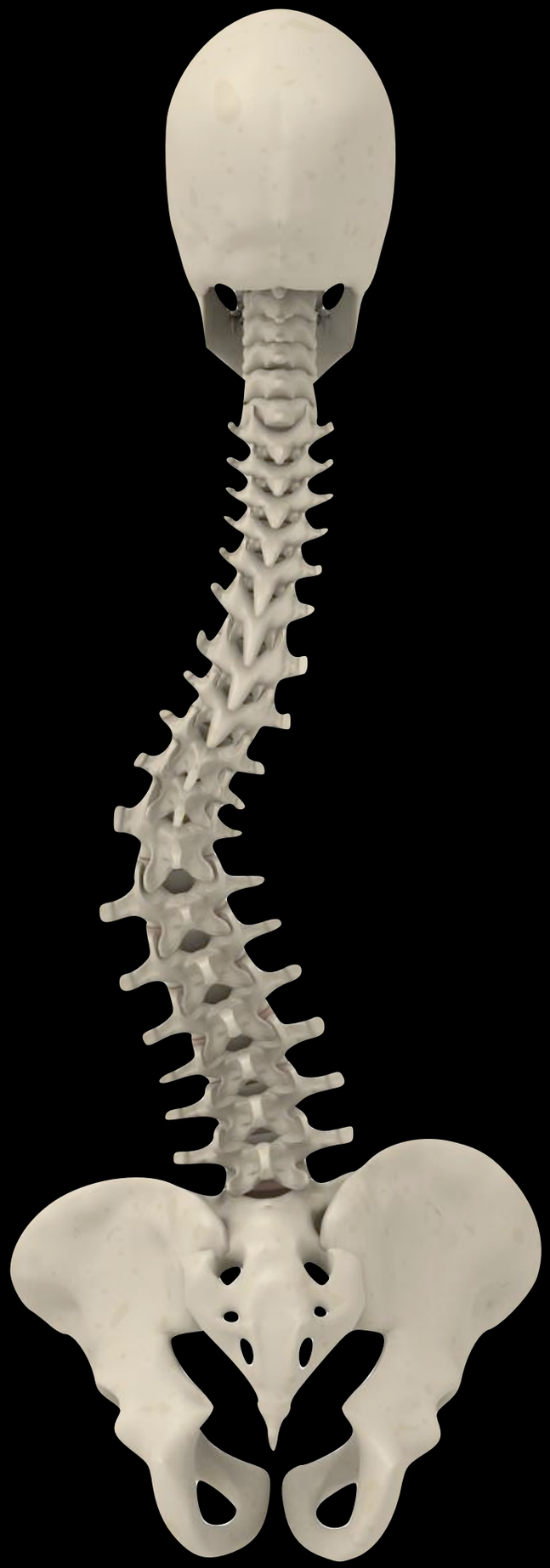
Ryggkirurgi ved Retts syndrom
Skoliose, kirurgi og oppfølging

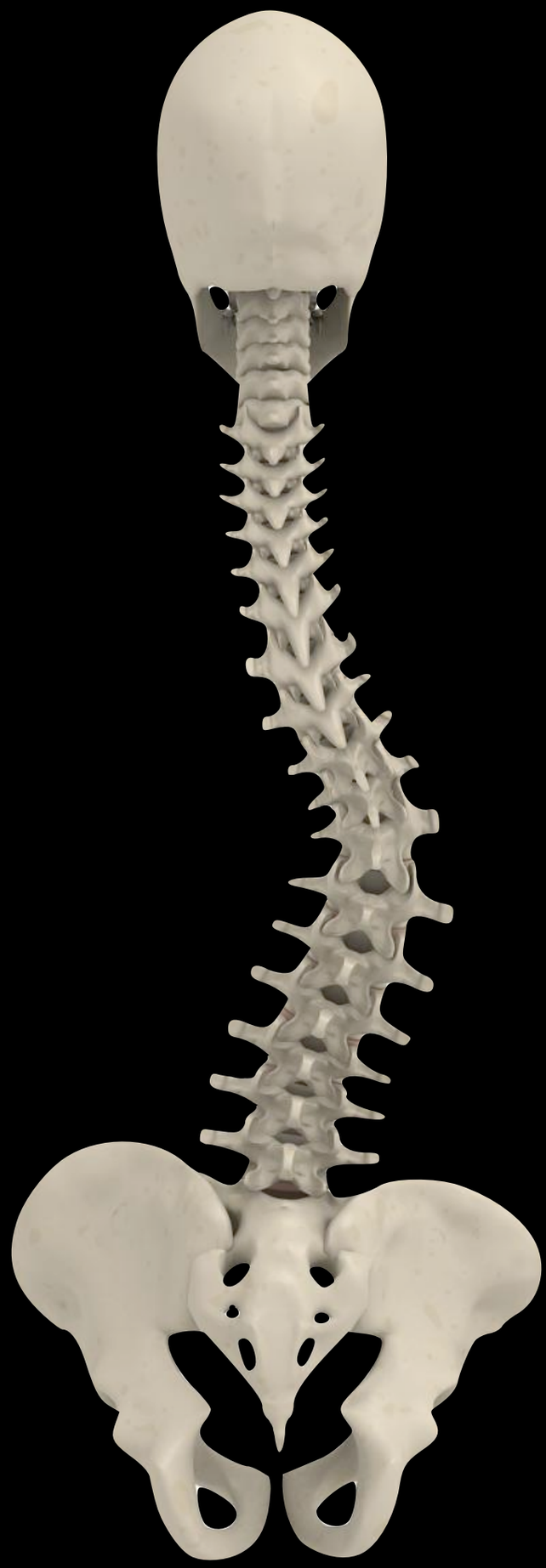
Kjetil Kivle

OUS Rikshospitalet

25.04.19

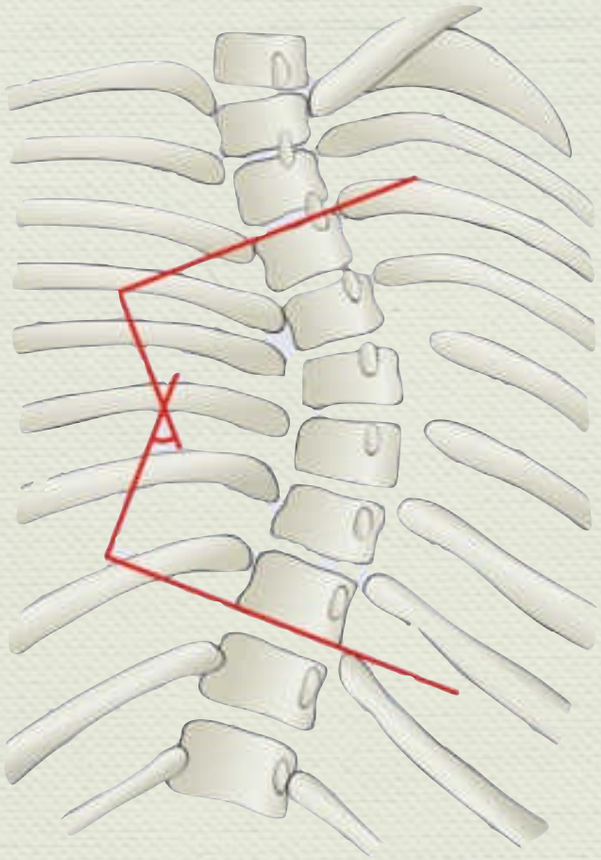
Skoliose

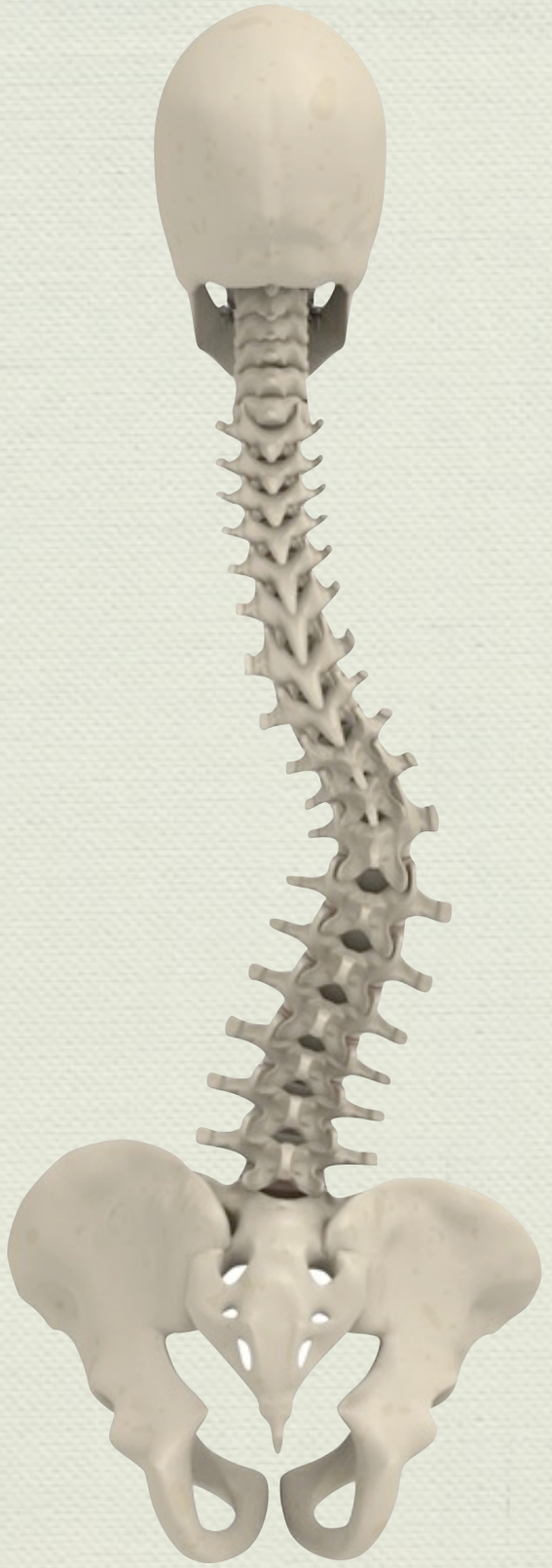




Hva er skoliose?

Sidelengs krumning i coronal planet > 10 º (Cobbs vinkel)





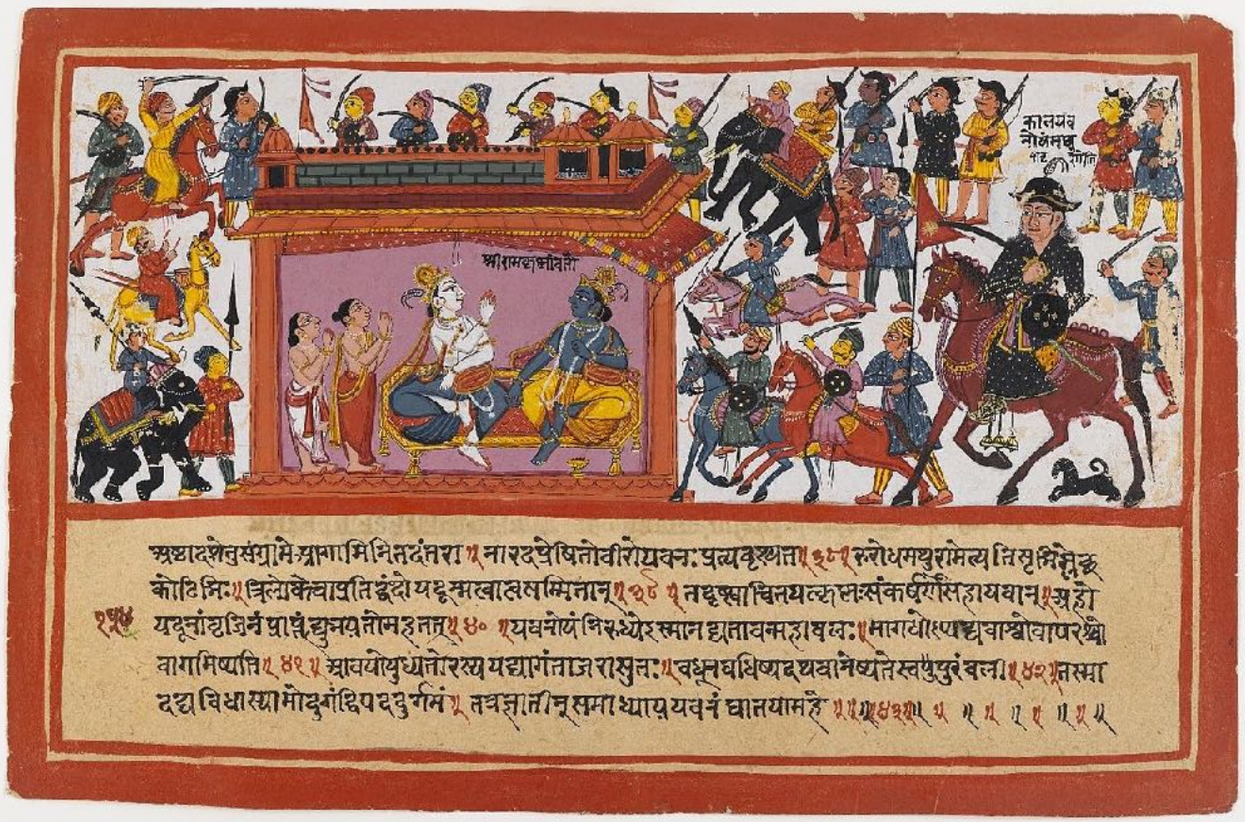
Skoliose (gresk)

σκολίωσις = krum / skjev

Srimad Bhagwad Mahapuranam

Hindu (3500-1800 f.Kr.)

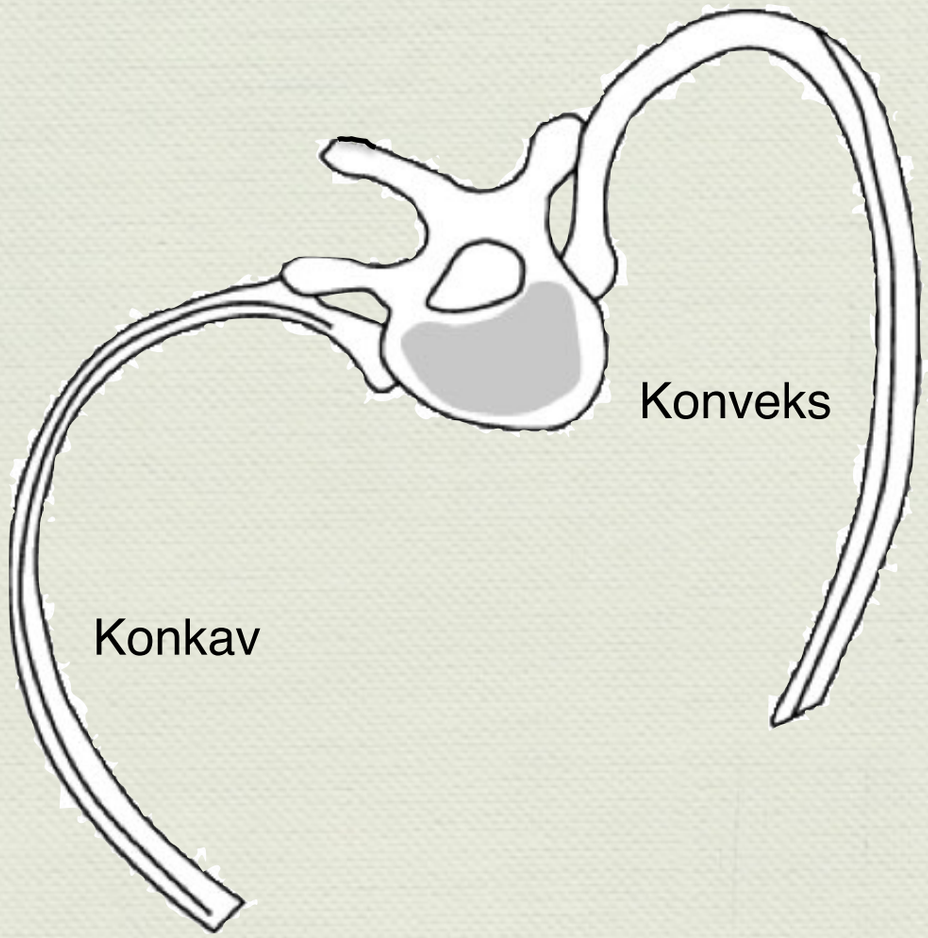
Første beskrivelse av spinal deformitet



Hva er skoliose?

Strukturell deformitet i 3D

Adam©

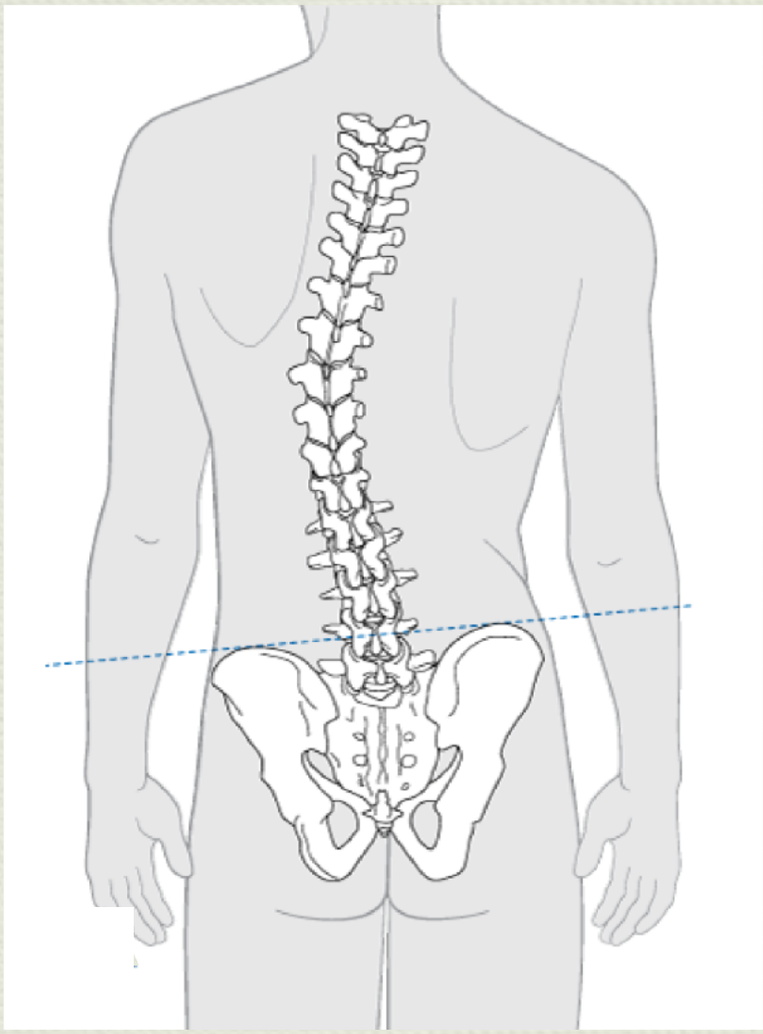


Rotasjon i transversalplan - gibbus

Hva er skoliose?

Bekkenskjevhet

Vialle©

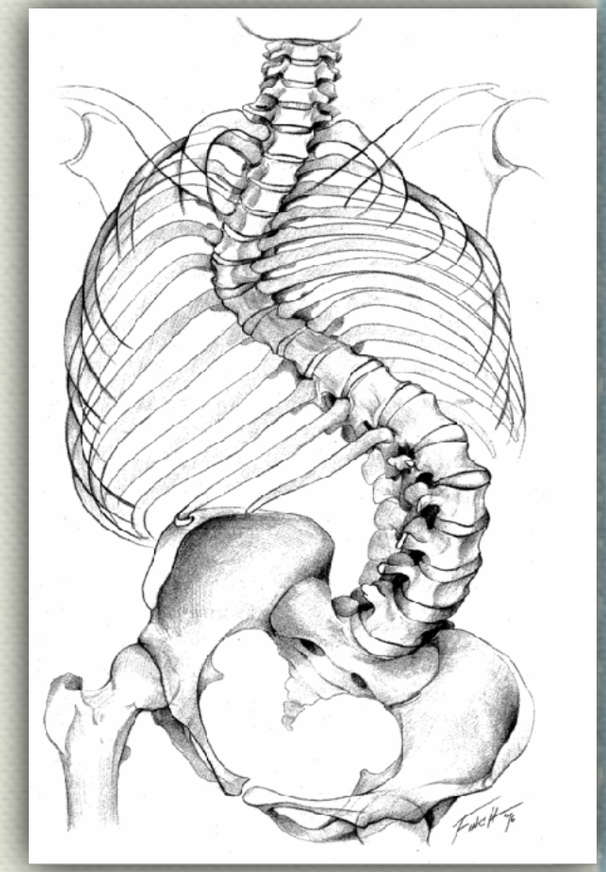


AO©

Inndeling skoliose

- Idiopatisk (ca 80%)
- Kongenitt (medfødt vertebra anomali)
- Nevromuskulær skoliose
- Syndrom skoliose

  Retts syndrom



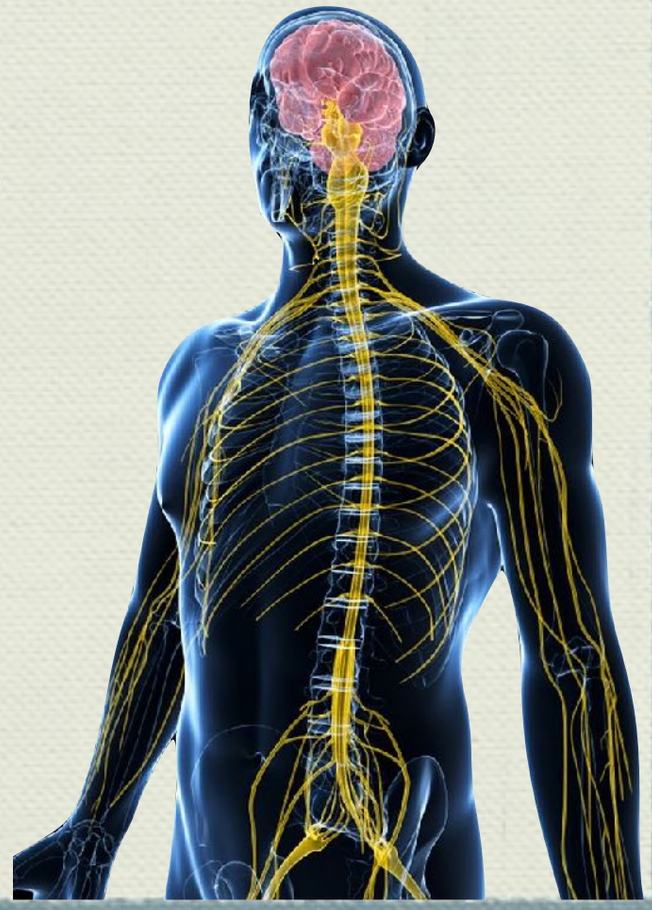
Bilder røntgen

vs

Bilder røntgen

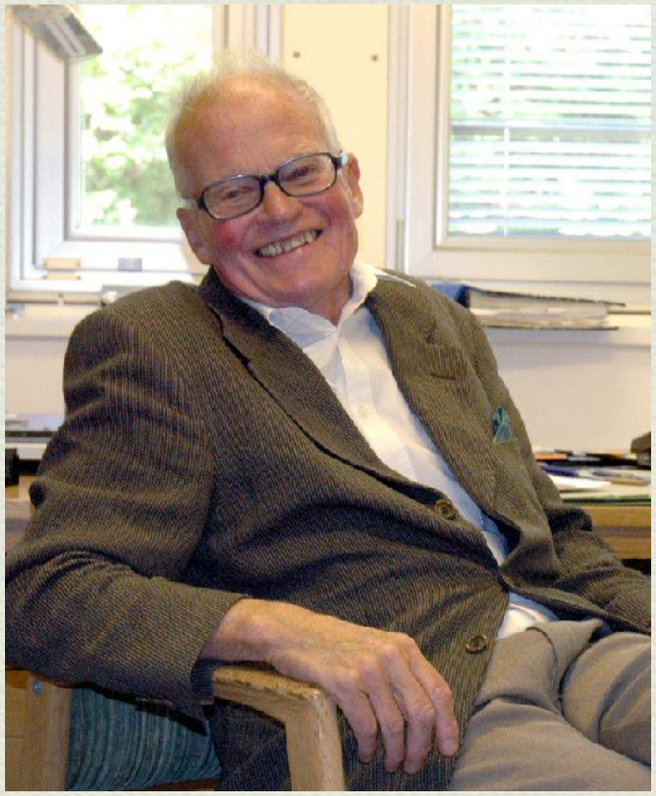
Fellestrekk ved nevromuskulære skolioser

- Kurvene øker etter vekstslutt
- Kurvene blir fort rigide (ikke alle)
- Lange kurver (C-kurver) hos ikke-gåere
- Bekken skjevhet

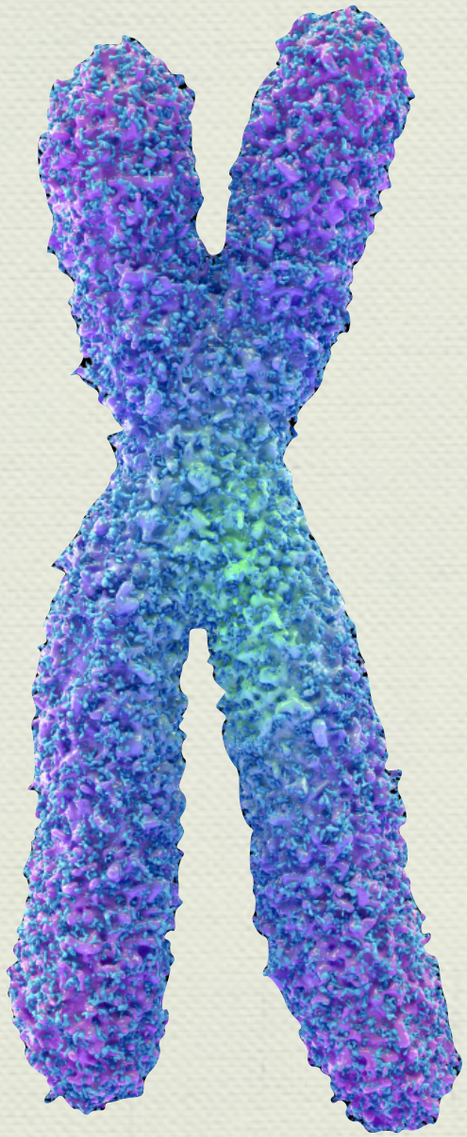


Skoliose ved Retts syndrom

Andreas Rett

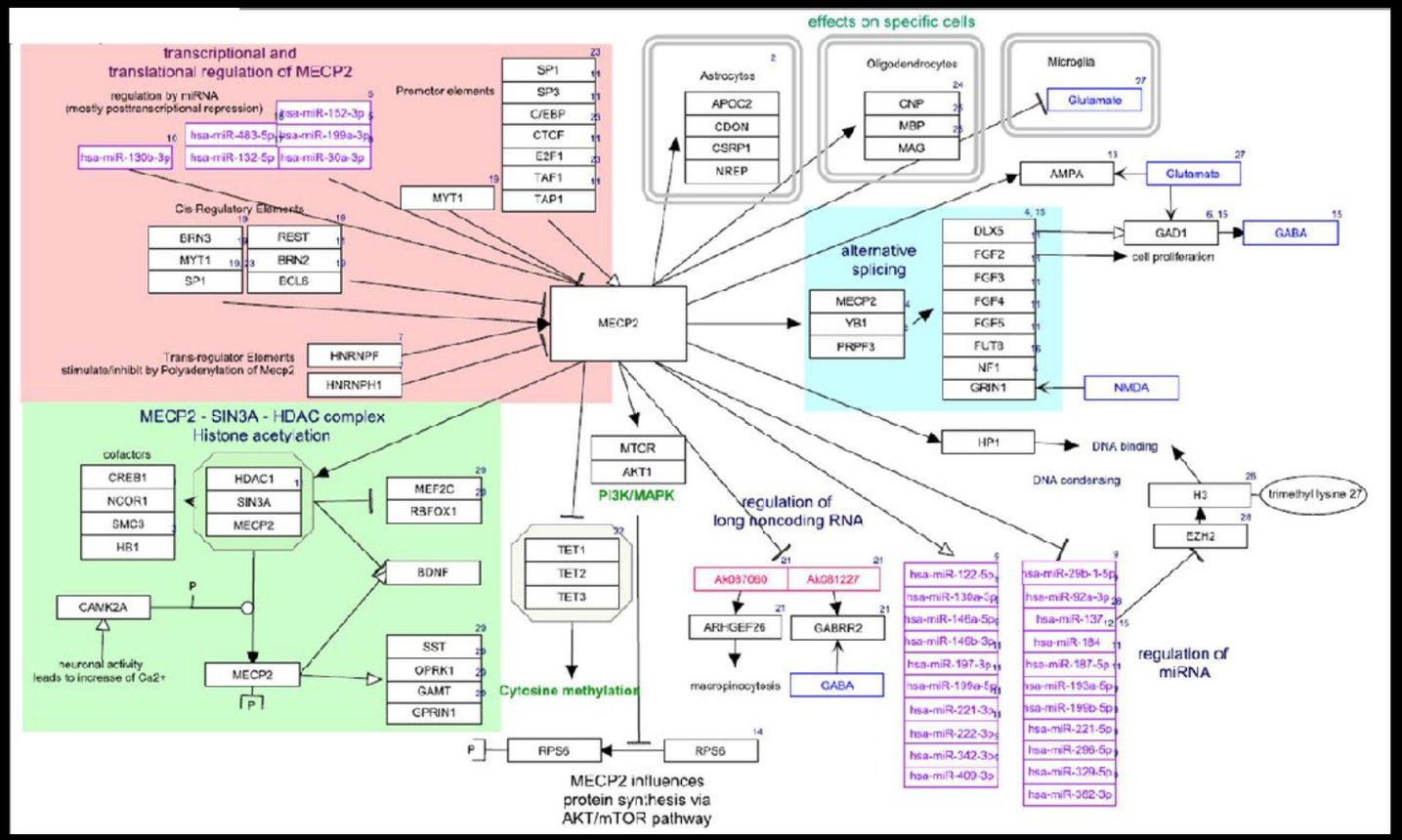


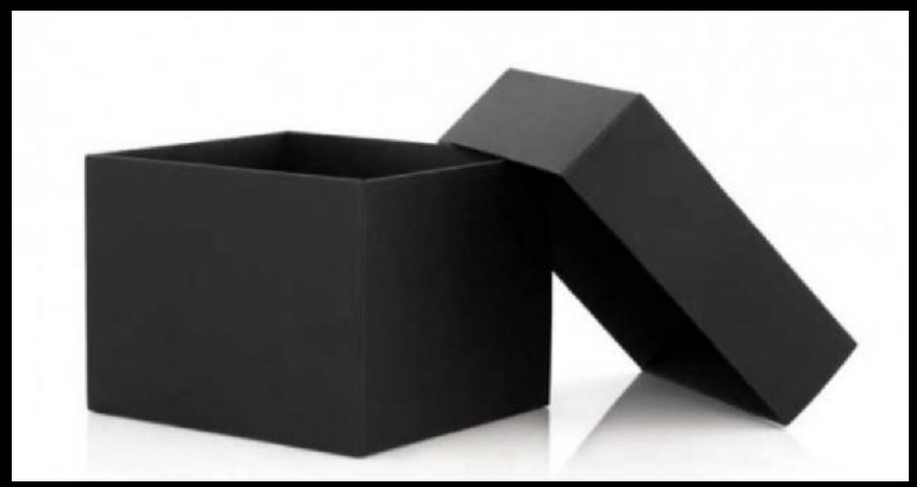
Bengt Hagberg



- X- kromosom
  - MECP2-gen => MeCP2 protein (kromatin)

    ⇑⇑ CNS - viktig for synapser og mRNA


effects on specific cells
transcriptional and translational regulation of MECP2
regulation by miRNA (mostly posttranscriptional repression)
hsa-miR-152-3p
hsa-miR-483-5p
hsa-miR-199a-3p
hsa-miR-130b-3p
hsa-miR-132-5p
hsa-miR-30a-3p
Promotor elements
SP1
SP3
C/EBP
CTCF
E2F1
TAF1
TAP1
MYT1
Cis Regulatory Elements
BRN3
REST
MYT1
BRN2
SP1
BCL6
Trans-regulator Elements
stimulate/inhibit by Polyadenylation of Mecp2
HNRNPF
HNRNPH1
MECP2
Astrocytes
APOC2
CDON
CSRP1
NREP
Oligodendrocytes
CNP
MBP
MAG
Microglia
Glutamate
AMPA
Glutamate
GAD1
GABA
cell proliferation
alternative splicing
MECP2
YB1
PRPF3
DLX5
FGF2
FGF3
FGF4
FGF5
FUT8
NF1
GRIN1
NMDA
HP1
DNA binding
DNA condensing
H3
trimethyl lysine 27
EZH2
MECP2 - SIN3A - HDAC complex
Histone acetyation
cofactors
CREB1
NCOR1
SMC3
HR1
HDAC1
SIN3A
MECP2
MEF2C
RBFOX1
BDNF
CAMK2A
P
neuronal activity leads to increase of Ca2+
MECP2
P
SST
OPRK1
GAMT
CPRIN1
MTOR
AKT1
PI3K/MAPK
TET1
TET2
TET3
Cytosine methylation
regulation of long noncoding RNA
AK097060
AK081227
ARHGEF26
GABRR2
macropinocytosis
GABA
hsa-miR-122-5p
hsa-miR-138a-3p
hsa-miR-146a-5p
hsa-miR-146b-3p
hsa-miR-197-3p
hsa-miR-199a-5p
hsa-miR-221-3p
hsa-miR-222-3p
hsa-miR-342-3p
hsa-miR-409-3p
hsa-miR-29b-1-5p
hsa-miR-92a-3p
hsa-miR-137
hsa-miR-184
hsa-miR-187-5p
hsa-miR-193a-5p
hsa-miR-199b-5p
hsa-miR-221-5p
hsa-miR-296-5p
hsa-miR-329-5p
hsa-miR-382-3p
regulation of miRNA
P
RPS6
RPS6
MECP2 influences protein synthesis via AKT/mTOR pathway



Skoliose ved Retts syndrom

Utvikling og kjennetegn

Spine
SPINE Volume 41, Number 10, pp 856–863

DEFORMITY

The Natural History of Scoliosis in Females With Rett Syndrome

Jennepher Downs, BApplSci(physio), MSc, PhD,* Ian Torode, FRCS, FRACS,† Kingsley Wong, MBBS, MPH,‡

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Scoliosis in Rett Syndrome: Progression, Comorbidities, and Predictors

John T. Killian MD [a], Jane B. Lane RN, BSN [a,b], Hye-Seung Lee PhD [c],

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Spinal deformity and disability in patients with Rett syndrome

ROLF RIISE[1] | JENS IVAR BROX[1] | ROGER SORENSEN[1] | OLA H SKJELDAL[2,3]

1 Department of Orthopedic Surgery, Oslo University Hospital, Rikshospitalet, Oslo. 2 Section of Neurology, Department of Pediatrics, Oslo University Hospital, Rikshospitalet, Oslo. 3 Department of Research, Innlandet Hospital Thrust, Brumunddal, Norway.

Correspondence to Dr Rolf Riise at Department of Orthopedic Surgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway. E-mail: rolf.riise@rikshospitalet.no

RESEARCH Open Access

Twenty years of surveillance in Rett syndrome: what does this tell us?

Alison Anderson[1], Kingsley Wong[1], Peter Jacoby[1], Jenny Downs[1,2] and Helen Leonard[1*]

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

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1 Department of Orthopedic Surgery, Oslo University Hospital, Rikshospitalet, Oslo. **2** Section of Neurology, Department of Pediatrics, Oslo University Hospital, Rikshospitalet, Oslo. **3** Department of Research, Innlandet Hospital Thrust, Brumunddal, Norway.

Correspondence to Dr Rolf Riise at Department of Orthopedic Surgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway. E-mail: rolf.riise@rikshospitalet.no

2011

n= 29 (Rikshospitalet)

- Gj. snitt i studie 14,5 år: 87% med skoliose (median 41°)

  $^1/_2$ (n=16) C-kurve (nevromuskulær)

  $^1/_3$ (n=9) Dobbeltkurve

- Dårlig funksjon (særlig gangfunksjon)

  => C-kurve

C-kurve

Dobbeltkurve

RESEARCH Open Access

Twenty years of surveillance in Rett syndrome: what does this tell us?

Alison Anderson[1], Kingsley Wong[1], Peter Jacoby[1], Jenny Downs[1,2] and Helen Leonard[1*]

2014

n= 423 (Australia, registerstudie) voksne >18 år

- 85% skoliose - 40% operert
- 60% hadde gangfunksjon m/u hjelpemiddel
- Betydelige komorbiditeter
- Overlevelse: 78% 20 år - 60% 37 år

Medical condition, n (%)	
Pneumonia	55 (17.2)
Urinary tract infection, pyelonephritis, bladder infection	48 (15.0)
Ear infection	36 (11.2)
Tonsillitis	23 (7.2)
Asthma	20 (6.2)
Bronchitis	19 (5.9)
Respiratory illness	13 (4.1)
Heel cord, foot surgery	12 (3.7)
Kidney stone	5 (1.6)
Insulin resistance	5 (1.6)
Polycystic ovaries/ovarian cyst	4 (1.3)

DEFORMITY

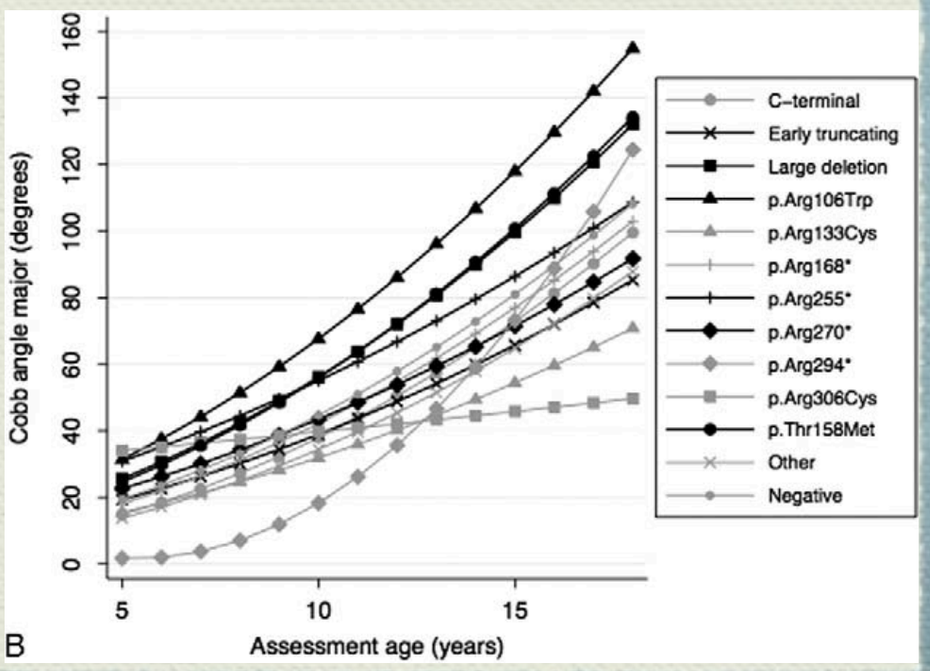
The Natural History of Scoliosis in Females With Rett Syndrome

Jennepher Downs, BApplSci(physio), MSc, PhD,* Ian Torode, FRCS, FRACS,† Kingsley Wong, MBBS, MPH,‡

2016

n= 394 (Australia - registerstudie)

- Gj. snitt debut skoliose 11 år
  75% av alle ved 15-års alder
- Alvorligst utvikling uten gangfunksjon
- Ulike mutasjoner
  => ulik utvikling skoliose



DEFORMITY

The Natural History of Scoliosis in Females With Rett Syndrome

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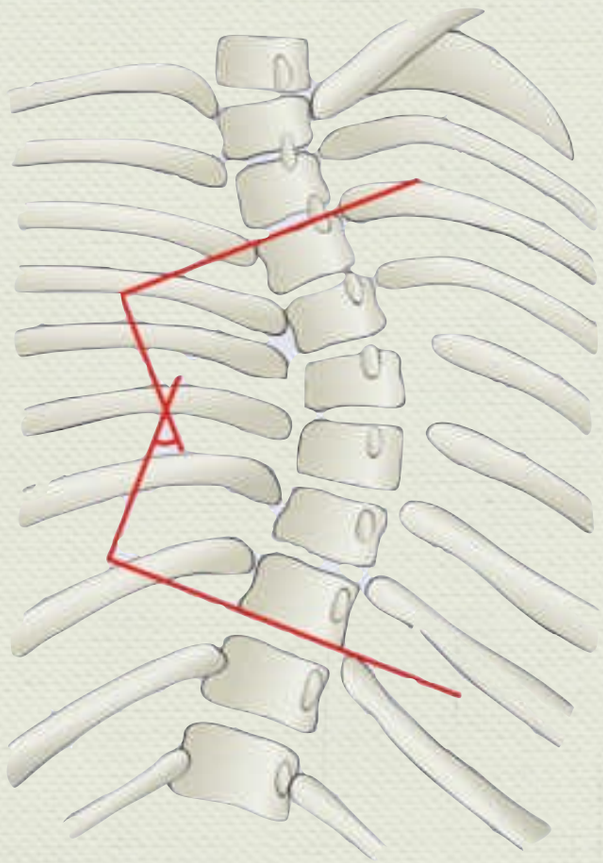
2016

n= 394 (Australia - registerstudie)

- Ved 10 år sannsynlighet for skoliose > 60º:
  - Gangfunkjson og Cobb∠ < 25º **13** %
  - Ikke gangfunkjson og Cobb∠ > 25º **99** %



Pediatric Neurology

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Original Article

Scoliosis in Rett Syndrome: Progression, Comorbidities, and Predictors

John T. Killian MD [a], Jane B. Lane RN, BSN [a,b], Hye-Seung Lee PhD [c],

2017

n= 913 (USA - registerstudie)

- Mer alvorlig sykdom (⇑CSS)=> ⇑⇑ risiko skoliose (p<0,001)
- Andel med alvorlig skoliose (>40°):
  - 13% ved 9 år
  - 38% ved 12 år

    =>70% operert
- Av skolioseopererte: 86% ble operert ved alder 9-15 år

Påvirker skoliosen pasientens liv?

- < 50º - vanligvis lite
- > 50º - kan påvirke:
  - Ståbalanse / gangfunkjson
  - Sittebalanse

  Ved stor bekkenskjevhet
  - Hindre gangfunksjonen
  - Hindre selvstendig sitteevne

- >70-90º - kan påvirke hjerte- og lungefunksjon

Behandlingmuligheter ved skoliose

Konservativ behandling

- Korsett har ingen klar dokumentert effekt ved Retts syndrom

- Bør vurderes ved kurve 20-45º < 10 år

- Ofte vanskelig å gjennomføre > 10 år grunnet
  ⇓ compliance og økende dystoni/spastisitet

- Fysioterapi for å opprettholde gang-/ståfunksjon

Konservativ behandling
Korsett / skall

- Stabilisere rygg og bekken -
  sitte uten å bruke hendene til å støtte
- Mindre smerter?
- Korsett brukes i stående og sittende stilling (ikke natt)
- Kan være livslang behandling

Kirurg - Mål

- Stabilisere rygg og deformitet
- Bedre sittebalanse
- Bedre forholdene for pårørende/støtteapparat
- Forenkle hygiene
- Redusere smerte?
- Bedre lungefunksjon?
- Redusere sannsynlighet trykksår?

Kirurgi

SPINE Volume 34, Number 17, pp E607–E617
©2009, Lippincott Williams & Wilkins

Guidelines for Management of Scoliosis in Rett Syndrome Patients Based on Expert Consensus and Clinical Evidence

Jenny Downs, PhD,*‡‡ Anke Bergman, MPH,* Philippa Carter, MBBS,* Alison Anderson, BSc,* Greta M. Palmer, FANZCA,† David Roye, MD,‡ Harold van Bosse, MD,§ Ami Bebbington, BSc,* Eva Lena Larsson, OTR, PhD,¶ Brian G. Smith, MD,‖ Gordon Baikie, MD,** Sue Fyfe, PhD,†† and Helen Leonard, MBChB*

- Kirurgi ved kurve 40 - 50º
- Kirurgi helst > 10 år, men ikke vente på utvokst
- Fortrinnsvis bakre fiksasjon og fusjon
- Fikasjson til bekkenet ved bekkenskjevhet hos ikke-gåere

Table 5. Final Guidelines Endorsed by the Expert Panel for the Management of Scoliosis in Rett Syndrome

Monitoring and intervention before diagnosis of scoliosis

All children with a clinical diagnosis of Rett syndrome should undergo genetic testing as genotype may influence the development and management of scoliosis

Because of the high prevalence of scoliosis in Rett syndrome, families should be given information about this early in the child's clinical course

Physical assessment of the spine should be conducted at the time of diagnosis of Rett syndrome and at least every 6 mo thereafter

Therapy should aim to:

- Develop, maintain, and promote walking for as long as possible
- Optimize strength of back extensors
- Maintain flexibility of the spine
- Implement a postural management scheme that includes appropriate support for correct sitting posture and sleeping posture supports

Monitoring after a diagnosis of scoliosis

- Referral should be made to an orthopedic surgeon when there is clinical concern regarding scoliosis
- Physical examination of the spine should be conducted at least every 6 mo, but the frequency of assessment should be increased in the following situations:
  - Abnormal early development/never learning to walk
  - Low muscle tone
  - During growth spurts
  - Early age of onset
  - Greater Cobb angle
  - Children with genotypes known to be at higher risk of more severe scoliosis (p.R168X, p.R255, p.R270X)
- Physical assessment in Rett syndrome should include:
  - Sitting balance and symmetry of weight bearing in sitting
  - Level of walking ability and time spent walking
  - Total distance walked
- At each visit, height and weight should be measured

Imaging

- Request an initial x-ray if there is evidence of a curve
- It is preferable to assess skeletal maturity with a hand and wrist radiograph but assessment of the iliac crest growth plate is also an option
- Six monthly x-rays are suggested if the Cobb angle is more than 25° before skeletal maturity and 12 monthly x-rays after skeletal maturity until evidence of no further progression
- Plain radiography is sufficient in monitoring the progression of the curve. The following views should be obtained and should include shoulder to pelvis:
  - Standing upright AP and lateral spinal radiographs for patients who can stand at their initial visit
  - Sitting AP and lateral spinal radiographs for patients who cannot stand
  - Supine AP and lateral spinal radiographs for patients who cannot sit
- AP films alone may be used in follow-up x-rays

Therapy and conservative management

- Involve physiotherapists and occupational therapists as soon as scoliosis has been diagnosed
- Physiotherapy should be used to maintain musculoskeletal well-being in children with Rett syndrome and scoliosis. There is not yet evidence that physiotherapy will prevent progression of an established scoliosis
- Aim to prolong ambulation as long as possible. Aim to increase the distance that the child can walk and/or the length of time the child can stay on their feet (at least 2 hr per d where possible)
- For those who cannot walk, use standing frames for at least 30 min a d
- Aim to maintain range of movement of joints
- Symmetrical seating is valuable for the child's comfort and functioning
- Assess, monitor, and optimize Vitamin D levels. Improve dietary intake of calcium and time spent in daylight to promote bone health
- In severe scoliosis where surgery is not indicated, the management plan should include:
  - The provision of supported seating to optimize posture
  - Monitoring and treatment of pressure sores
  - A low threshold for antibiotic use during respiratory infections to minimize the effects of restrictive lung disease

Spinal bracing

- There is no consensus that bracing is beneficial in reducing the progression of scoliosis in Rett syndrome but it may used if seating and trunk activation cannot be achieved
- If tolerated, bracing should be used in the skeletally immature child, to help delay surgery
- The following potential complications of bracing must be considered: pressure sores, respiratory impairment, discomfort, skin irritation, exacerbation of gastroesophageal reflux, and the potential to decrease trunk strength, flexibility, and physical activity

Preoperative considerations

- Surgery should be performed in a specialist center due to the high risk of anesthetic and postsurgical complications
- Surgery should not be delayed until skeletal maturity has been achieved, however, caution should be used before performing surgery in children younger than 10 yr of age due to the following problems: decreased trunk height, pulmonary restriction, "crankshaft," and secondary curvatures
- Surgery should be considered when the Cobb angle is approximately 40°–50°
- Surgical objectives should include:
  - Achieving a spine that is balanced and fused
  - Restoration of the normal sagittal profile
  - Achieving level shoulders and hips
  - Improving the well-being and functioning of the child
  - Improving carer well-being
- There should be a period of hyperalimentation if weight is less than the 5th centile
- The following markers of nutrition should be assessed: BMI, hemoglobin, electrolytes, albumin (<3.5 mg/dL), white cell count
- Patients with Rett syndrome need special anesthetic consideration in line with other neuromuscular disorders. They are highly sensitive to analgesia, sedatives, and volatile anesthetic agents

(*Continued*)

- In addition to the preoperative assessment used in all scoliosis surgery, the following must be considered before anaesthetizing a child with Rett syndrome:
  - Breathing patterns (hyperventilation, breath holding)
  - Preoperative arterial blood gases/capillary gases
  - Gastroesophageal Reflux
  - Autonomic disturbance
  - Seizure history, management, and medications
  - Preoperative ECG to identify possible prolonged QT syndrome

Surgical considerations

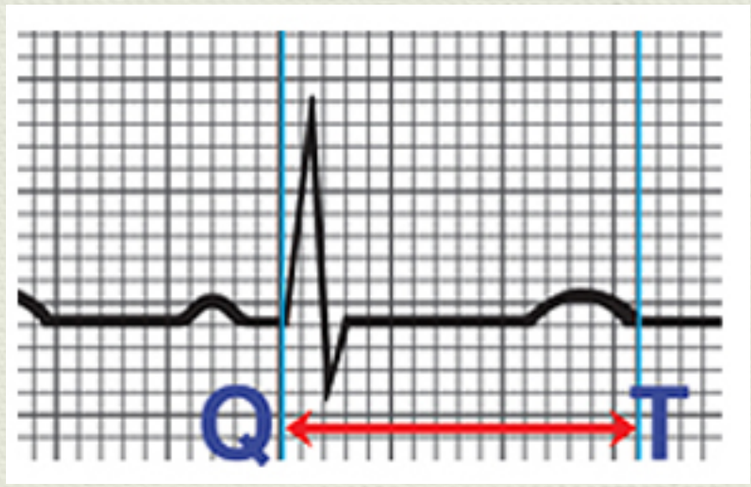
- In the majority of cases it will be possible to use a posterior-only spinal fusion. This is the definitive management of neuromuscular scoliosis in girls with Rett syndrome
- If anteroposterior surgery must be used, a single-stage approach is preferable to reduce anesthetic and surgical complications but a staged procedure may be appropriate in the presence of significant co-morbidities
- Fixation to the pelvis is indicated if pelvic obliquity exists in the nonambulant child. There is no consensus about the degree of obliquity that indicates fixation
- If a reliable signal can be obtained, motor-evoked potentials and/or somatosensory-evoked potentials can be used to detect neurological injury during neuromuscular scoliosis surgery

Postoperative considerations

- Admit to HDU/ICU postoperatively
- Care needs to be taken with regards the titration of analgesia so that pain relief is adequate and sedation is minimized to ensure respiratory effort is not compromised. Postoperative analgesia must be closely monitored by a specialist pediatric pain team with 24-hr cover or intensive care specialists
- Frequent and aggressive chest physiotherapy should be used. Non-invasive positive airway pressure support may be required postextubation (*e.g.*, BIPAP)
- A clear management plan should be constructed when the patent is transferred back to the ward
- Seek expert advice to optimize nutritional status
- Consult parents or caregivers to help assess the child postoperatively
- Mobility postoperatively:
  - Log roll for bed mobility
  - Sitting on edge of bed day one postoperative
  - Transfer to chair postoperative day 2
  - Walking (if possible) postoperative day 3
- Postoperative reviews should be carried out at:
  - 6 wk
  - Then every 2–3 mo over the first yr
  - Annually thereafter
- The following should be used to assess surgical outcome: complications including bleeding, infection and duration of ICU stay; Cobb angle and achievement of fusion; respiratory status; sitting balance, function and quality of life; parent and carer satisfaction

Kirurgi ved Rikshospitalet

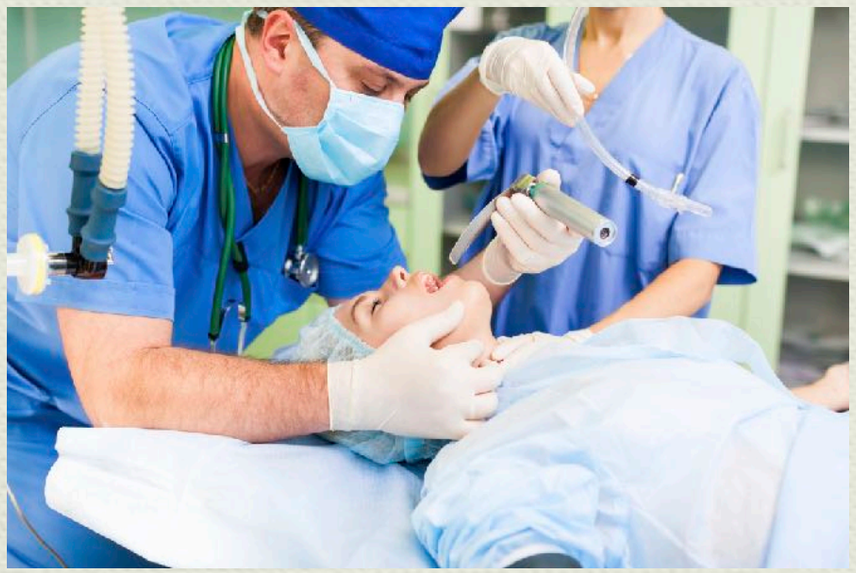
- Preoperativt med pediater/barnenevrolog:
  - Optimalisere epilepsibehandling
  - Reflux
  - EKG - forlenget QT?
  - Vurdering pustemønster
  - Risiko aspirasjon/luftveisproblematikk



Kirurgi ved Rikshospitalet

- Tett samarbeid med anestesileger
- Særlige tiltak for redusere risiko for aspirasjon/

luftveisproblemer - intubert første døgn



orphanaesthesia

Anaesthesia recommendations for patients suffering from

Rett syndrome

Anaesthesiologic procedure

- Inhalational and intravenous anaesthetic agents are generally considered to have potent anticonvulsant properties. Many of these agents, including the barbiturates, propofol, and the volatile agents, have been used successfully.

- As the residual effects of anaesthetic agents may impact on both upper airway control and postoperative respiratory function, whenever feasible, short-acting agents whose effects dissipate rapidly, such as remifentanil, should be considered.

- Use of thiopental and succinylcholine, prokinetics such as cisapride, antipsychotics such as thioridazine, tricyclic antidepressants such as imipramine, antiarrhythmics such as kinidin, amiodarone, sotalol as well as erythromycin and ketaconazole should be avoided because of the potential to provoke QT abnormalities and cardiac arrhythmias.

- These patients are excessively sensitive to sedative drugs, and delayed recovery from anaesthesia has been reported. Hence, the drugs should be titrated to maintain an optimal depth of anaesthesia and avoid overdose. Spontaneous ventilation rather than controlled ventilation is preferred, as this would require administration of less anaesthetic agents.

- Additionally, anatomical malposition of the vessels may occur in these patients. The use of ultrasound guidance may be invaluable to aid in gaining adequate vascular access for major surgical procedures [12].

ASC - all screw construct

Bilder røntgen

Bilder operasjon

Bilder røntgen

Bilder røntgen

Bilder røntgen

Bilder røntgen

Resultater etter kirurgi

Eur Spine J (2014) 23 (Suppl 1):S72–S75
DOI 10.1007/s00586-014-3170-9

ORIGINAL ARTICLE

Surgical correction of scoliosis in Rett syndrome: cord monitoring and complications

T. Hammett · A. Harris · B. Boreham · S. M. H. Mehdian

2014
n=11 (UK, retrospektiv)

- Skoliose redusert 71° -> 21°

- 8 av 11 fikk ≥ 1 komplikasjon
  Pneumoni hyppigst
  Ingen nevrologiske

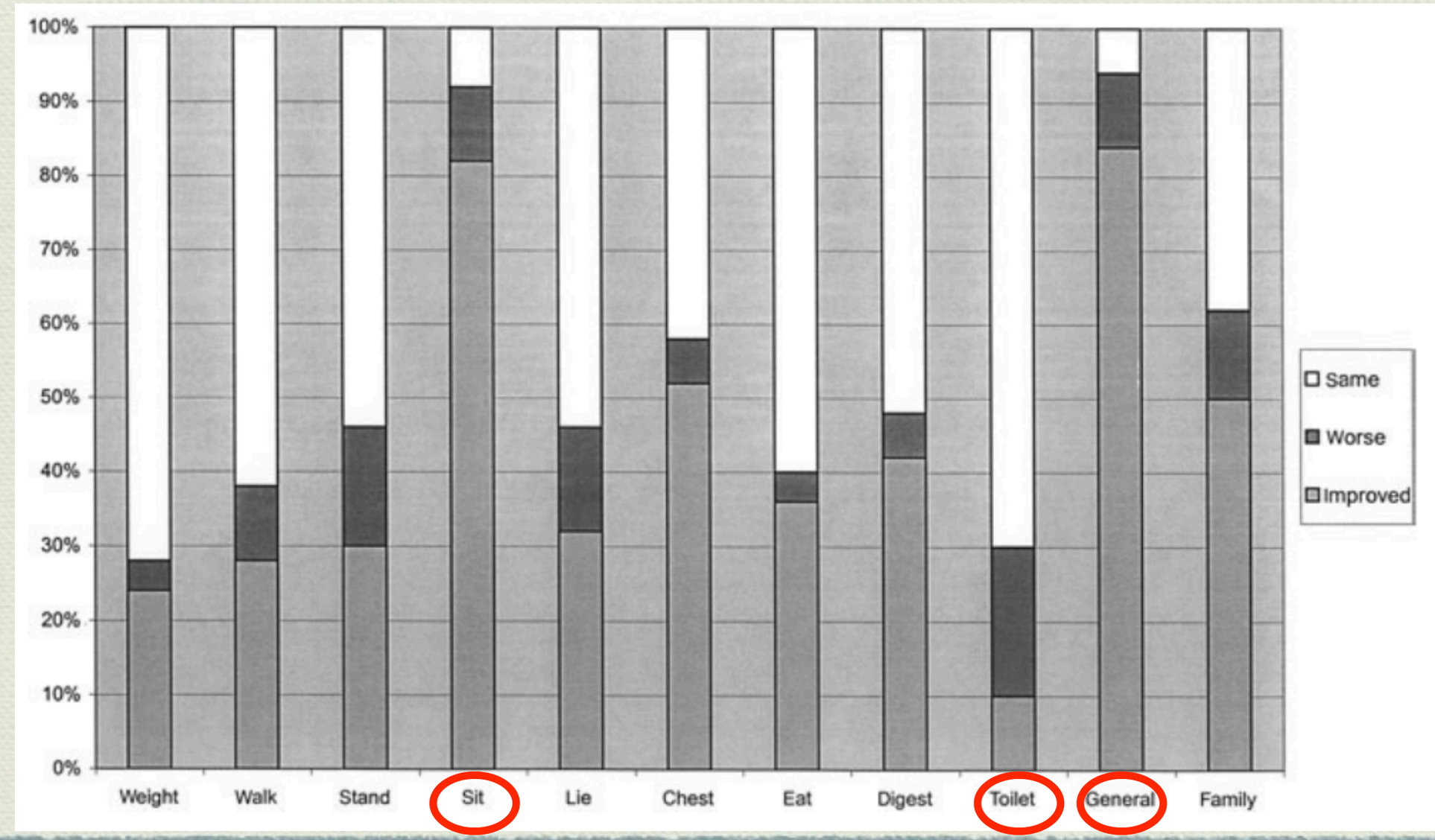
Resultater etter kirurgi

Special Article

Results of Surgery for Scoliosis in Rett Syndrome

Alison M. Kerr, FRCP; Peter Webb, FRCS; Robin J. Prescott, PhD; Yvonne Milne, BSc, MBE

2003
n=50 (UK)

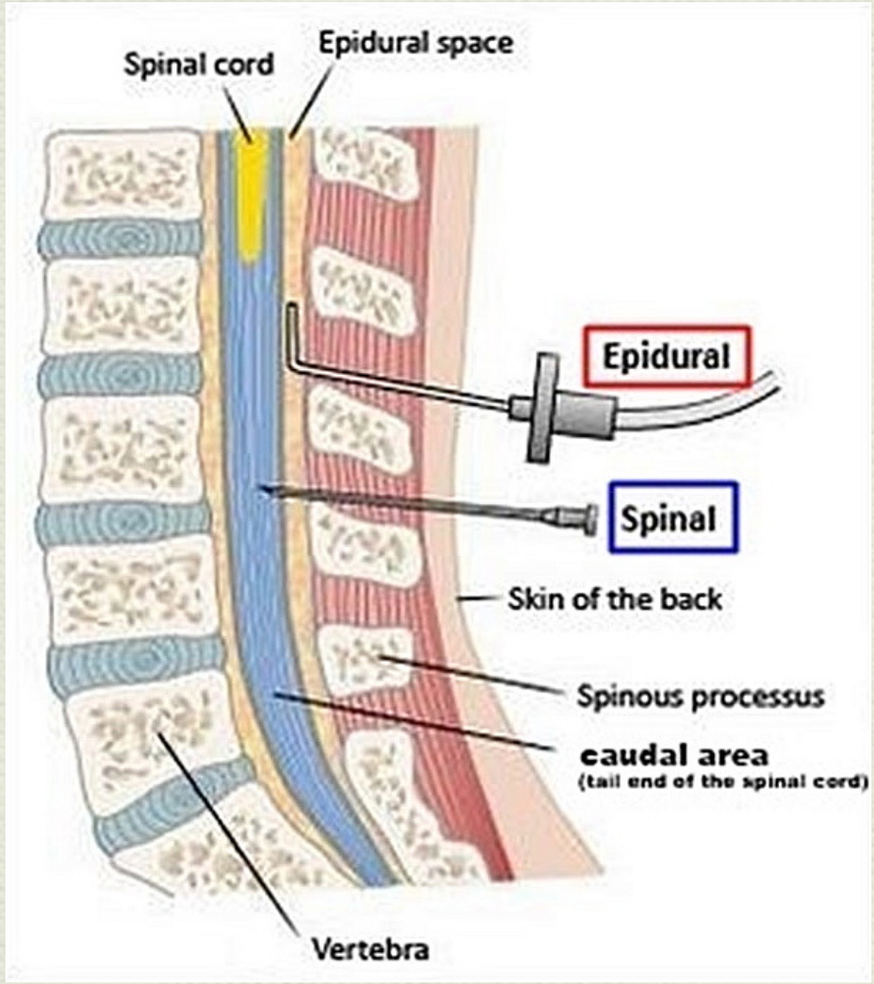


Postoperativt regime - RH

Vanligvis intensivavdeling første døgn (luftveier)

Andre døgn på intermediærpost

Multimodal smertebehandling
- Morfin spinalt - preoperativt
- Epdiural - trappes gradvis ned
- Opiater (per oral/PEG)
- NSAID
- Paracetamol



Mobiliseres fra første postoperative døgn

Oppfølging etter kirurgi - RH

Standard polikliniske
kontroller ved
3, 6, 12 og 24 måneder med
røntgen-kontroll.

Kontroller utover dette ved
behov.

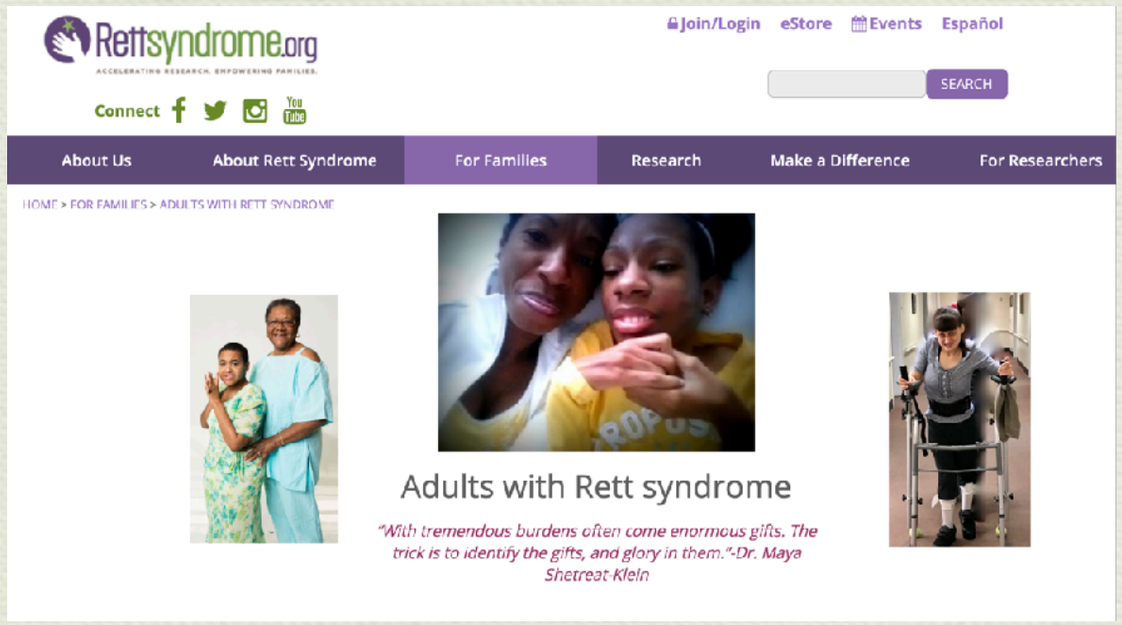
Fysioterapi for å sikre
mobilisering

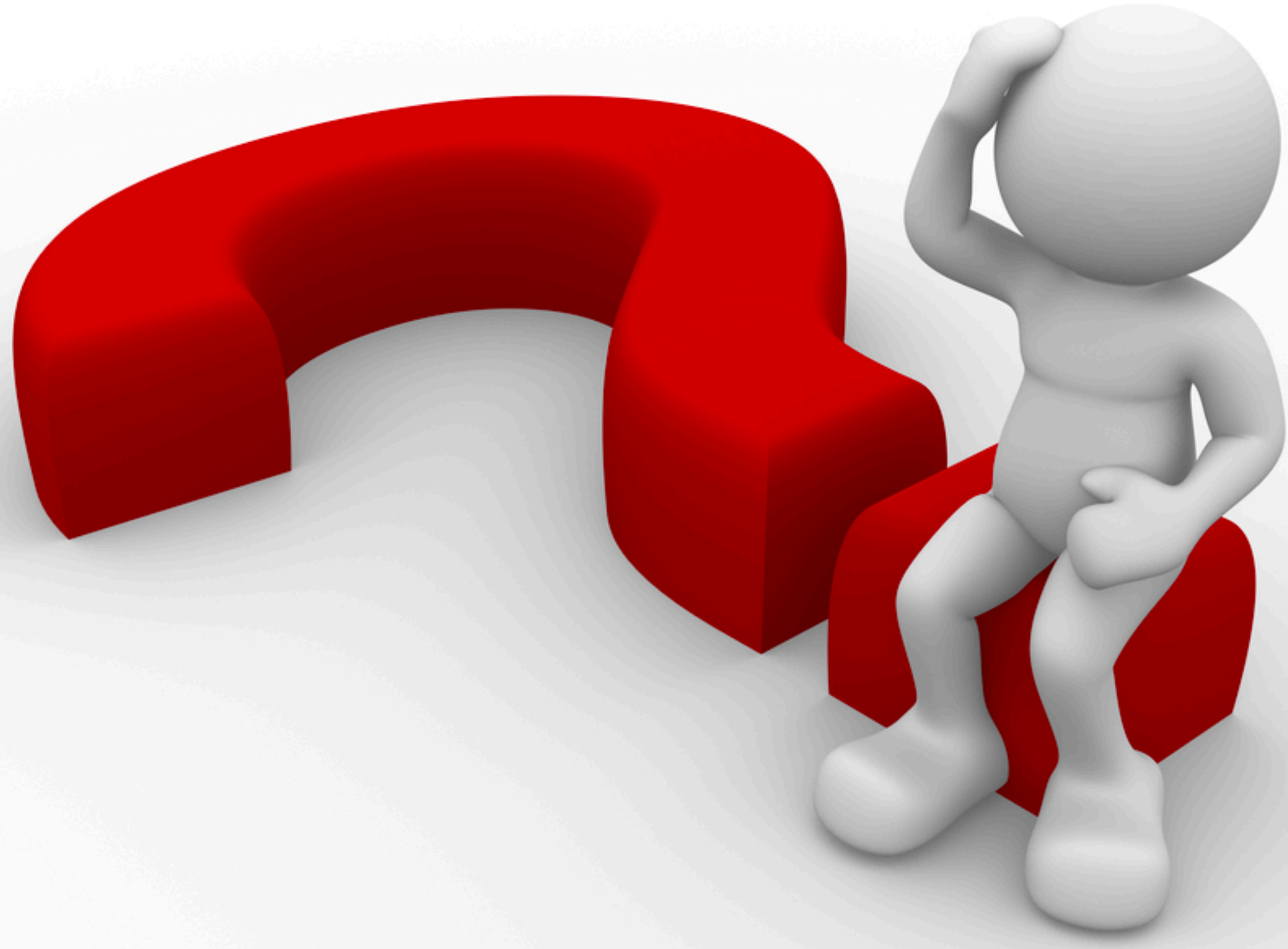
Oppfølging av opererte pasienter

Oppfølging i samarbeid med habiliteringen

Kontroll av ryggkirurg ved behov (økende skjevhet, smerter, tegn på infeksjon)

Redusert sjanse for implantatsvikt > 2 år, men forutsetter tilheling (fusjon)





Takk