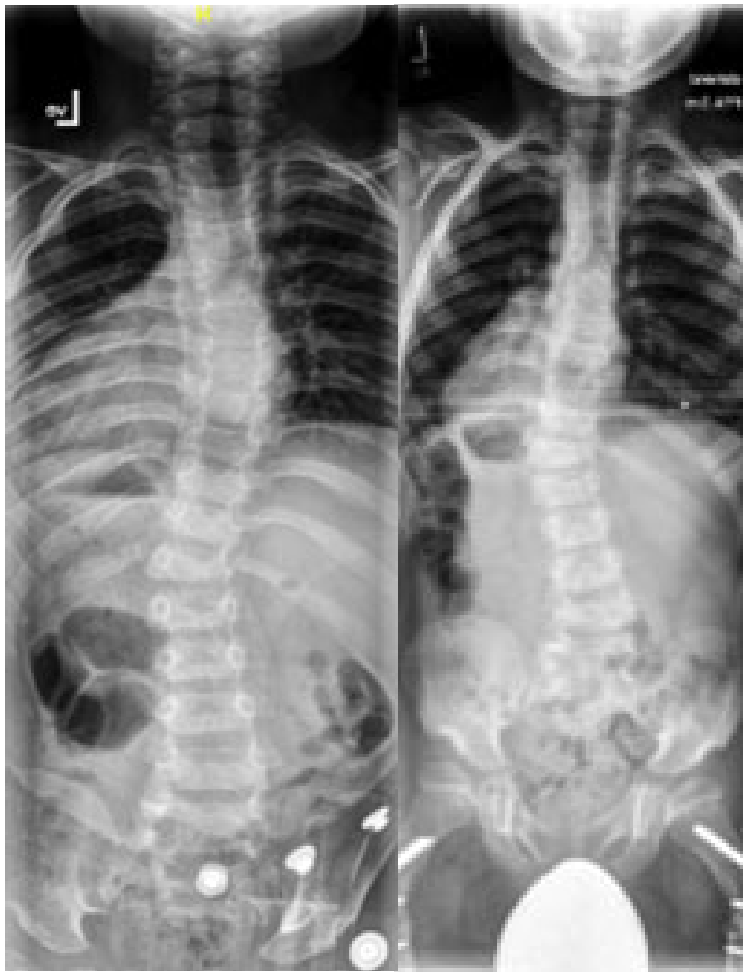
# Spinal deformities in MPS

- Cervical spine problems need to be addressed first
  - Spine fusion for deformities carries a high risk of severe neurologic compromize due to cervical spine anomalies
- Decompression and fusion of cervical spine often necessary
- In thoracolumbar kyphosis short posterior fusion from end to end vertebra and decompression by posterior approach (N=10)
  - No need for anterior approaches

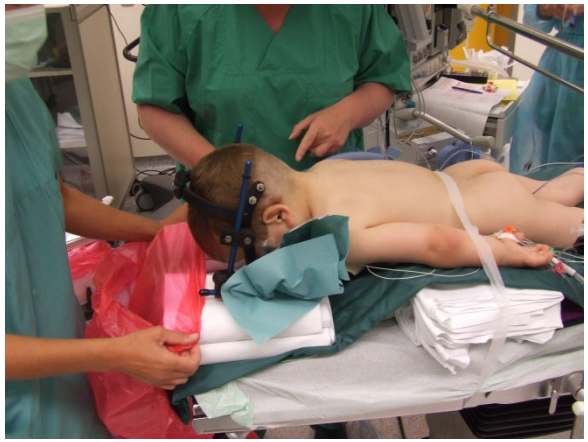
# Scoliosis in MPS

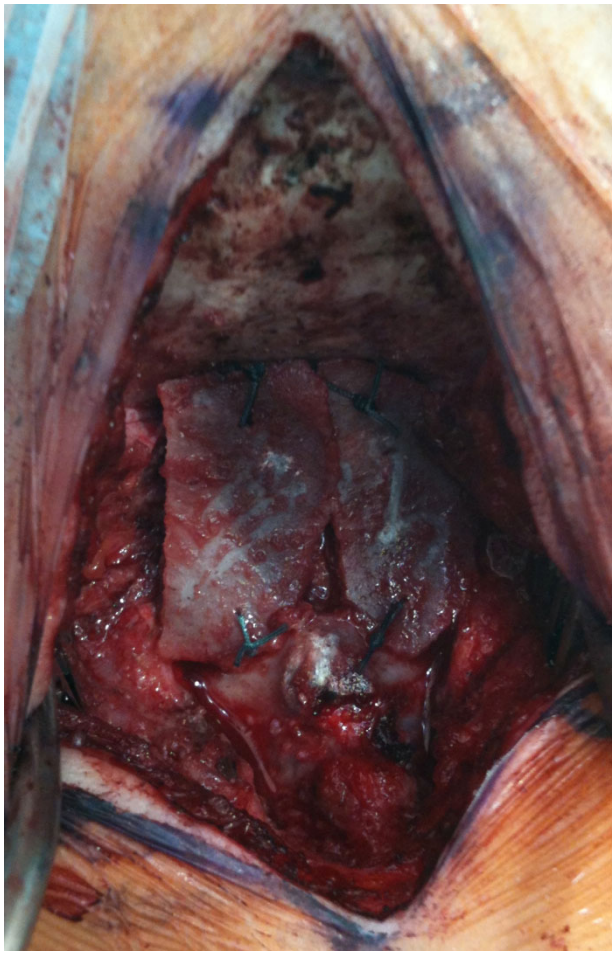
- Similar to kyphosis as a result of vertebral deformity
- Slow or no progession
- Spine fusion may become necessary in adolescence
- Always combine with decompression if necessary

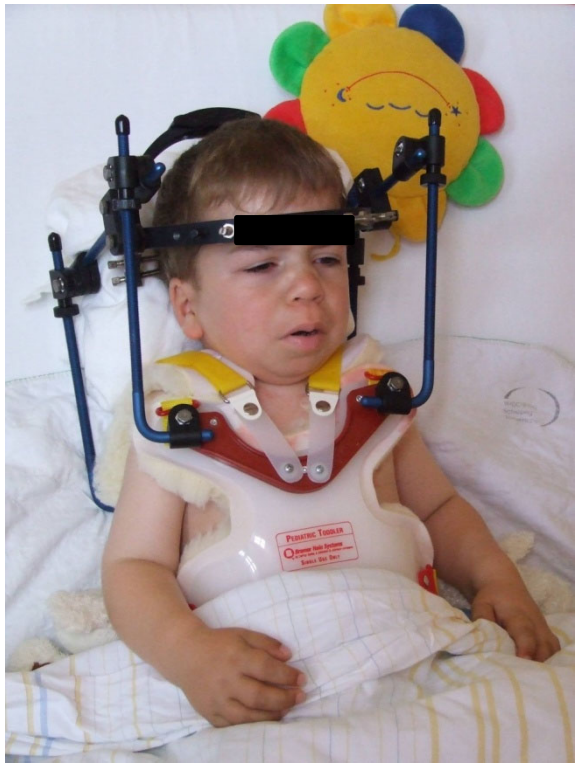


# Cervical stenosis in small children

## Stabilization in young patients



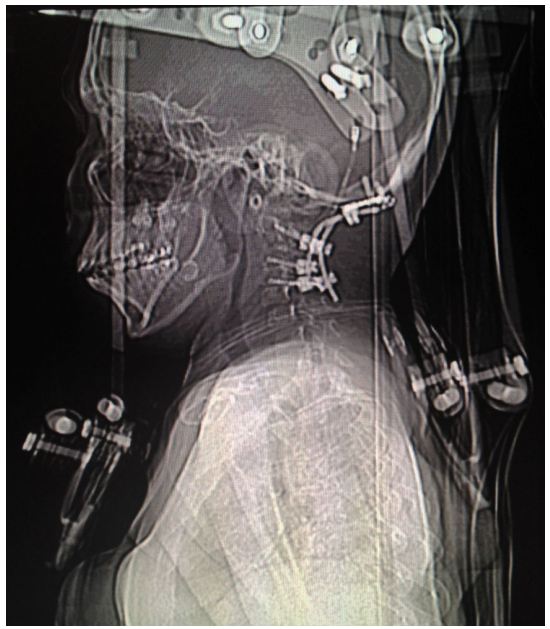


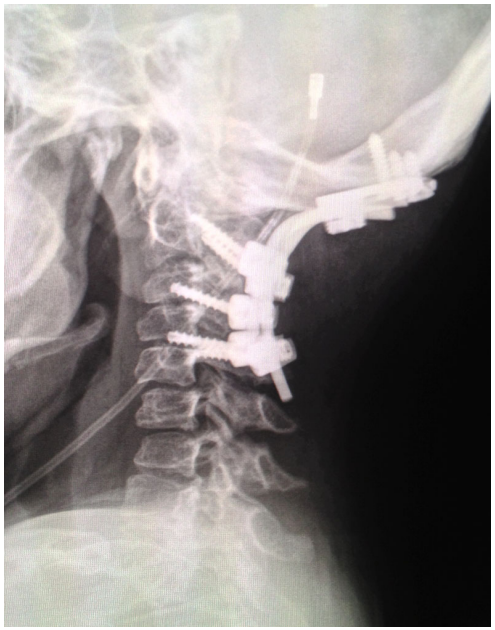


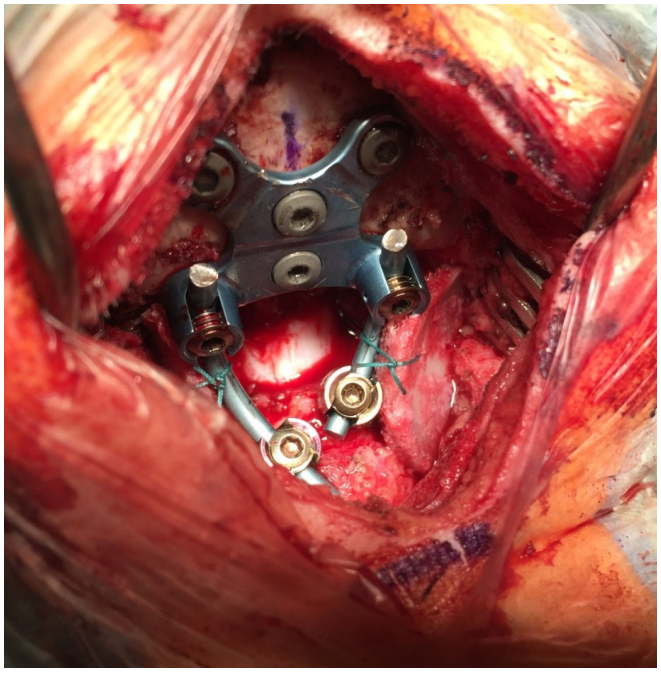
# Spine – Cervical stenosis in older children, > 4 years old

- Surgical procedures

- Decompression and stabilization

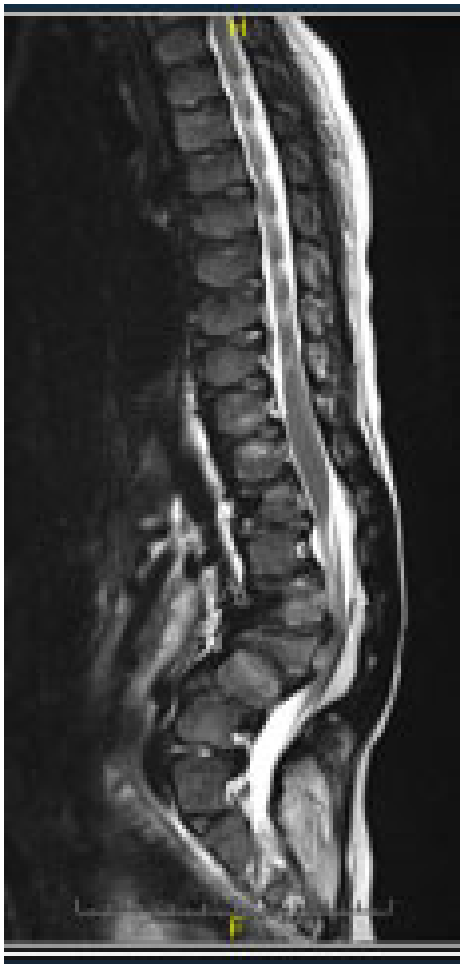






# Indications for surgey

- Kyphosis > 40°
  - Chan, Mackenzie, 2009
- Kyphosis > 70, scoliosis > 50°
  - White et al, 2009
- Presence of myelopathy
- Anterior-posterior vs posterior only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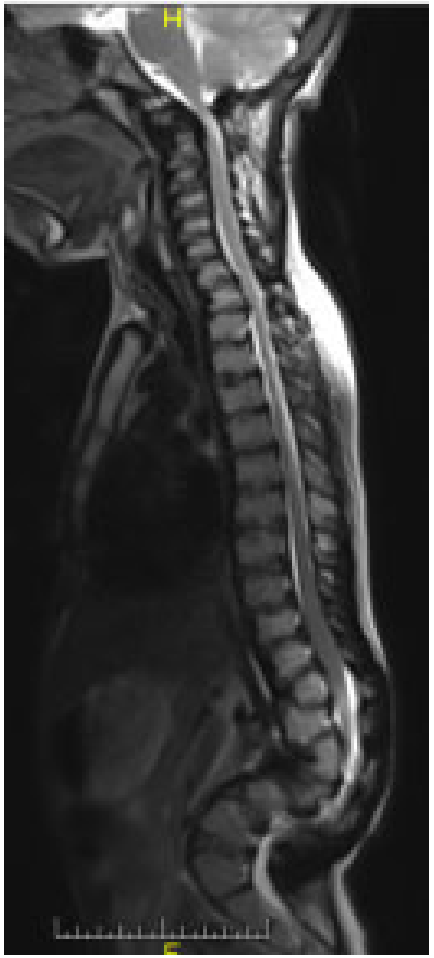
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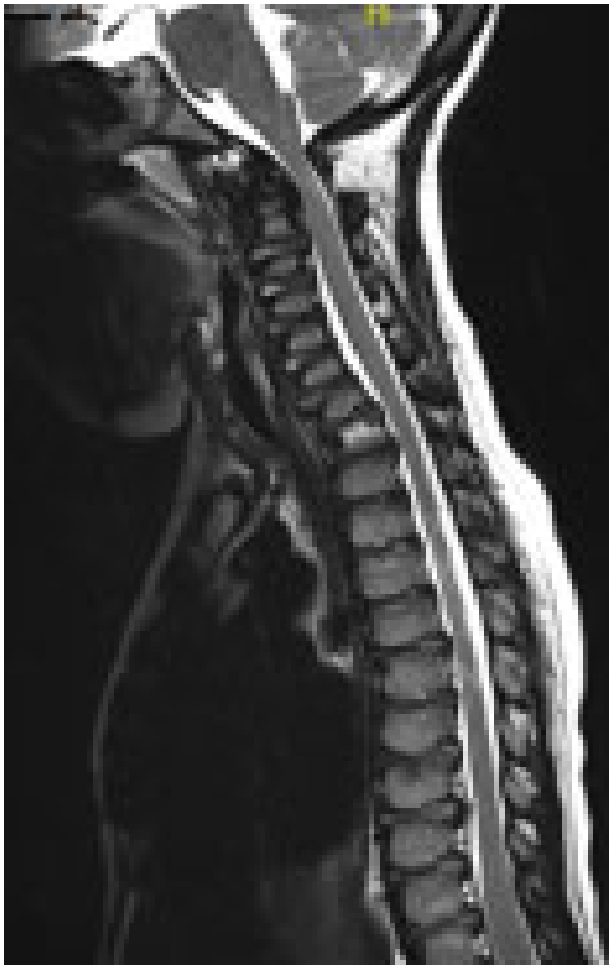

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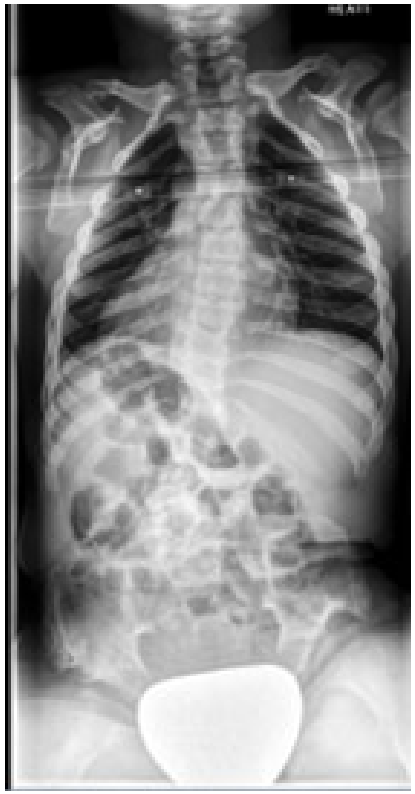
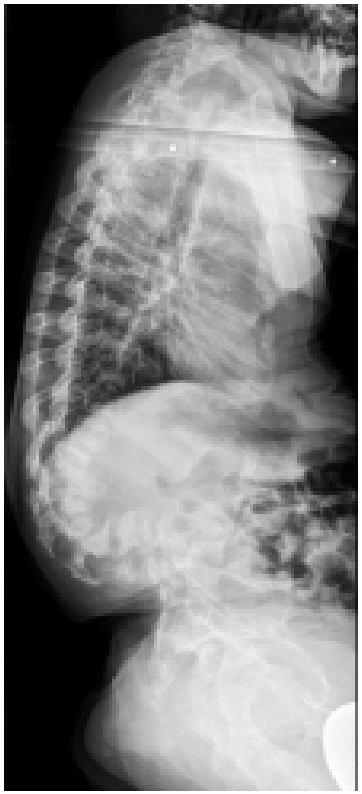
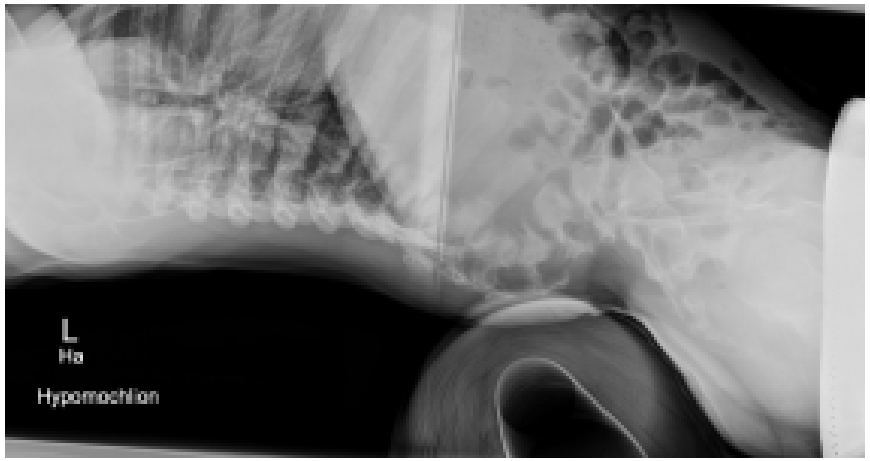
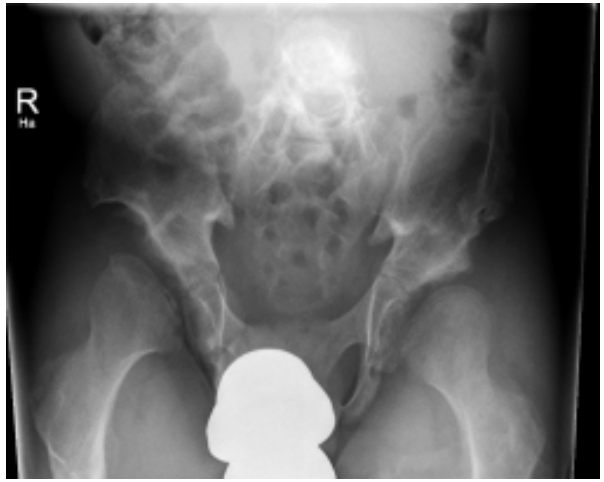
# W.,C. 16 year old male with MPS type 1

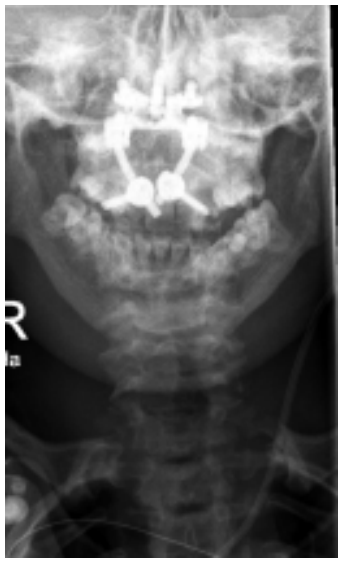




116°

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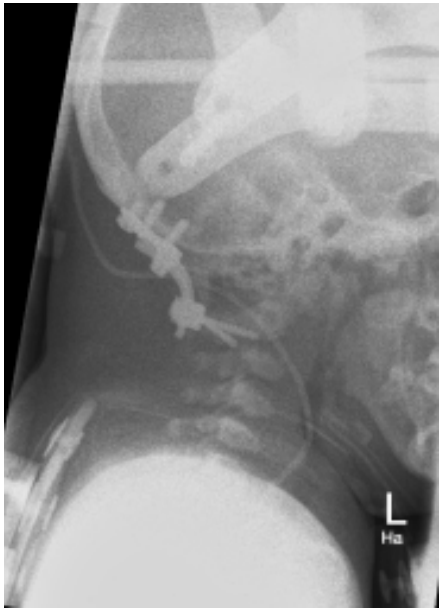
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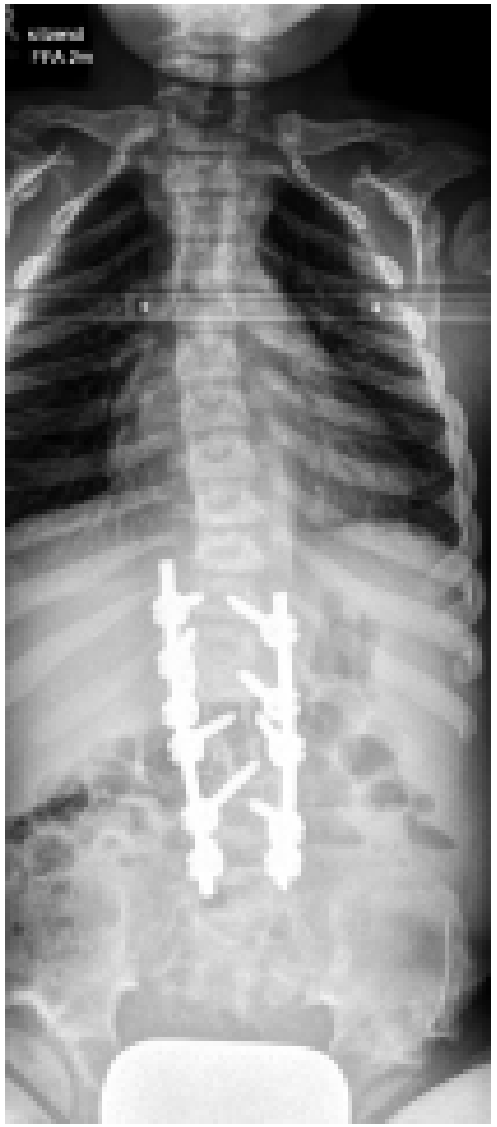

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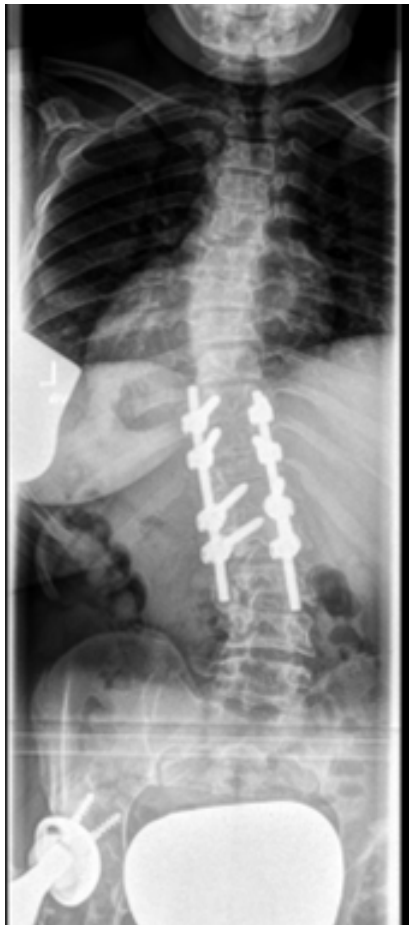
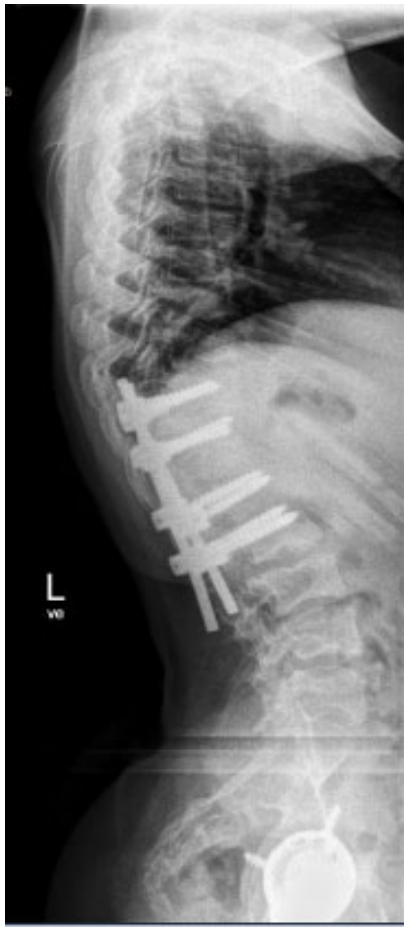
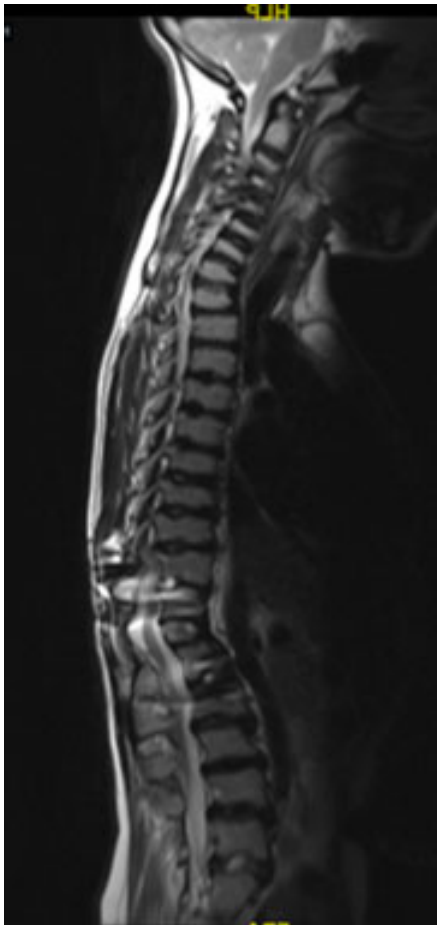
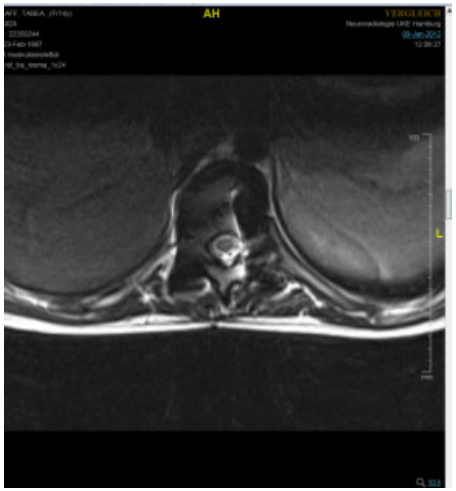
# G, T., 19 year old girl with MPS type 4, no ERT







8 years follow-up after posterior only correction of kyphosis
note remodelling of spinal canal

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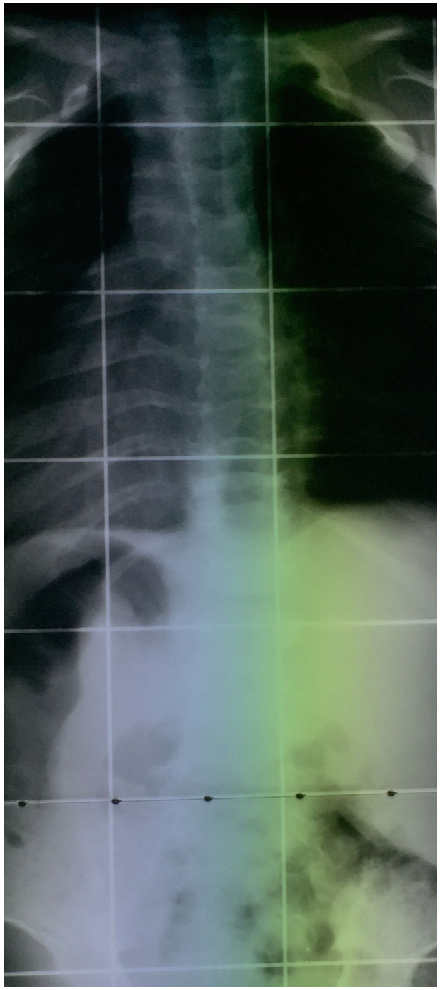
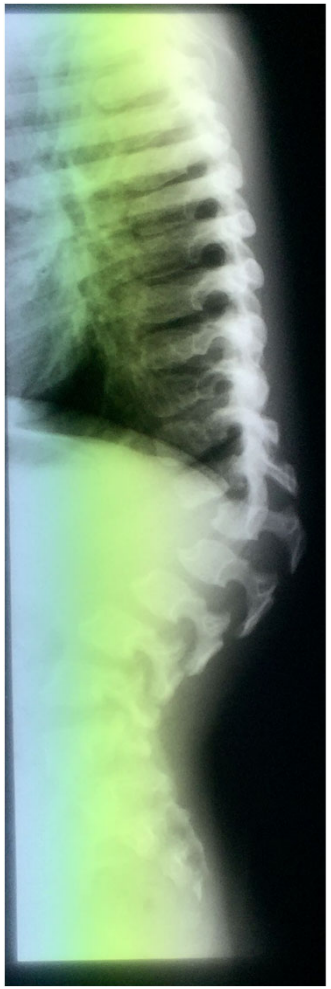
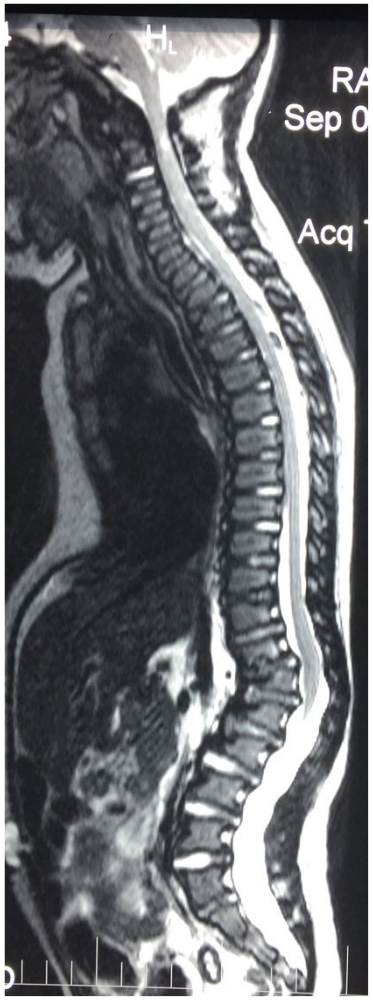
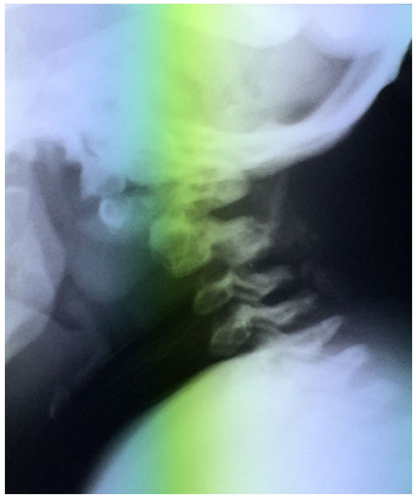
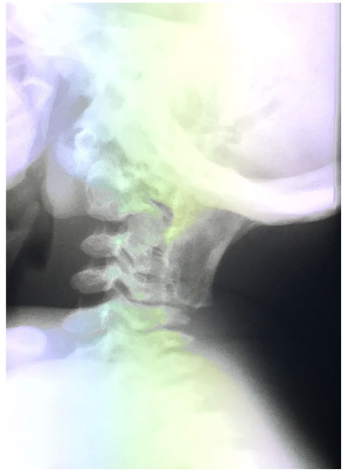
# 3 year old boy with MPS type I









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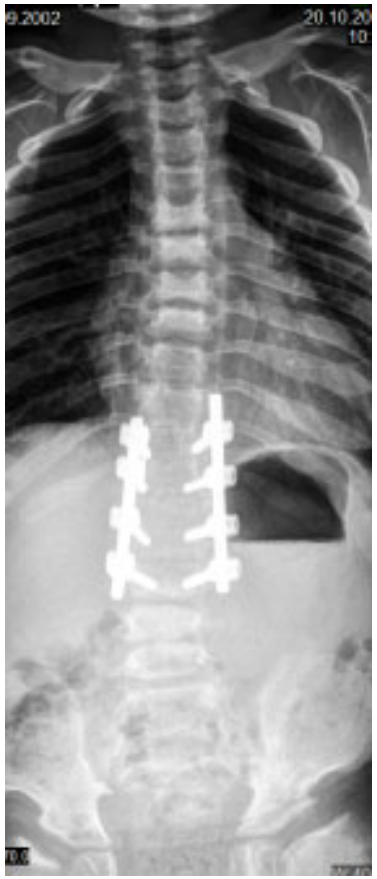
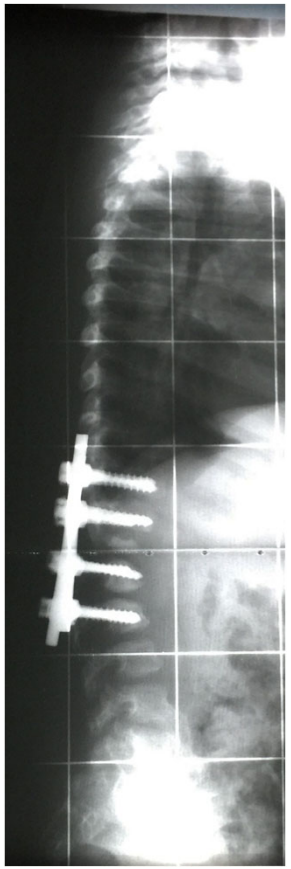
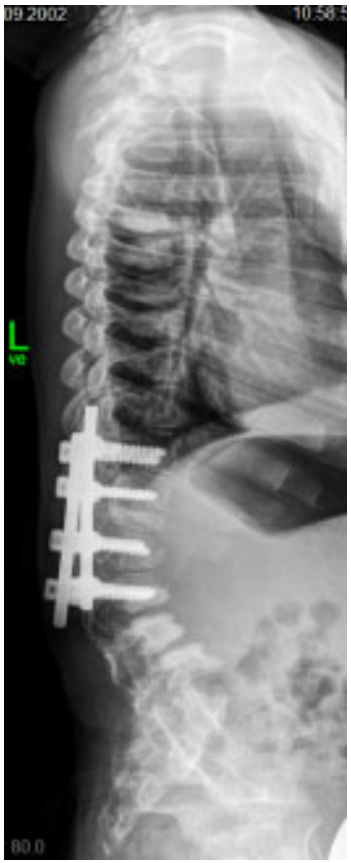
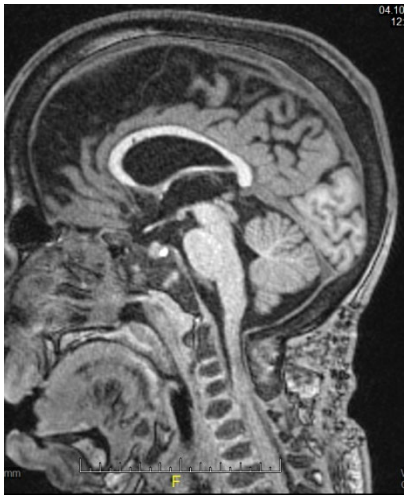
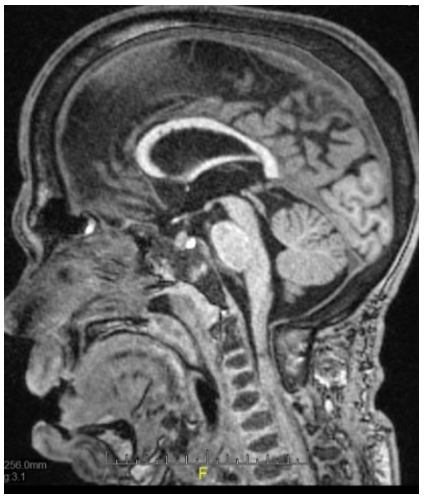
# 9 years follow-up

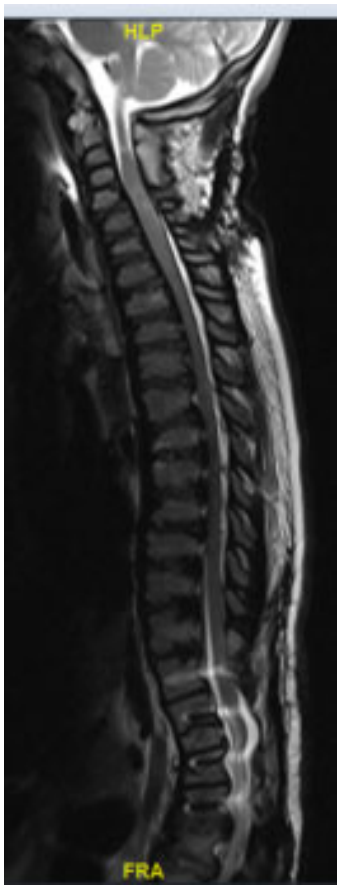













Fusion seems to promote remodelling of spinal canal and prevent recurrent spinal canal stenosis

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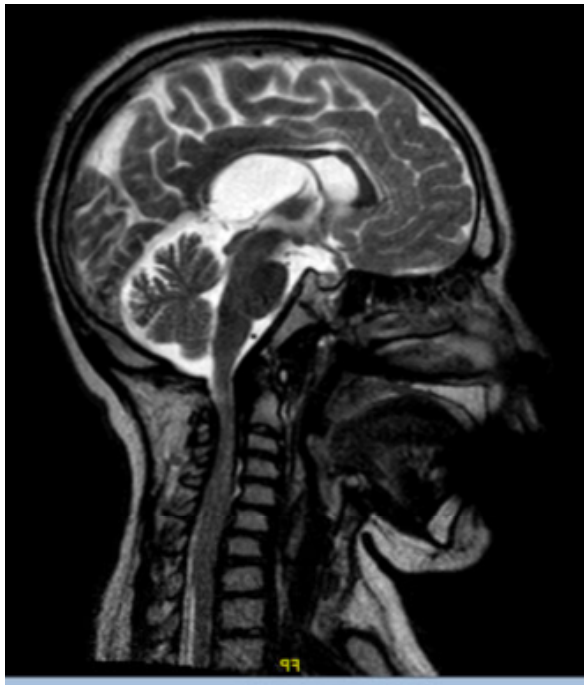
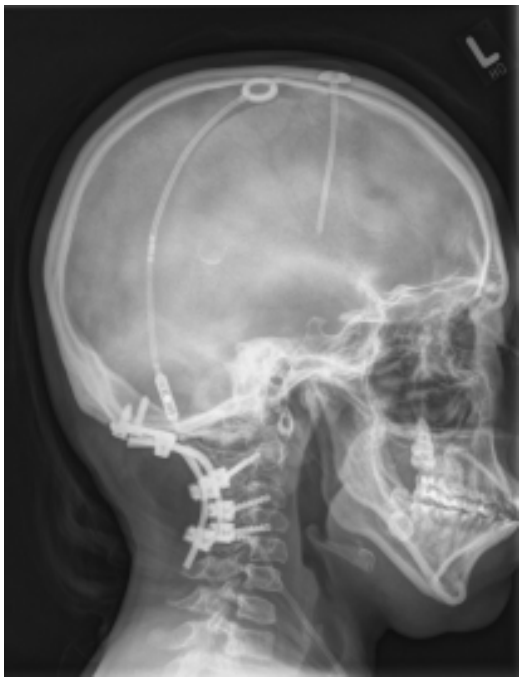
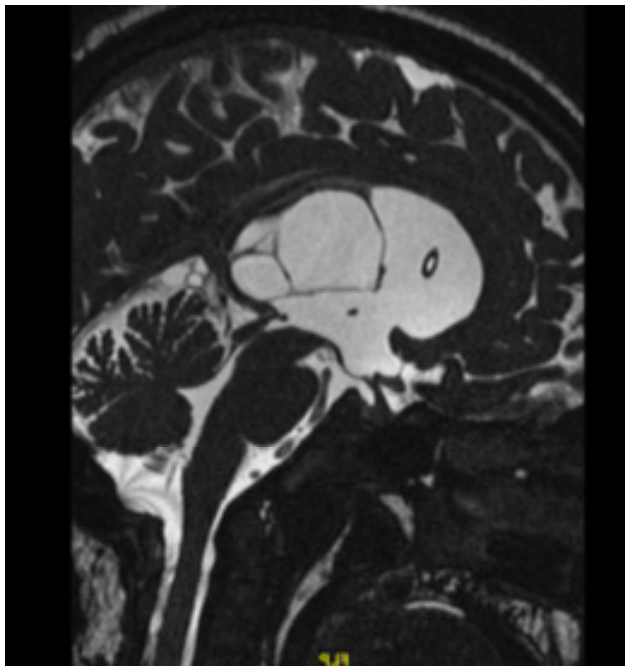
# 22 year old girl wit MPS type 1, 8 years after cervical spine decompression and fusion







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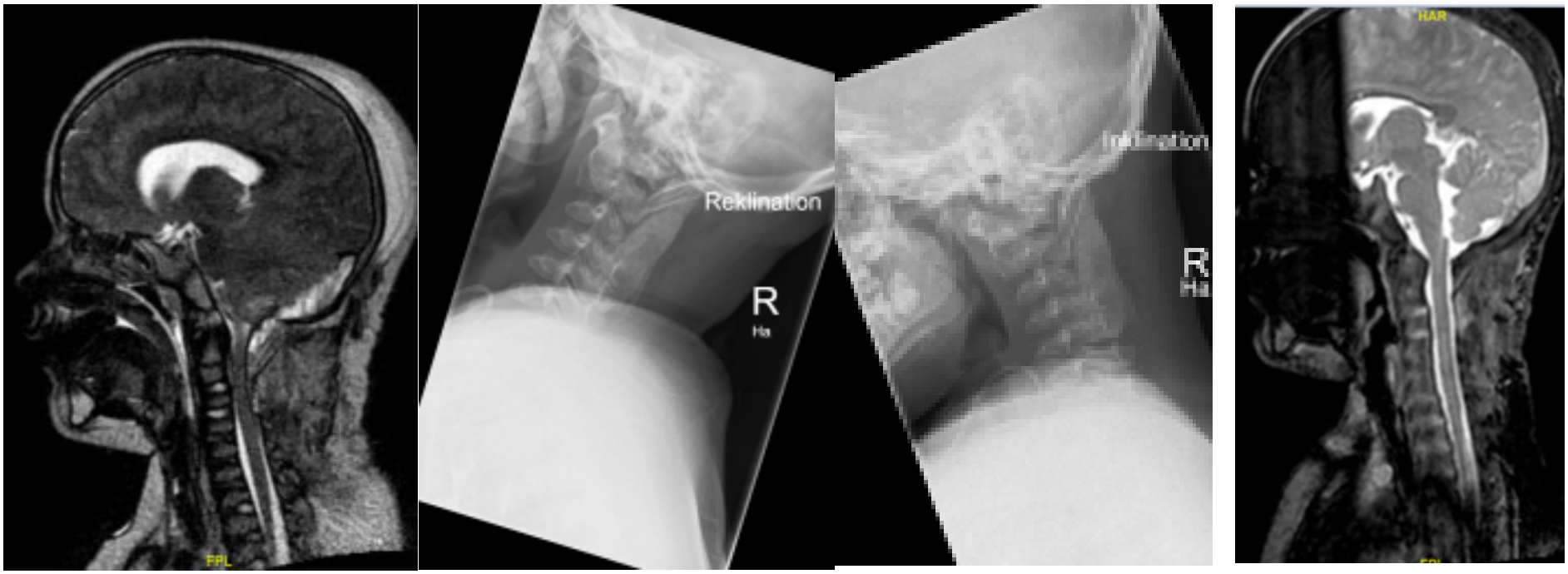
# 9 year old female with MPS type 1, 6 years after cervical spine fusion and decompression



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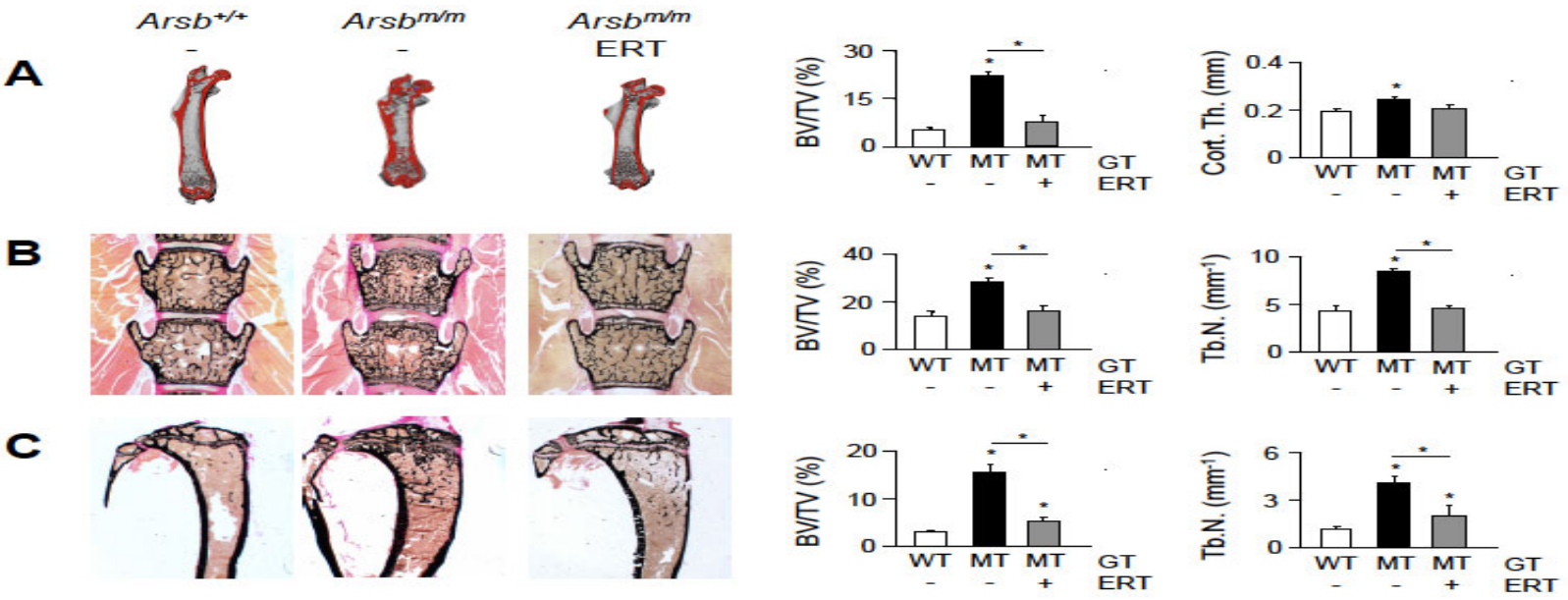
# Unpublished data (Hamburg) type VI mouse and ERT




ERT normalizes trabecular bone and cortical thickness

- A = Femur
- B = Spine
- C = Tibia

The future ??

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# Summary

- Always investigate cervical spine in MPS
- In case of deformity and cervical spine abnormality address cervical spine first
- Progressive kyphosis > 45° is an indication for surgery
- Surgery can be performed posterior only with no need for anterior decompression
- Fusion seems to lead to remodelling of spinal canal, but watch adjacent levels
- There seems to be limited use for growth preservation surgery

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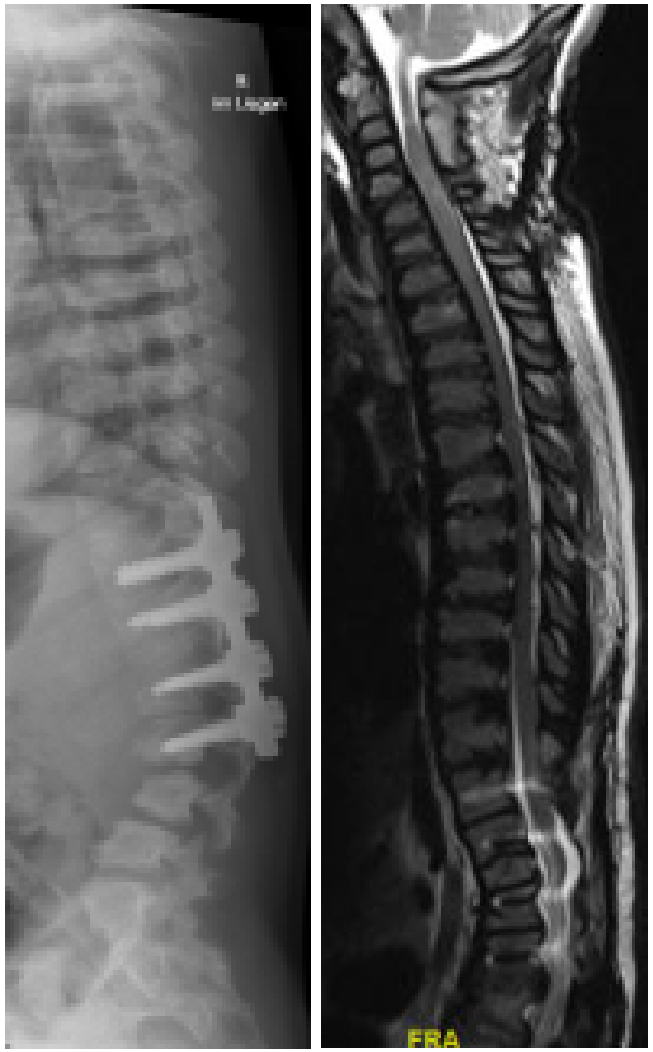
# Decompression vs fusion Hamburg experience

- Decompression
  - often results in recurrent spinal canal stenosis
  - May result in instability
- Fusion
  - Seems to avoid GAG-accumulation and promotes spinal canalremodelling
  - May produce instability and spinal canal stenosis at adjacent levels



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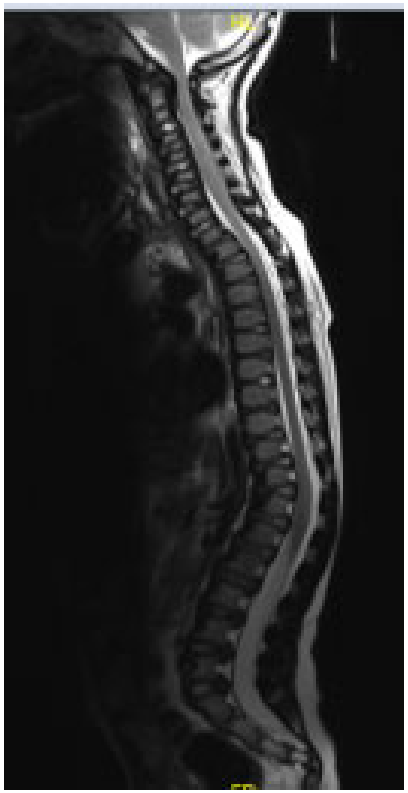
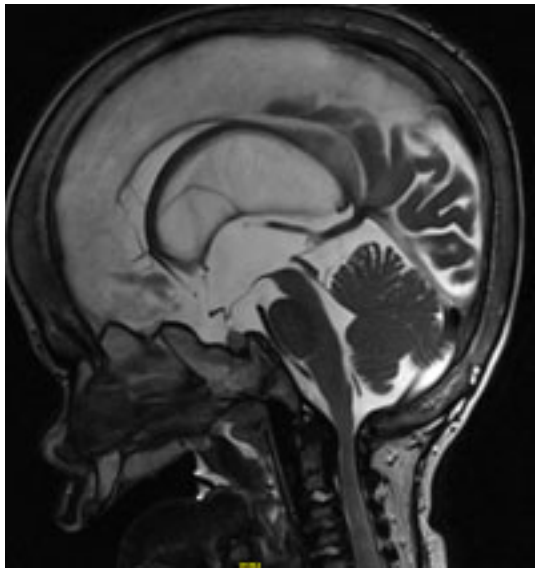
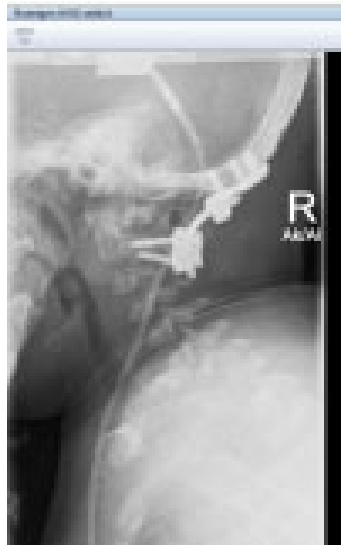
# Evers, Emily 2006, Typ 1
# Enzymersatz und KMT

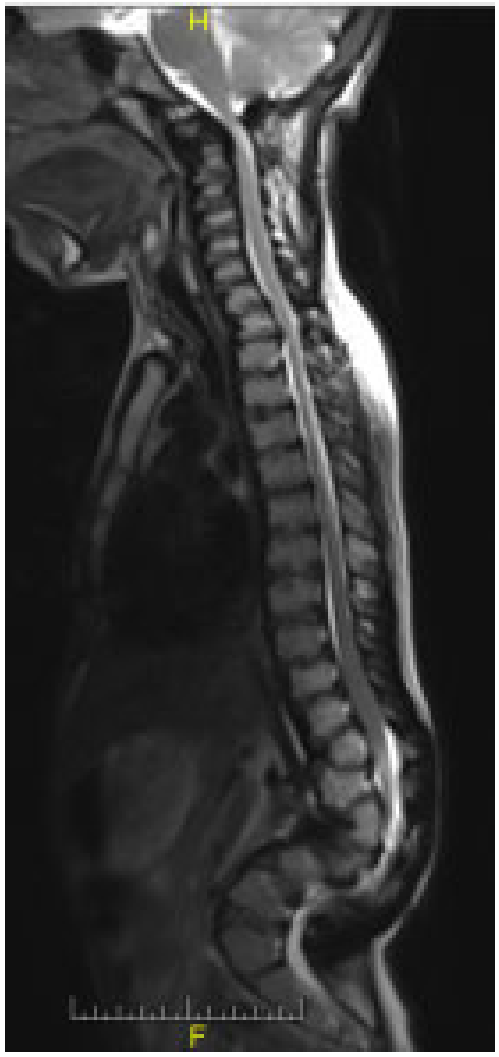






# MPS I

- Growth hormone treatment under investigations
- HSCT preserves mental abilities and improves life expectancy and quality of life
- BMT does not alter natural history of muskuloskeletal disorders in type 1
  - Weisstein, 2004
- Effects of HSCT
  - Growth of odontoid process may normalize
  - Spinal instability and spinal cord compression may still occur but may be less common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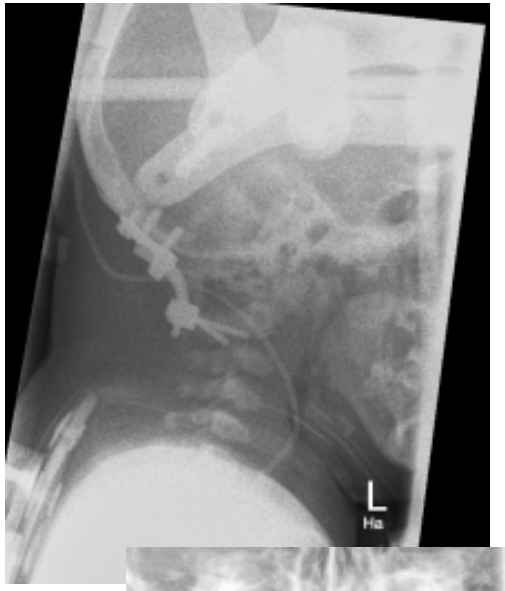
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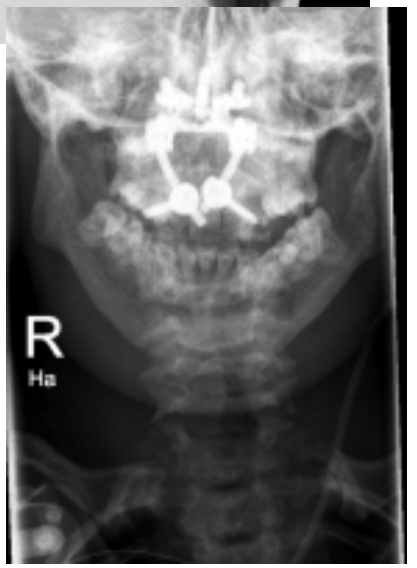
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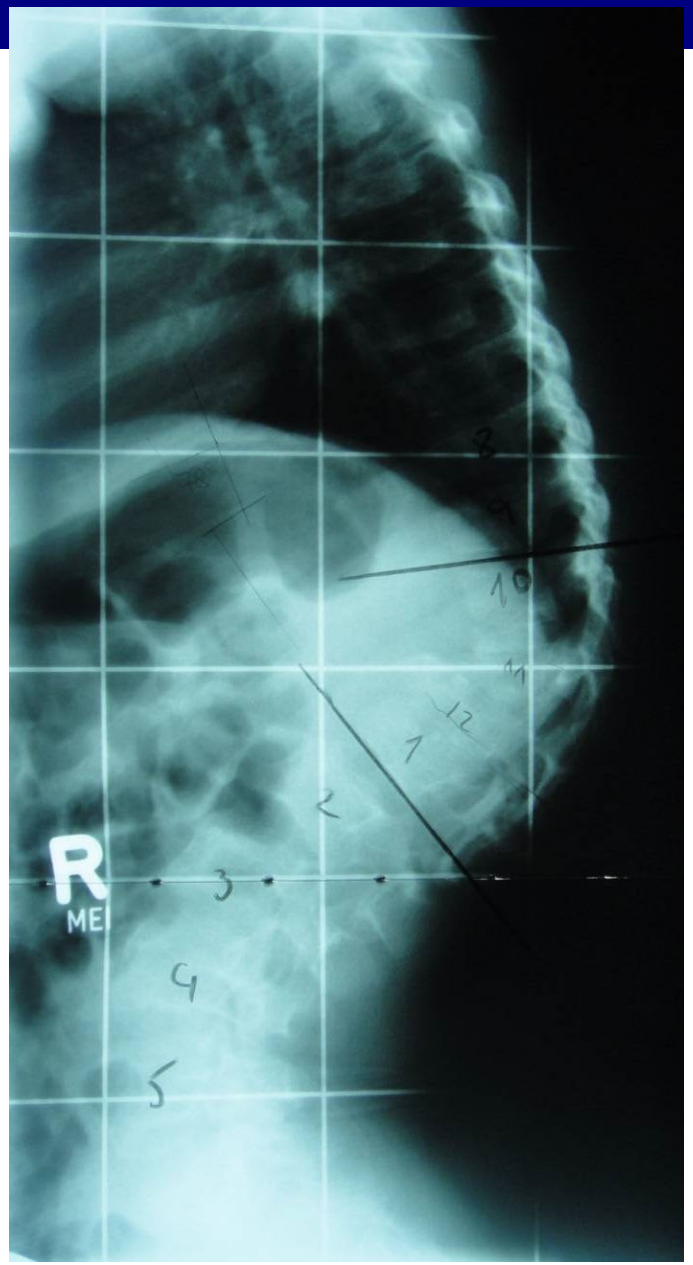
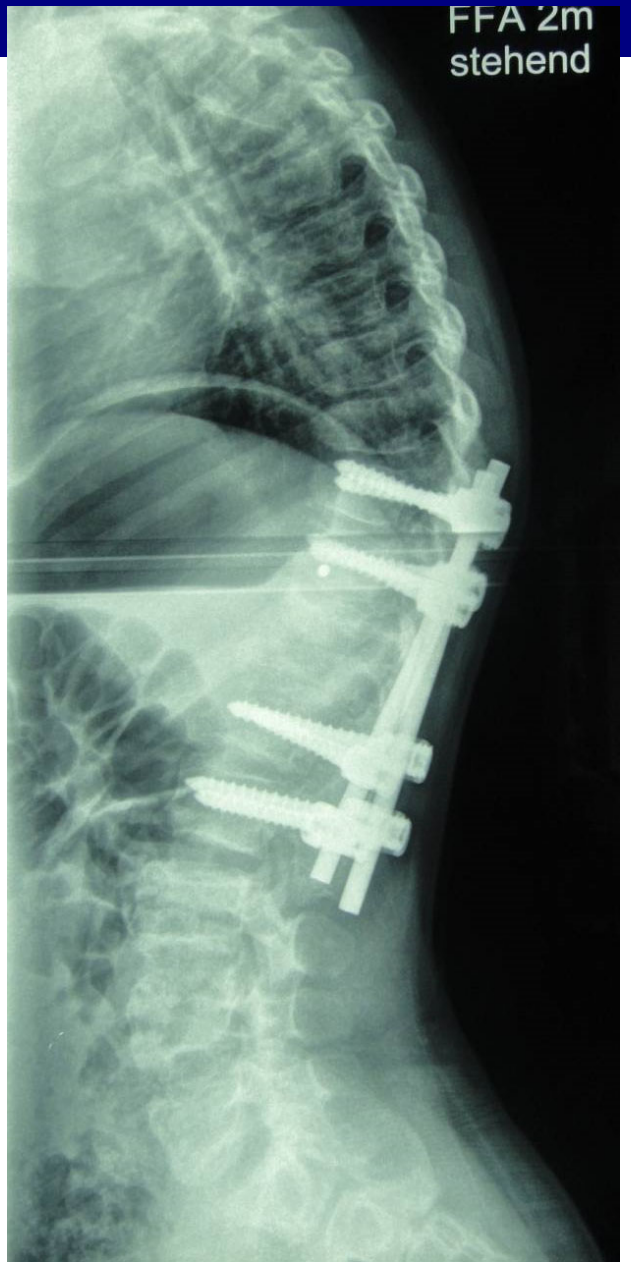
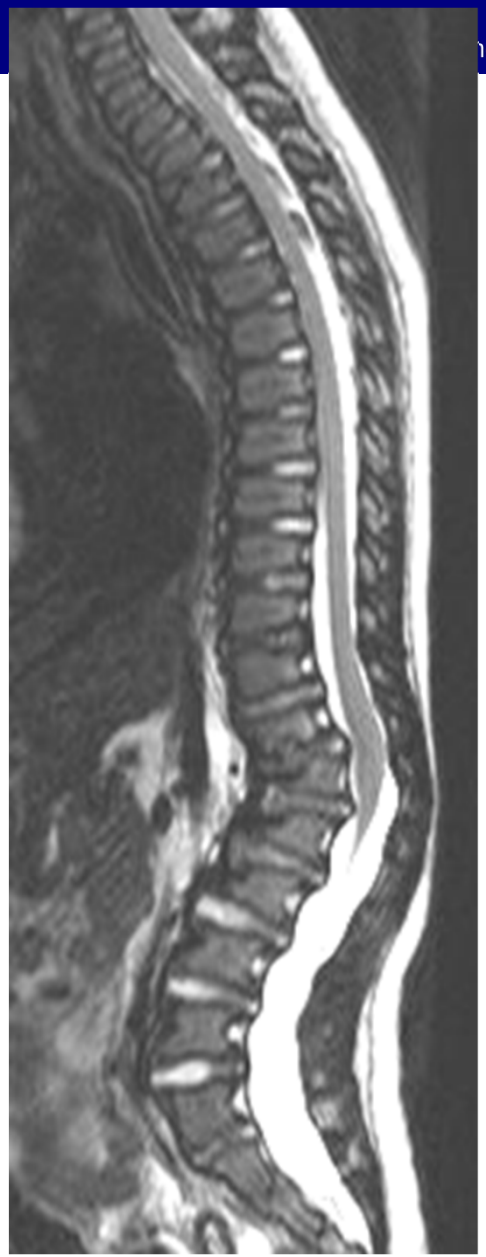
# Correction by PSO

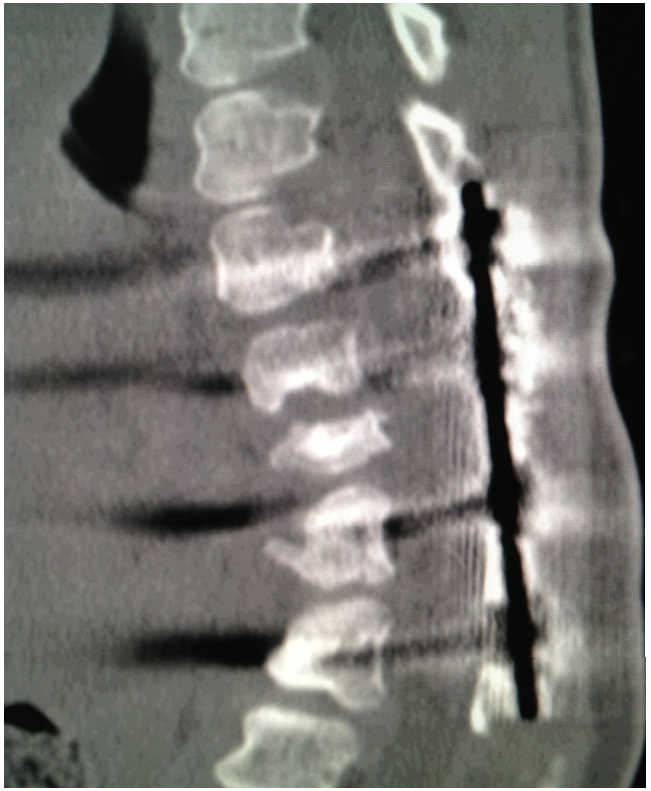


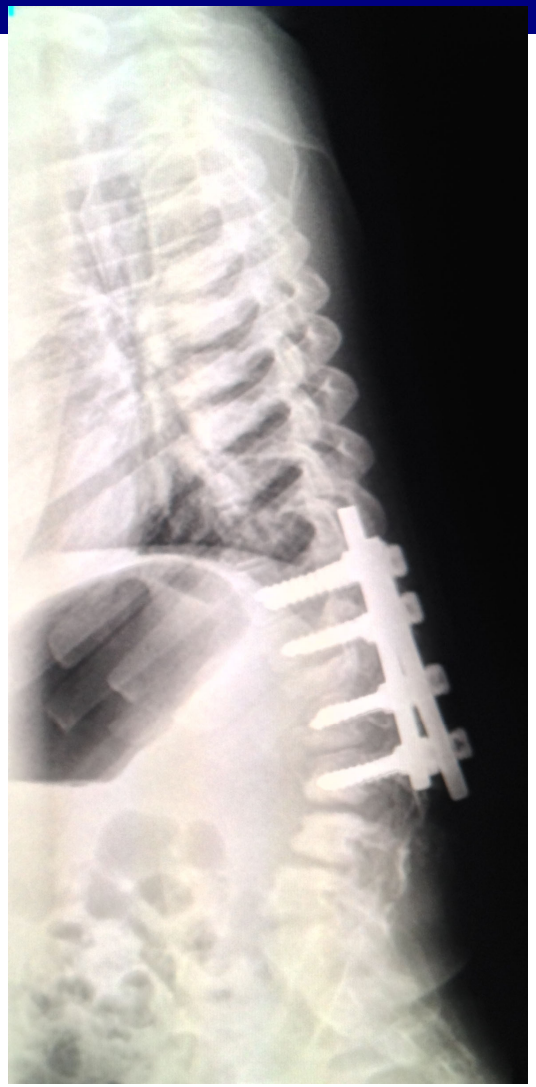



# MPS Typ I, 7 J., Kurzstreckige Spondylodese (T10-L2)









# Enzymatic treatment

- May prevent mental retardation
- Does not change musculoskeletal features

# What is dysostosis multiplex?

- A constellation of radiographic abnormalities resulting from defective endochondral and membrannous growth
  - Hypoplystic vertebral bodies
  - Shallow acetabuli
  - Enlargement of skull
  - J-shaped sella turcica
  - Broadening of the clavicles and ribs
  - Hypoplastic epiphyses
  - Thickened diaphyses
  - Short metacarpals with proximal tapering (bullet shape)

# MPS Disease Spectrum

| MUCOPOLYSACCHARIDOSIS | | | | | |
|---|---|---|---|---|---|
| **Type** | **Eponym** | **Deficient Enzyme** | **Accumulated Products** | **Incidence** | **Neurologic Symptoms** |
| MPS 1 | Hurler syndrome | α-L-iduronidase | Heparan sulfate<br>Dermatan sulfate | 1 in 100,000 | Mental retardation<br>Retinal degeneration |
| MPS 11 | Hunter syndrome | Iduronate sulfatase | Heparan sulfate<br>Dermatan | 1 in 100,000 | Mental retardation |
| MPS III | Sanfilippo syndrome A | Heparan sulfamidase | Heparan sulfate | 1 in 100,000 | Developmental delay<br>Severe hyperactivity<br>Spasticity<br>Motor dysfunction |
| | Sanfilippo syndrome B | N-acetyl glucosaminidsase | | | |
| | Sanfilippo syndrome C | Acetyl-CoA:alpha-glucosaminide acetyl transferase | | | |
| | Sanfilippo syndrome D | N-acetyl glucosamine 6-sulfatase | | | |
| MPS IV | Morquio syndrome A | Galactose-6-sulfate sulfatase | Keratan sulfate<br>Chondroitin 6-sulfate | 1 in 75,000 | Motor dysfunction |
| | Morquio syndrome B | Beta-galactosidase | Keratan sulfure | | |
| MPS VI | Maroteaux-Lamy syndromq | N-acetyl galactosamine-4-sulfatase | Dermatan sulfate | | Motor dysfunction |

Wikipedia, modified

# Strategy

- Cervical spine decompression and fusion
  - soft tissue thickening resolves after spinal fusion (Stevens et al, 1991)

- mm

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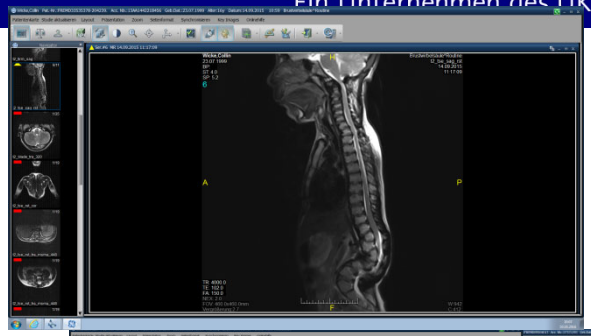
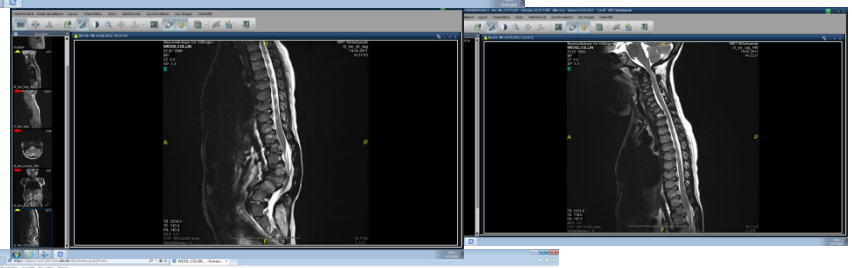
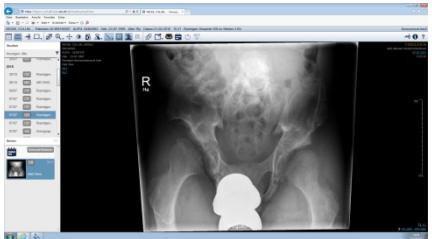
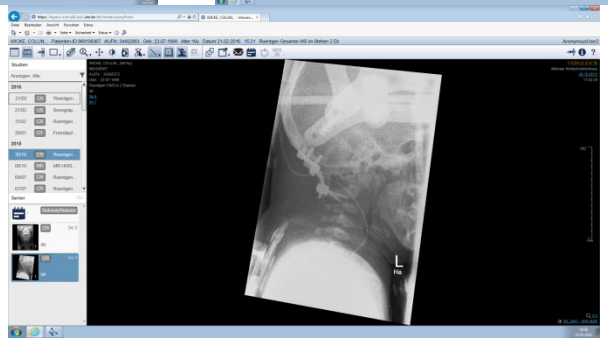
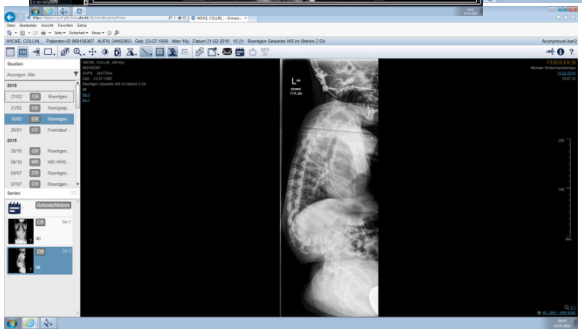
# Wicke,Collin

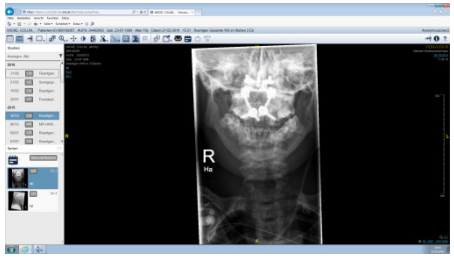


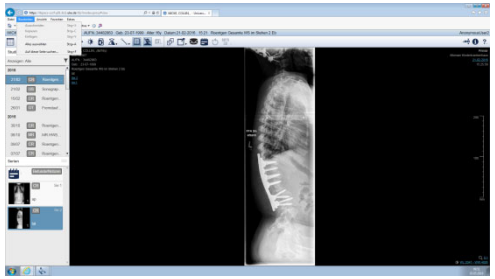


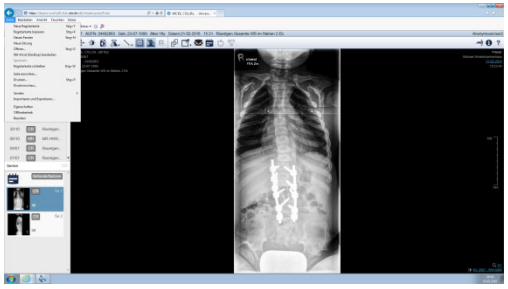


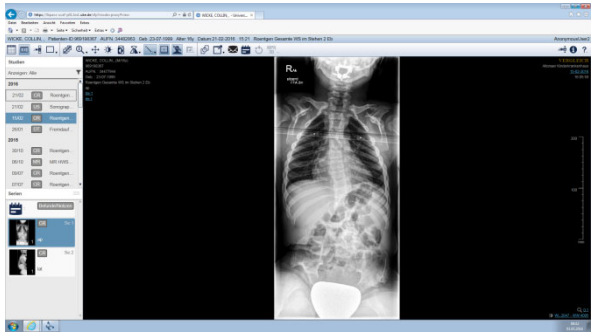












# MPS IV

- BMT not effective against bone manifestations
- Recombinant enzyme therapy targeted towards the bone tissue is currently being developed.

# MPS VI

- Investigations in a mouse model
- Bone morphology after ERT
- Enzyme replacement corrects trabecular bone pathologies in mice with mucopolysaccharidosis-VI

- Enzyme replacement corrects trabecular bone pathologies in mice with mucopolysaccharidosis-VI
  - *Schmidt, Breyer, Löbel, Müller, Yarar, Catalá–Lehnen, Stücker, Ullrich, Muschol (University Clinic Hamburg)*

# MPS type I (Hurler)

- Substantial improvement from bone marrow transplantation
- But spinal deformities can not be avoided
- Some positive influence on craniocervical junction with less myelopathy (Schmidt et al, Hamburg)
- Patients with initial deformity of >45° kyphosis are very likely to progress (Yasin et al, 2014)

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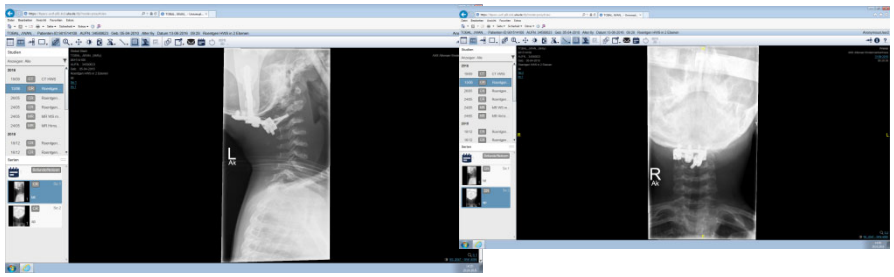
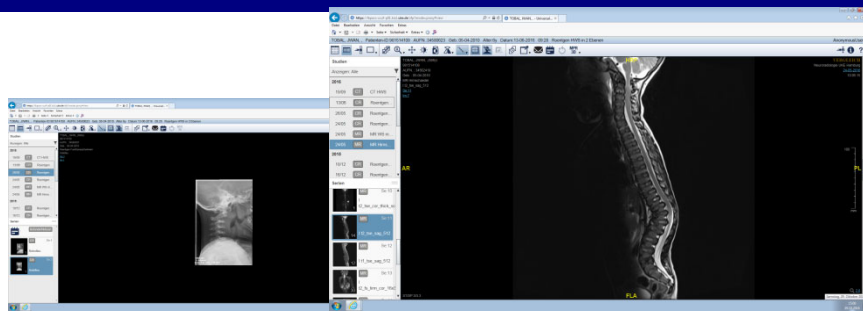
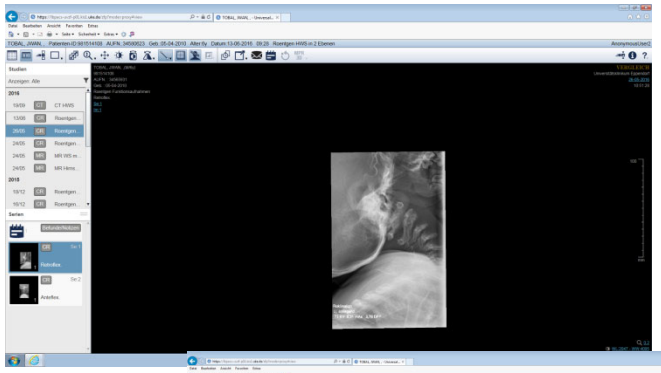
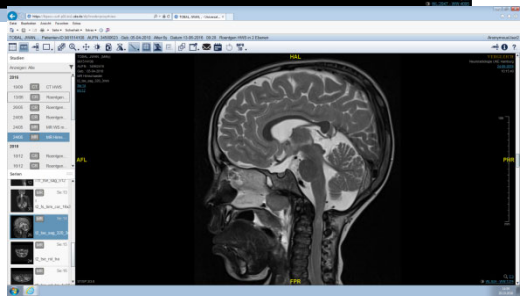
# Tobal, Jwan typ 4, 6 J
# keine med Therapie da Flüchtling









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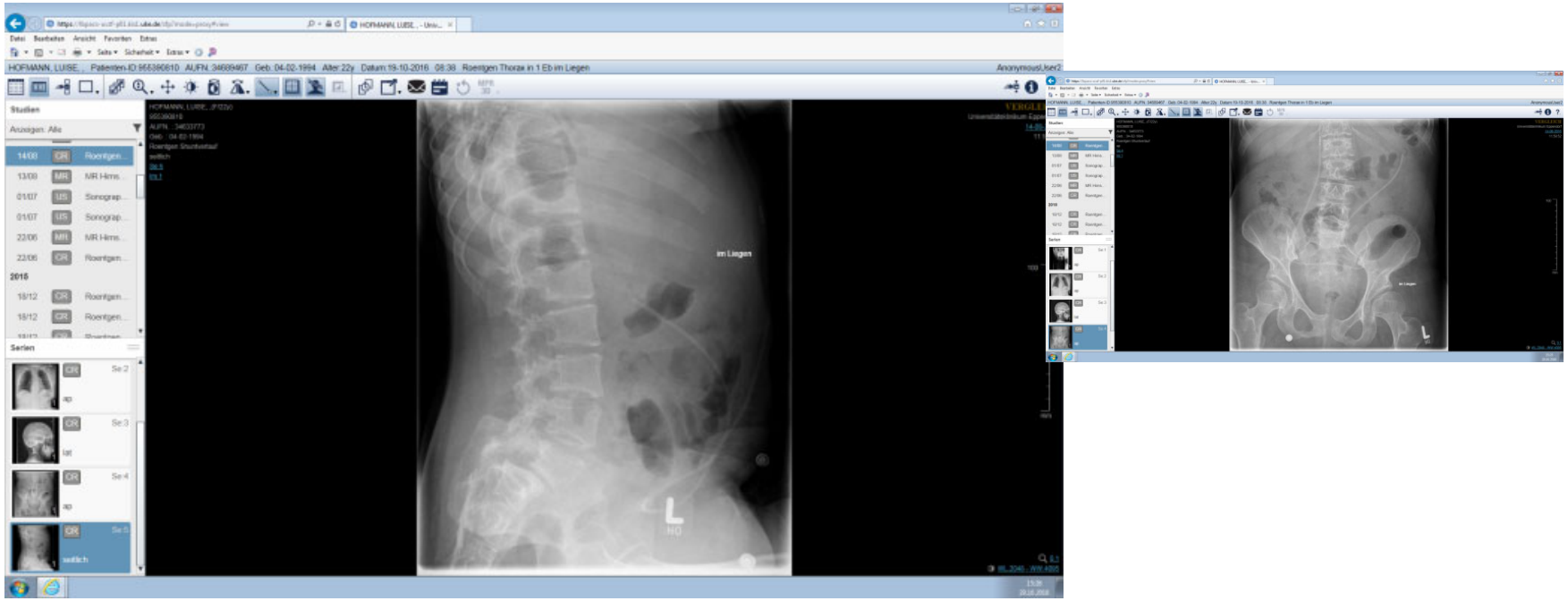

# Medical treatment type 1

- ERT and HSCT still have little impact on spinal deformity

- BMT does not reduce spinal deformity
  - Tandon et al, 1996 (n=12)
    - 10/12 had kyphosis, 1/12had scoliosis, 1/12 no deformity

- Growth of the odontoid process may normalize after HSCT but enlargement of odontoid process continues  spinal cord compression less common
  - Weisstein, 2004; Schmidt 2016