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ACHONDROPLASIA
HYPOCHONDROPLASIA

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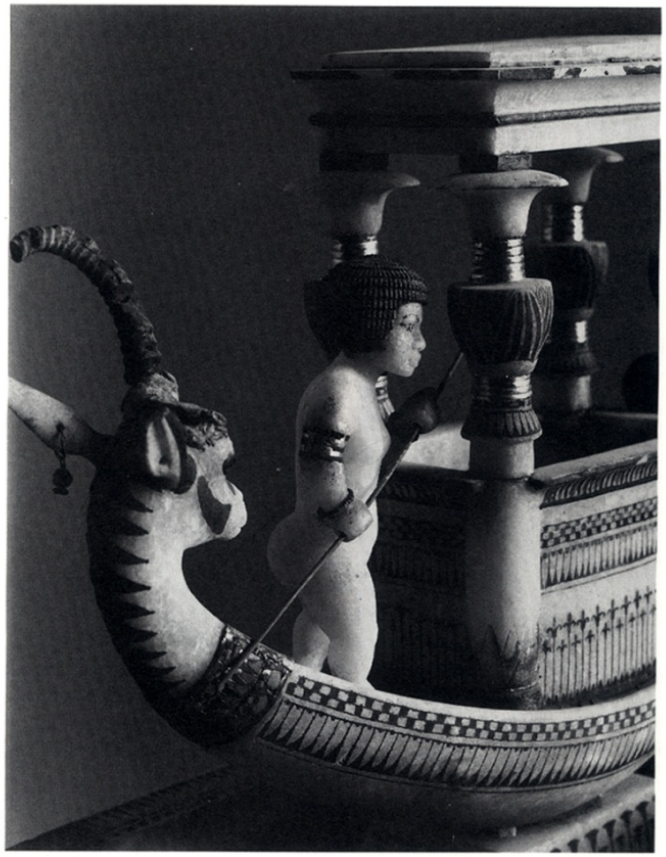
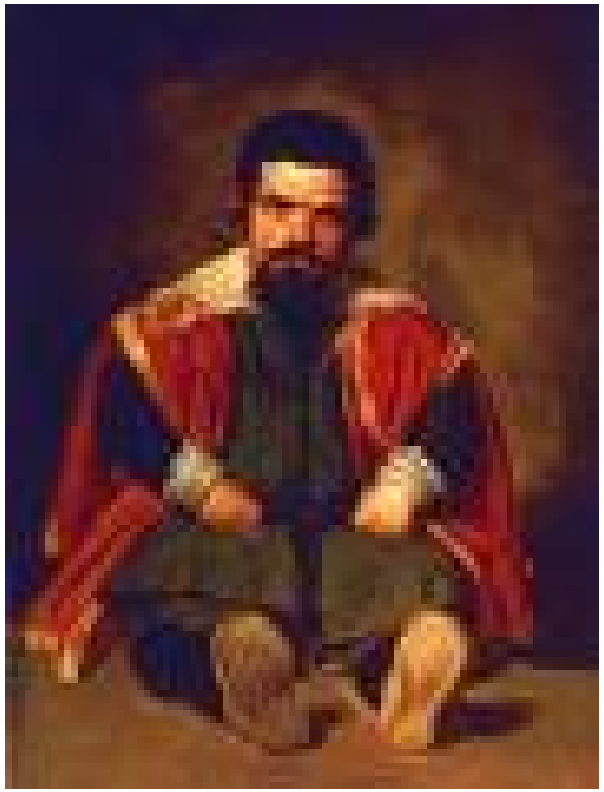
Groupe Hospitalier Armand Trousseau La Roche-Guyon

Jules PARROT, 1851: « achondroplasia »
Pierre MARY, 1900: description





Frequency

- The most common non-lethal chondrodysplasia
- Incidence 1/10 000 and 1/30 000 births
- Earlier frequent diagnostic confusions before *FGFR3* gene identification & overestimation
- 250 000 little people with achondroplasia all over the world
- No racial predisposition
- Influence of the prenatal diagnosis and paternal age increasing de-novo gene mutation unknown to date

Differential Diagnostic

- Short stature + micromelia + short hands + narrow thorax
  - Ellis Van Crefeld
  - Métatropique
  - Diastrophique
  - Jeune
  - Pseudoachondroplasia
  - Spondylo-epi(meta)physeal dysplasia
  - (Hypochondroplasia)

Antenatal diagnosis

- Third trimester (>23 weeks)
- Abnormal ultrasounds findings
  - Foreshortening of the limbs (<3P)
  - Increased biparietal diameter (>95P)
  - Low nasal bridge
- 3D CT scan (>28 weeks)
- (Possibility of *FGFR3* / amniotic sample)

– shortened long bones

– wide metaphyses

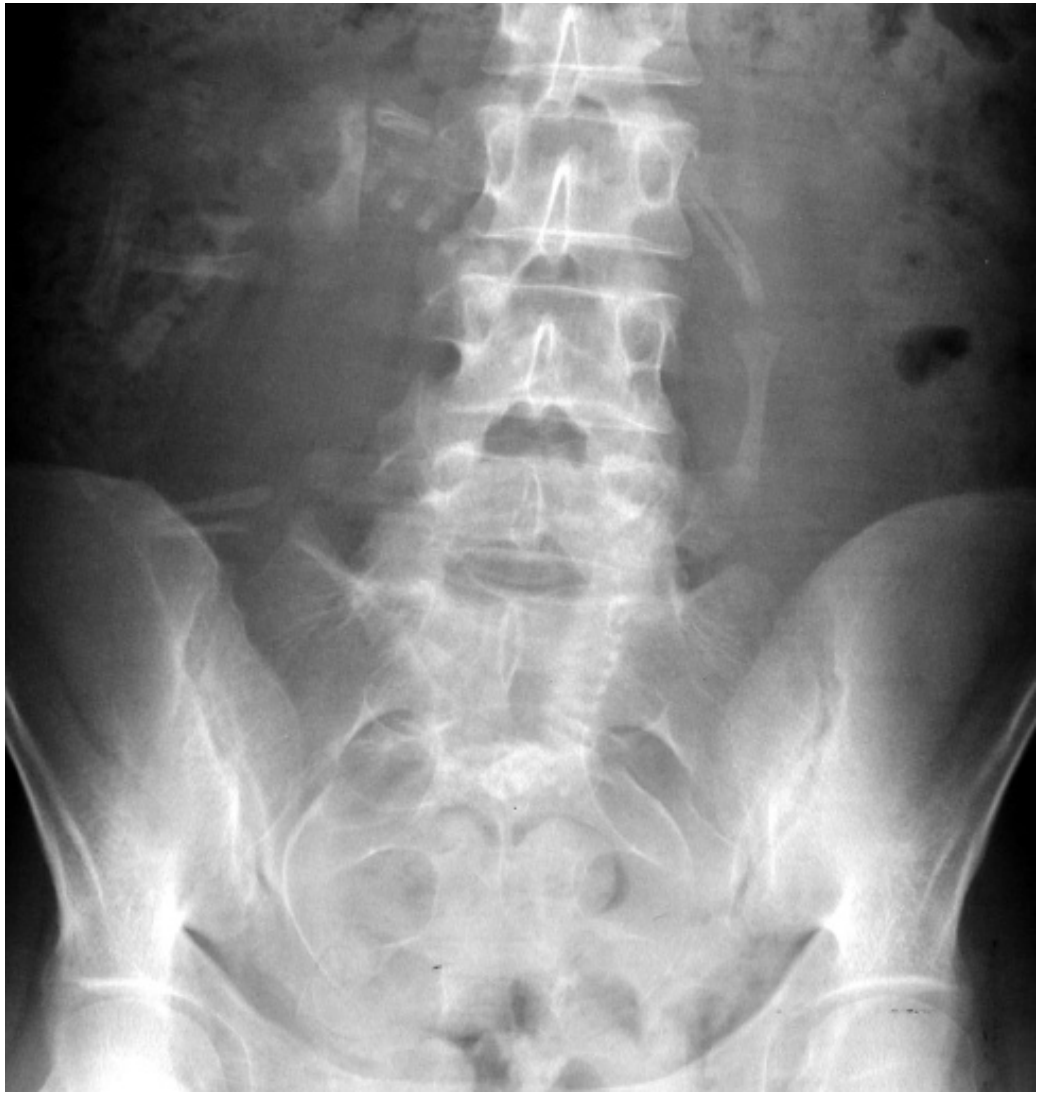
– slim and radiolucent proximal femur

– horizontal acetabular roof

– slightly flat vertebral bodies

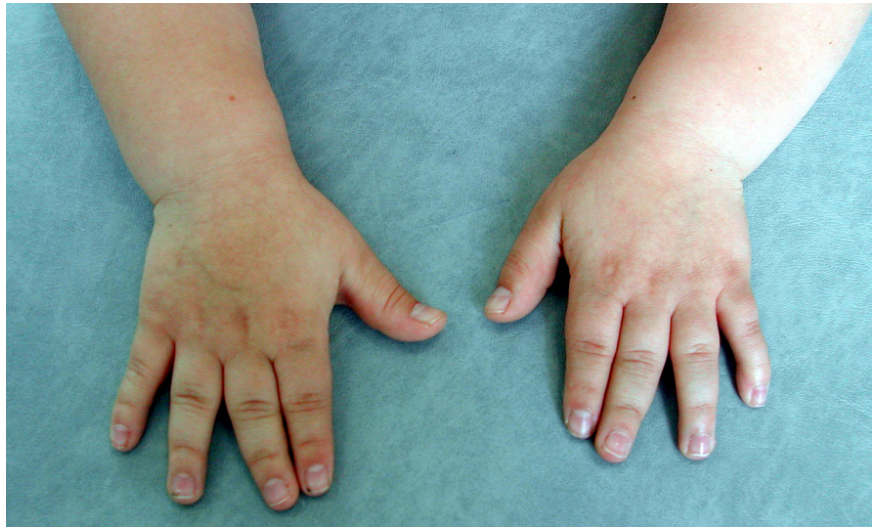
– medial spur from the anterior face

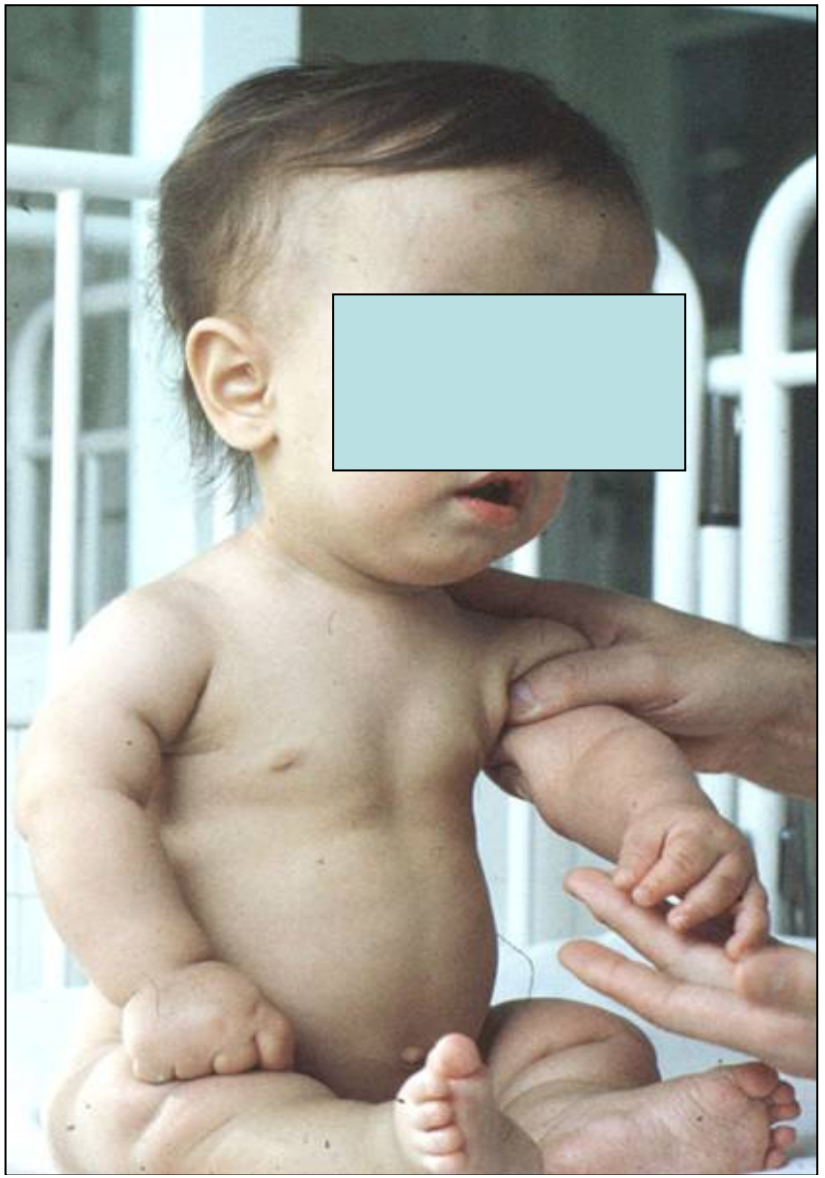
– round and square ilia



Achondroplasia is a clinical and radiological disease

- Post natal short stature
- Short limbs (proximal segment)
- long trunk, narrow thorax
- large head, frontal bossing
- Midface hypoplasia
- Short hands and fingers (trident)

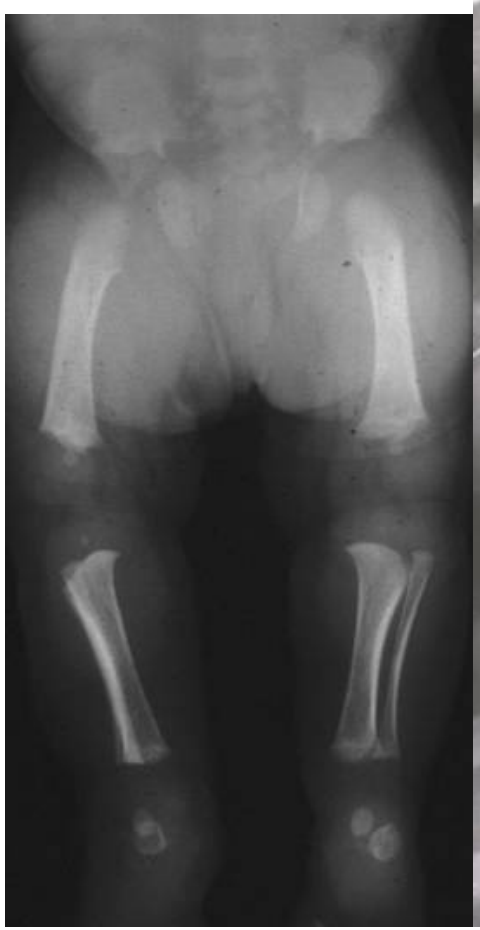


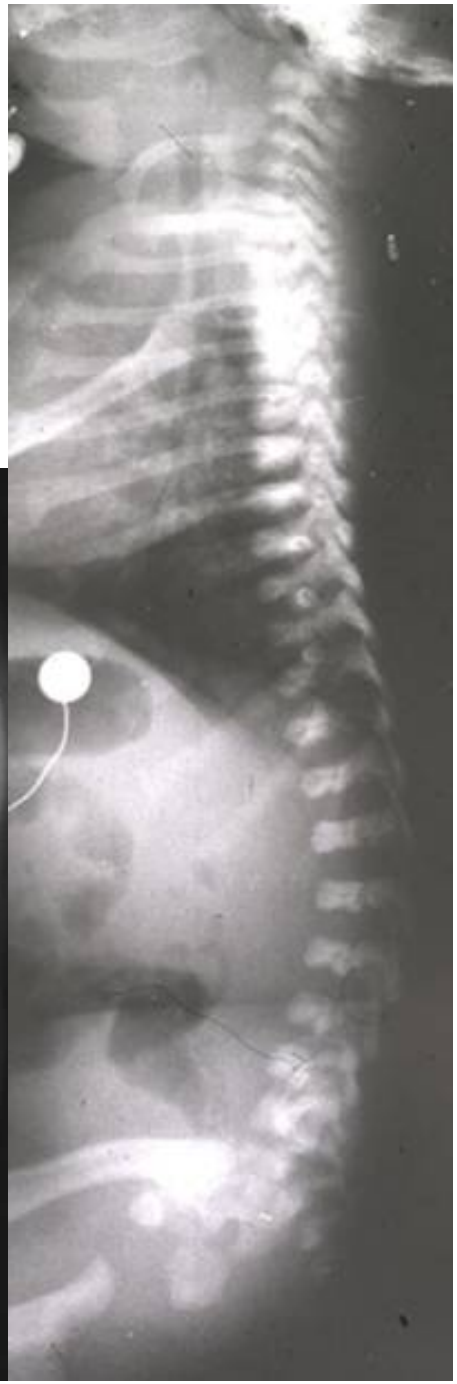


Hyperlordosis

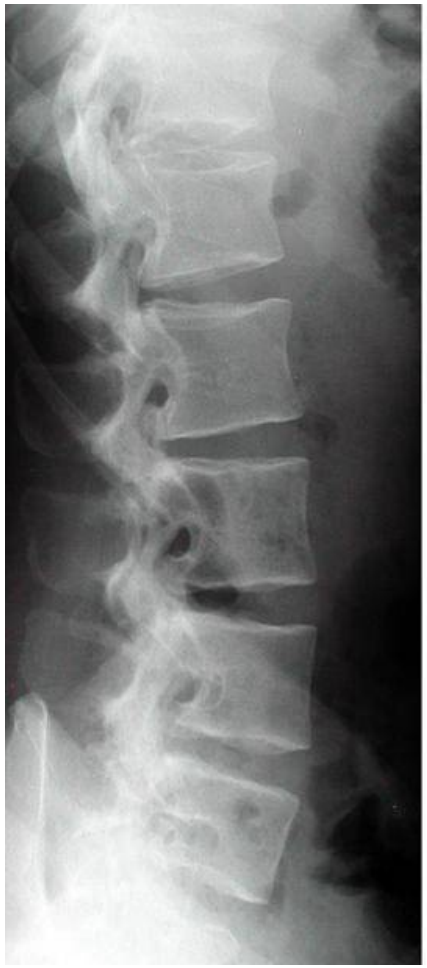
Skeletal rx Specific age-related criteria

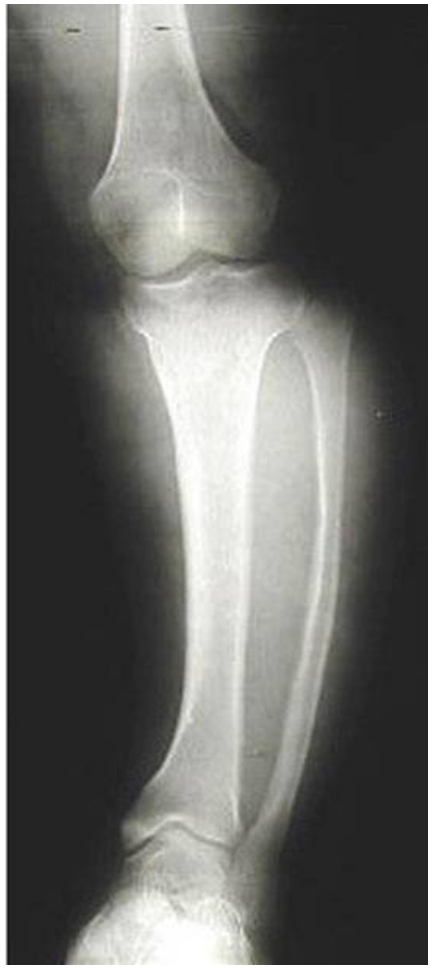
- New born period
  - Small and square iliac wings
  - Horizontalized acetabular roof
  - Enlarged metaphyses
  - Proximal femora radiolucence
  - Sharp-pointed extremity of femur profile
  - Prominent frontal bones
- Infancy
  - Delayed epiphysis development
  - Shortened pedicles (antero posterior diameter)
  - Platyspondyly
  - Anterior wedging of the lumbar vertebral bodies
  - Narrowing of the interpediculate distances from upper to lower spine
  - Small thoracic cage, enlarged ribs
  - Massive appearance of the phalanges





- Adulthood
  - Short pedicles on lumbar spine
  - Fibula overgrowth with bent tibia
  - Asymmetric femora condyles
  - Shortening femoral neck
  - with vertical orientation

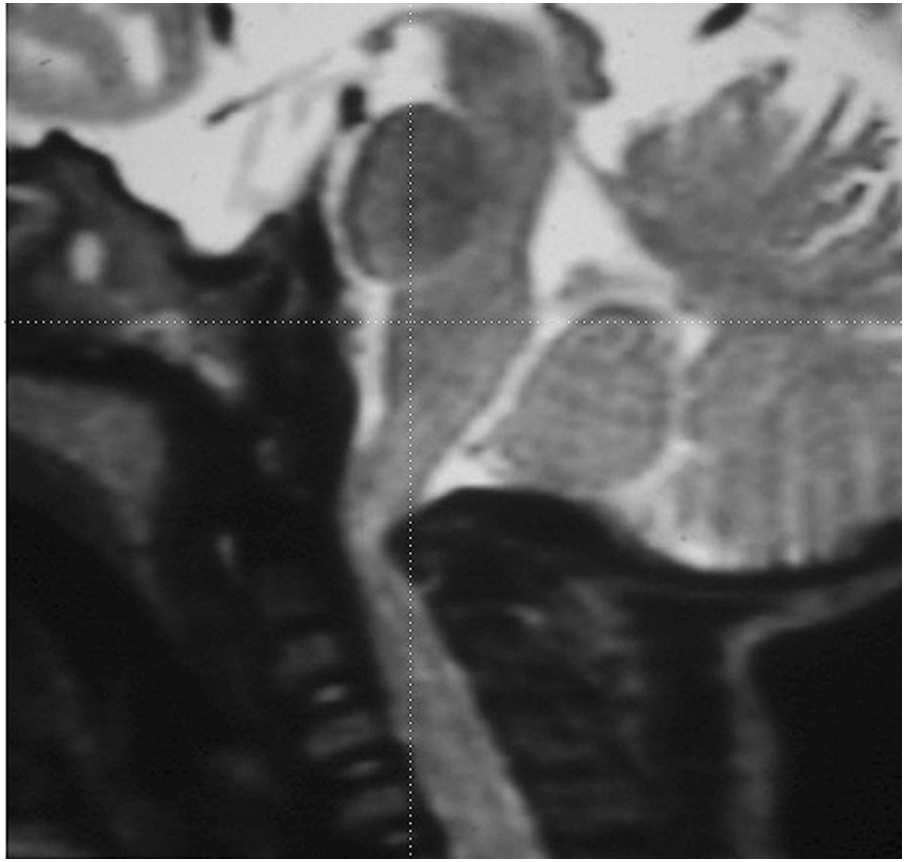


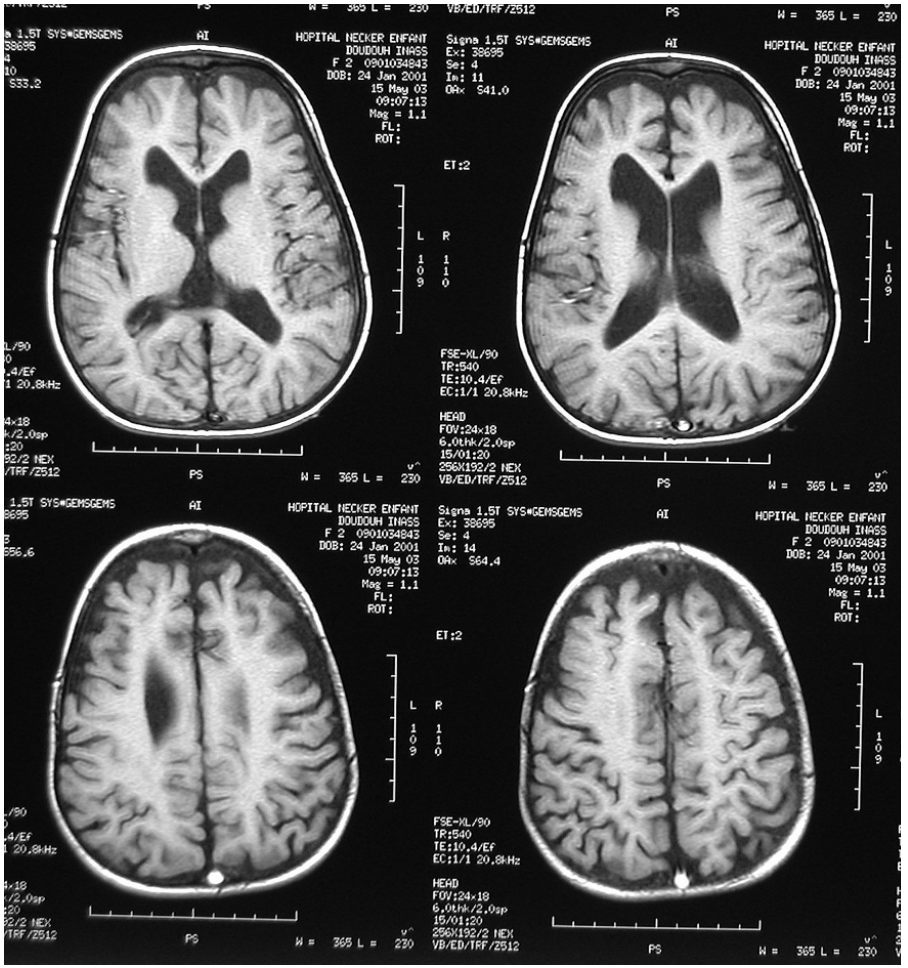


Natural history (1)

- new born and children
  - hypotonia (first months), muscle weakness
  - respiratory obstruction (microrhiny, macroglossia)
  - apnea (obstructive/ midface hypoplasia,
    central/ brain stem spinal cord compression)
  - gastro esophageal reflux
  - bronchitis, otitis
  - hydrocephalus (non active)

- specific complication
  = cervical cord compression

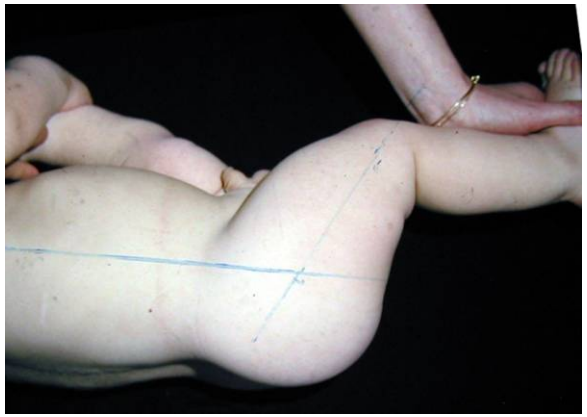


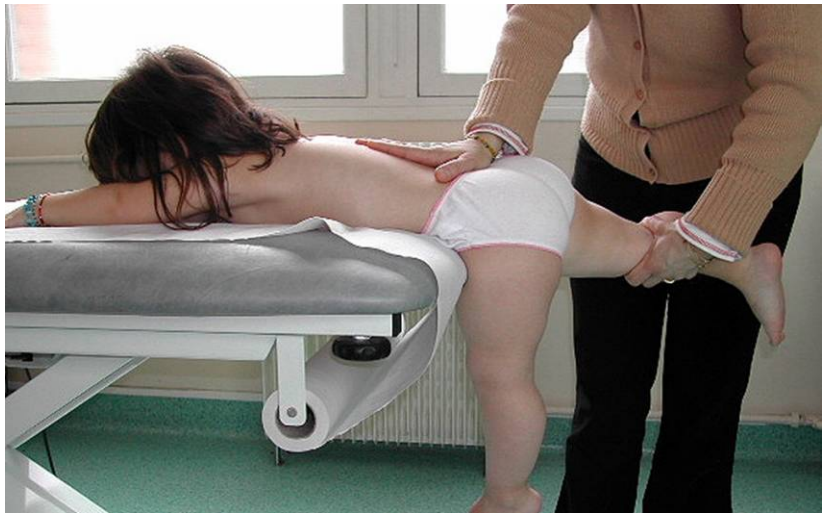


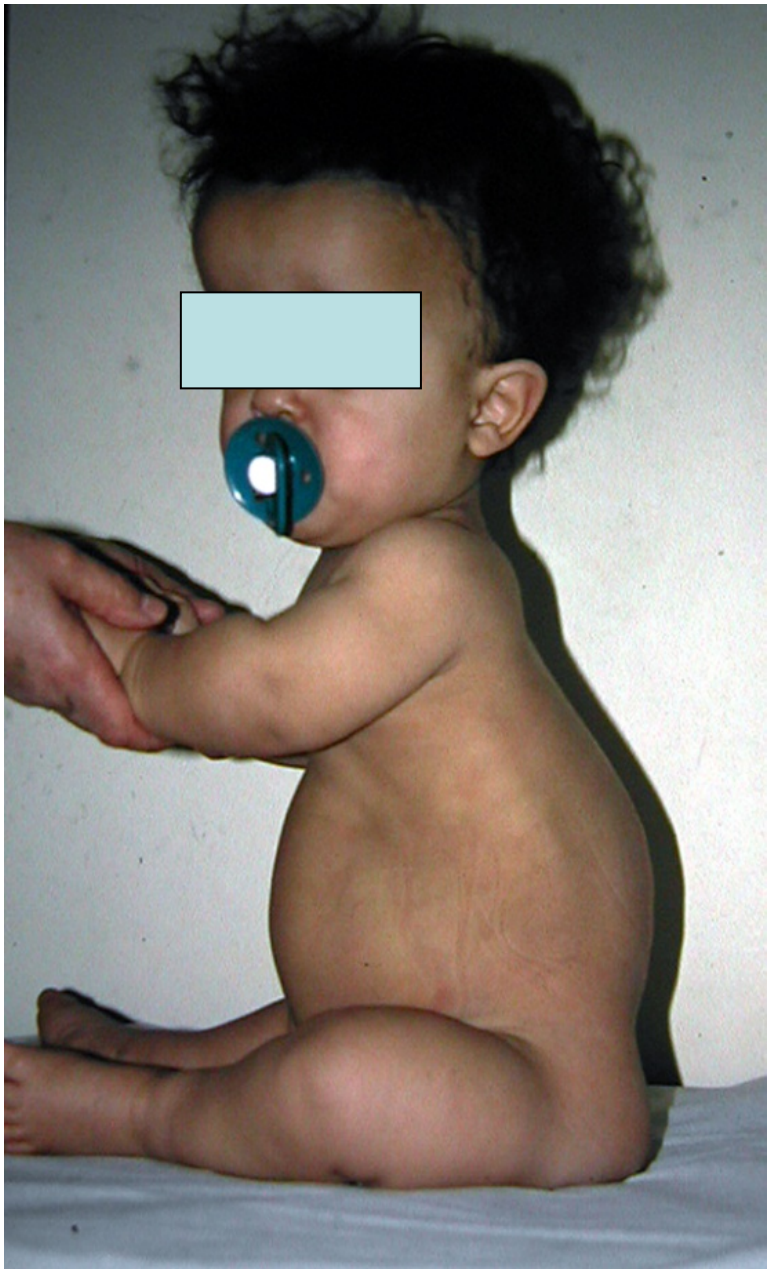
- Hypotonia aggravation, apnea, clonus
- 5 – 10%

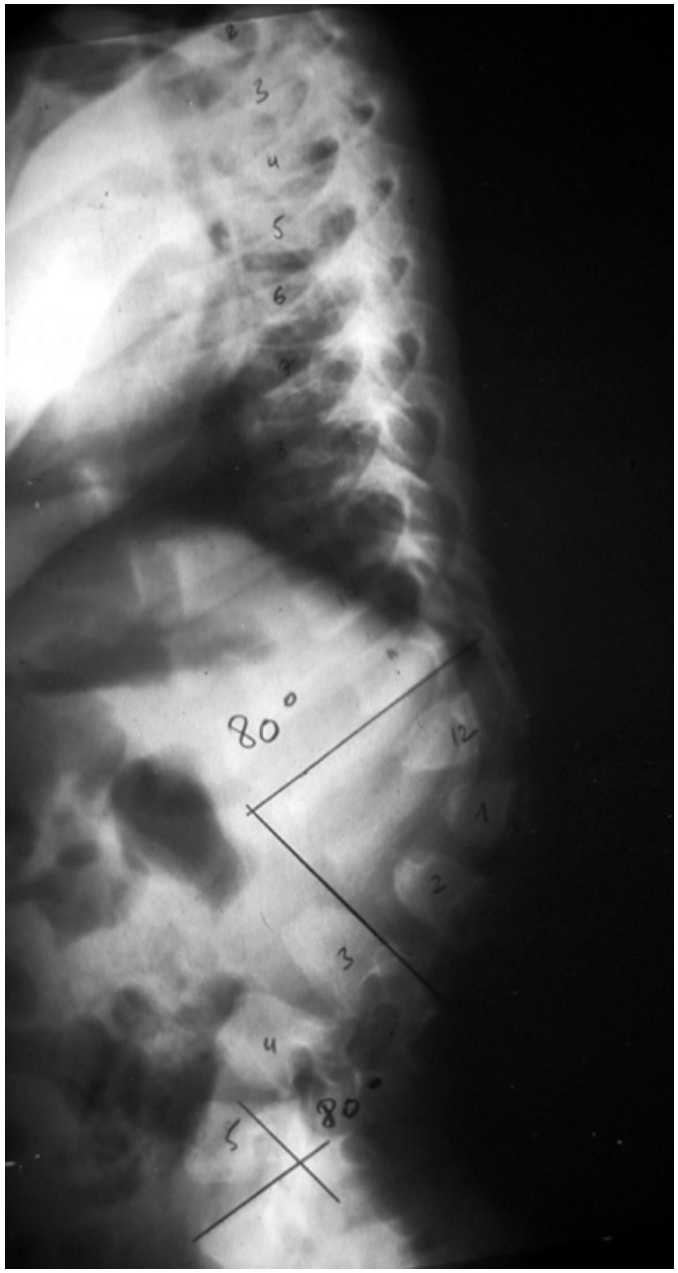
Natural history (2)

- <u>infancy</u>
  - Thoracolumbar gibbus
  - Lumbar hyperlordosis
  - Recurrent otitis media
  - Excess weight

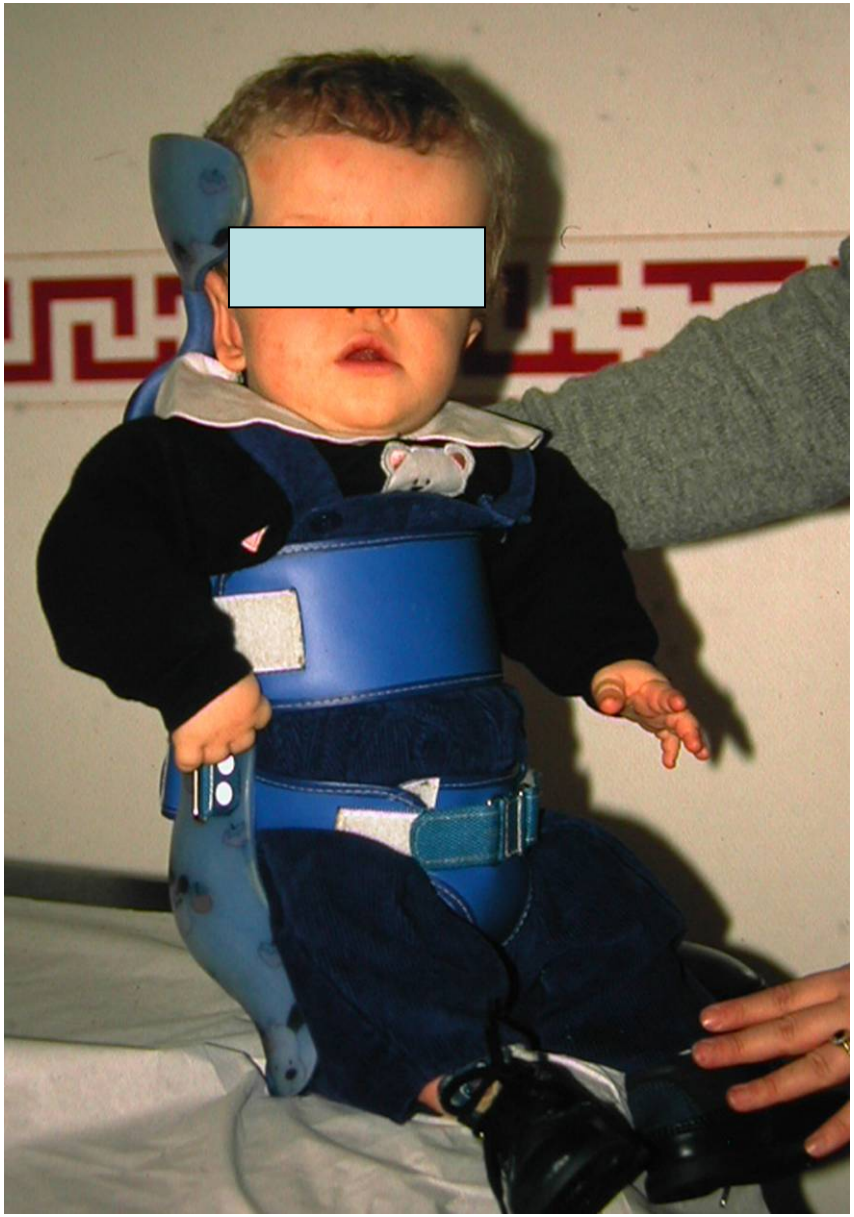






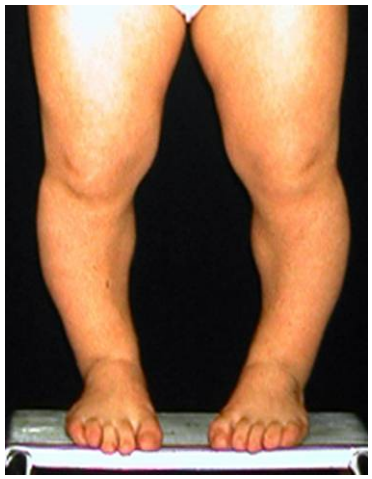


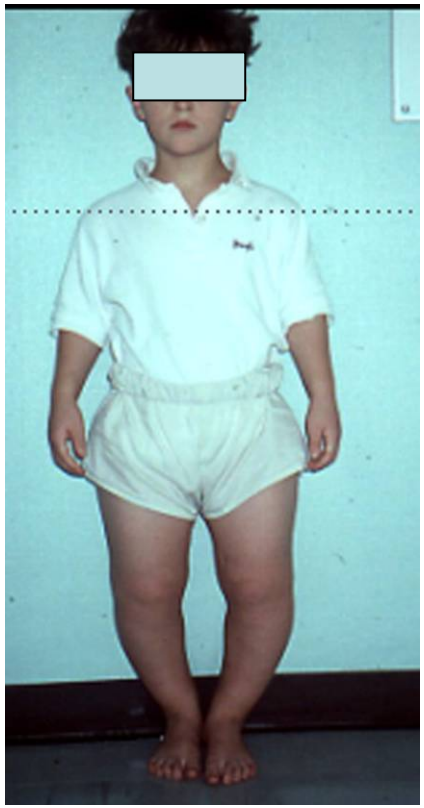
Cuneiform deformation of vertebral bodies



Slight corset, after 9 m if absence of breathing problems, and until walking

Natural history (3)

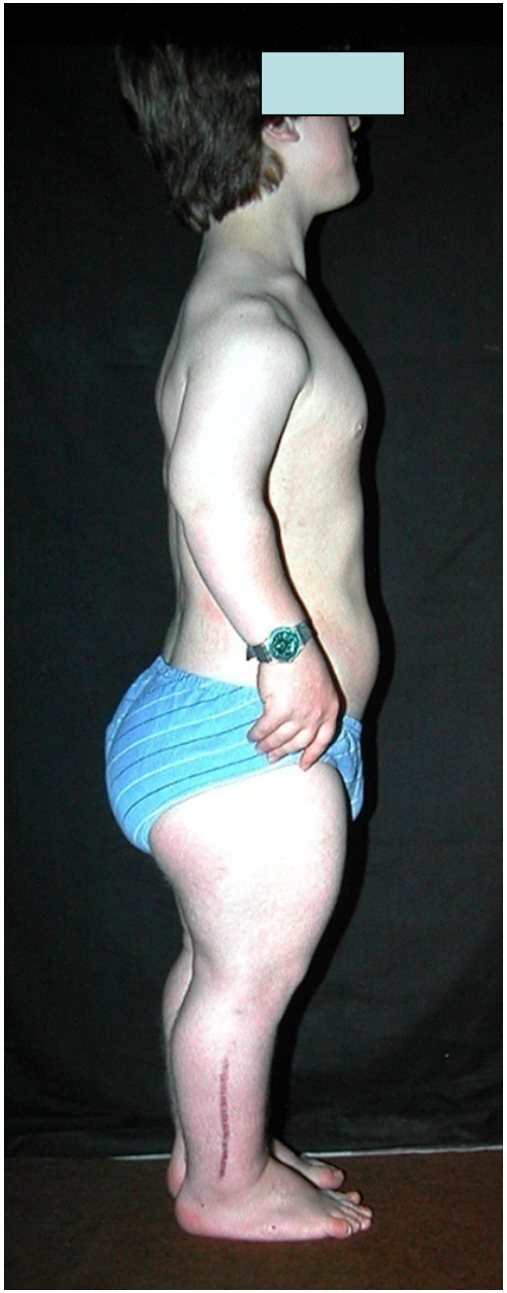


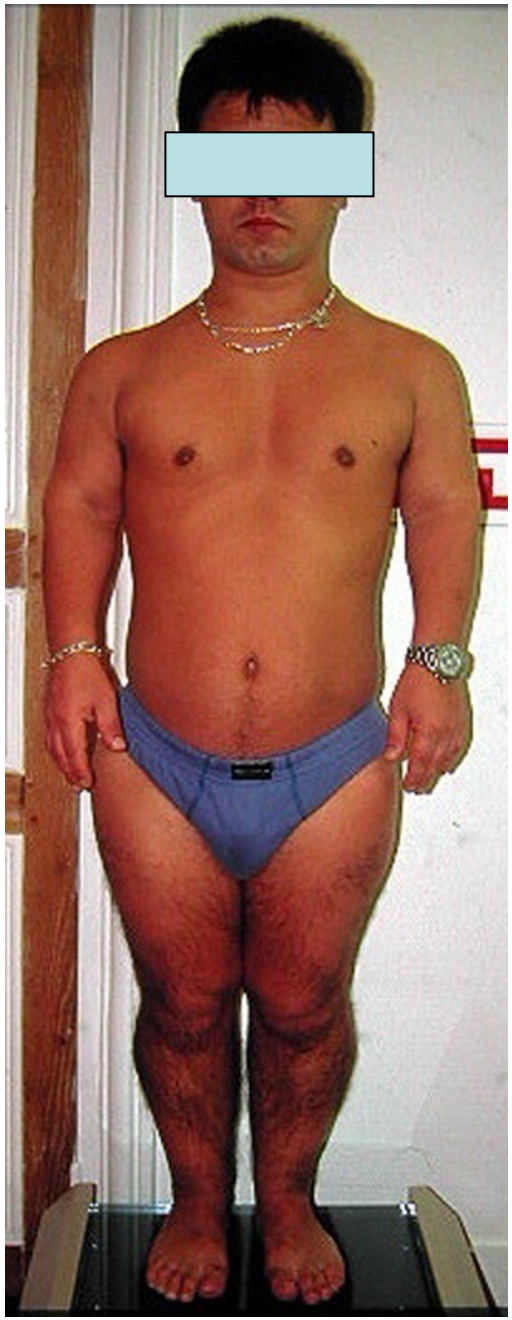


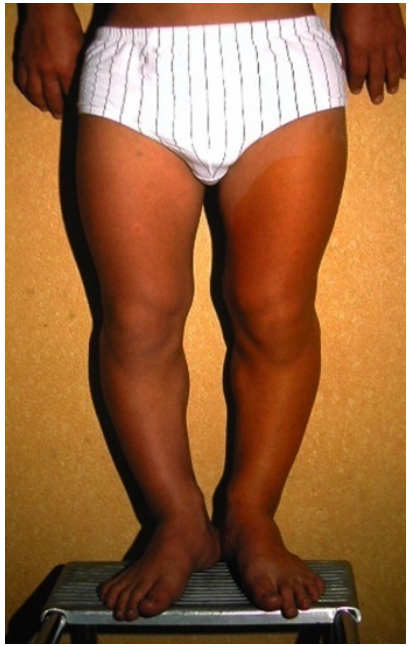
- <u>adolescence</u>
  - tibial bowing
  - hip flexum
  - lumbar hyperlordosis
  - vicious attitude of the joints
  - weight excess
  - orthodontic problems
  - psychological coaching

Natural history (4)

- Adult age
  - Variable final height: men 125 cm, 55kg / women 120 cm, 46 kg
  - Legs bowing
  - Spinal stenosis
  - Obesity
  - Metabolic complications
  - Psychological difficulties
  - Genetic counseling
  - Pregnancy accompaniment
  - Professional facilities







Management rules

- Regular follow up, prevention+++
- Multidisciplinary team
- medical: pédiatric, ORL,+/- pneumology
- surgery: orthopaedic, neurosurgery,
- Coordination with local medical referent
- Psychological aspects (patient and family)
- Genetic counselling (Dg, conseil génétique)
- Community integration (creche, school, professionnal)

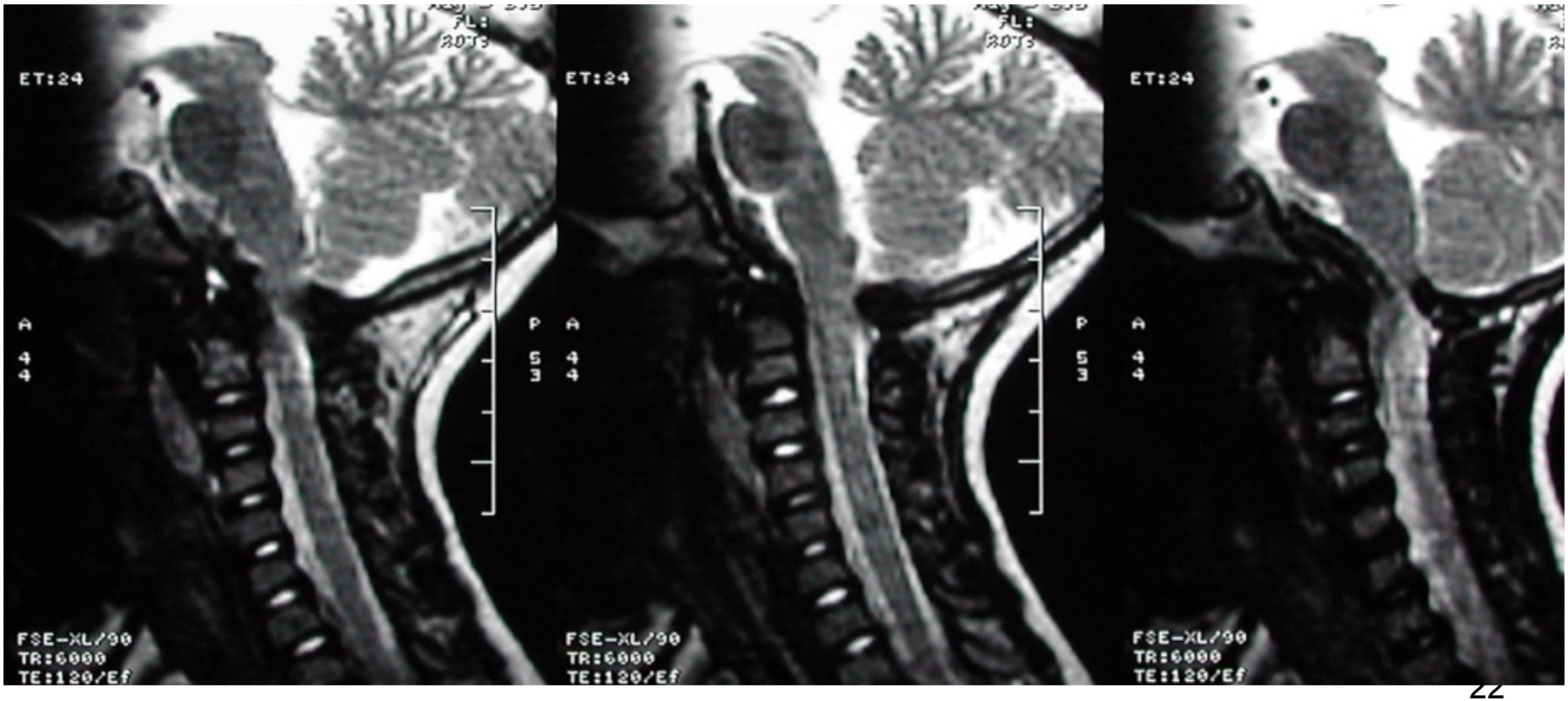
Standart follow up

âge	Intervenants	Fréquence minimale	problèmatiques	Ex. complémentaires	Prise en charge
0 – 12 mois	- systématique o pédiatre (PC, tonus, torticolis, sommeil, respiration, repas) o orthopédiste o ORL o généticien o psychologue o aide socio-familiale	. tous les 6 mois . tous les 6 mois . bilan à 1 an . autour de l'annonce . autour de l'annonce . à organiser	- 0 à 6 mois : rhinite obstructive bronchites ; RGO sténose occipito-cervicale -6 à 12 mois bronchites ; RGO otite séreuse sténose occipito-cervicale cyphose dorsale	- 6 mois : IRM charnière cervicale polysomnographie audiométrie - 1 an : rx membres inférieurs+rachis	Systématique - précautions posturales (attention au flessum et à la cyphose) - kiné (>9-12mois) - accompagnement psycho-logique parents - 100%, AJPP, AES, APPT
	- selon besoins o pneumologue o neurochirurgien	. selon besoin . selon besoin			Idem et, selon clinique - décompression médullaire
Entre 12 et 24 mois	- pédiatre - orthopédie	. tous les 6 mois . tous les 6 mois	- cyphose - apnées du sommeil - sténose occipito-cervicale - bronchites asthmatiformes - otite séreuse	- entre 12 et 18 mois : audiométrie - 2 ans radios mb inférieurs + rachis	- kiné (> 9 mois) - corset anticyphose (> acquisit. position assise) - aérateurs transtympaniques - conseils diététiques - accomp. psychologique
	- ORL - psychologue	. ≥ tous les ans . ≥ tous les ans			
Entre 3 et 10-12 ans	- pédiatre (signes pyramidaux, apnées du sommeil) - orthopédiste - ORL - rééducateur fonctionnel - psychologue	- bilan complet à 3 ans - ortho+ pédiatre /1an - selon besoin - selon besoin - régulièrement	- otite séreuse - anomalie statique vertébrale - incurvation membres inférieurs - surcharge pondérale - (sténose occipitale)	- 3 ans : bilan . audiométrie . +/- bilan psychologique	- lutte contre le flessum+++ (passage kiné > activité sportive active possible mais vigilance++) - aérateurs transtympaniques - recommandations scolaires (PAI) - recommandations diététiques - accomp. psychologique
Chez l'adolescent	- pédiatre - orthopédiste - généticien	- suivi annuel - suivi annuel - régulièrement (/ 2 ans ?)	- canal lombaire étroit - otites répétées - surcharge pondérale - difficultés psychologiques - dysharmonies maxillaires	- selon la clinique : . rx rachis et mb inférieurs . IRM médullaire . bilan auditif . bilan stomatologique . polysomnographie	- traitement ortho/chirurgical des déviations du rachis - traitement chirurgical du genu varum - explications du diagnostic - traitement orthodontique - conseil génétique - accomp. psychologique - kiné si besoin ou piscine - (allongement chirurgical mb inférieurs ?)
	- bilans réguliers o diététique o psychologue o orthodontiste	selon besoins, au moins / 3 ans ?			
Chez l'adulte	- orthopédique - rhumatologue/ - rééducateur fonctionnel - généticien - stomatologue - psychologue - ORL	- au moins tous les 3 ans (?), plus selon besoins	- sténose canal lombaire - apnées du sommeil - otites et baisse acuité auditive - surcharge pondérale - surcharge pondérale - difficultés psychologiques		- traitement fonctionnel ou chirurgical d'un canal lombaire étroit - traitement chirurgical genu varum - conseil génétique - accomp. psychologique - suivi grossesse

âge	Intervenants	Fréquence minimale	problèmatiques	Ex. complémentaires	Prise en charge
0 – 12 mois	- systématique o pédiatre (PC, tonus, torticolis, sommeil, respiration, repas) o orthopédiste o ORL o généticien o psychologue o aide socio-familiale	. tous les 6 mois . tous les 6 mois . bilan à 1 an . autour de l'annonce . autour de l'annonce . à organiser	- 0 à 6 mois : rhinite obstructive bronchites ; RGO **sténose trou occipital** -6 à 12 mois bronchites ; RGO otite séreuse **sténose trou occipital** cyphose dorsale	- 6 mois : **IRM** charnière cervicale **polysomnographie** audiométrie - 1 an : rx membres inférieurs+rachis	Systématique - **précautions posturales** (attention au flessum et à la cyphose) - kiné (>9-12mois) - accompagnement psycho-logique parents - 100%, AJPP, AES, APPT
	- selon besoins o pneumologue o neurochirurgien	. selon besoin . selon besoin			Idem et, selon clinique - décompression médullaire
Entre 12 et 24 mois	- pédiatre - orthopédie	. tous les 6 mois . tous les 6 mois	- cyphose - apnées du sommeil - sténose occipito-cervicale - bronchites asthmatiformes - otite séreuse	- entre 12 et 18 mois : **audiométrie** - 2 ans radios mb inférieurs + rachis	- kiné (> 9 mois) **- corset anticyphose** (> acquisit. position assise) - aérateurs transtympaniques - conseils diététiques - accomp. psychologique
	- ORL - psychologue	. ≥ tous les ans . ≥ tous les ans			
Entre 3 et 10-12 ans	- pédiatre (signes pyramidaux, apnées du sommeil) - orthopédiste - ORL - rééducateur fonctionnel - psychologue	- bilan complet à 3 ans - ortho+ pédiatre /1an - selon besoin - selon besoin - régulièrement	- otite séreuse **- anomalie statique vertébrale** **- incurvation membres inférieurs** **- surcharge pondérale** - (sténose occipitale)	- 3 ans : bilan . audiométrie . +/- bilan psychologique	- lutte contre le flessum+++ (passage kiné > activité sportive active possible mais vigilance++) - aérateurs transtympaniques - recommandations scolaires (PAI) - recommandations diététiques - accomp. psychologique
Chez l'adolescent	- pédiatre - orthopédiste - généticien	- suivi annuel - suivi annuel - régulièrement (/ 2 ans ?)	- canal lombaire étroit - otites répétées - surcharge pondérale **- difficultés psychologiques** **- dysharmonies maxillaires**	- selon la clinique : **. rx rachis et mb inférieurs** . IRM médullaire . bilan auditif . bilan stomatologique . polysomnographie	**- traitement ortho/chirurgical des déviations du rachis** **- traitement chirurgical du genu varum** - explications du diagnostic - traitement orthodontique - conseil génétique - accomp. psychologique - kiné si besoin ou piscine - (allongement chirurgical mb inférieurs ?)
	- bilans réguliers o diététique o psychologue o orthodontiste	selon besoins, au moins / 3 ans ?			
Chez l'adulte	- orthopédique - rhumatologue/ - rééducateur fonctionnel - généticien - stomatologue - psychologue - ORL	- au moins tous les 3 ans (?), plus selon besoins	**- sténose canal lombaire** **- apnées du sommeil** **- otites et baisse acuité auditive** **- surcharge pondérale** **- surcharge pondérale** - difficultés psychologiques		**- traitement fonctionnel ou chirurgical d'un canal lombaire étroit** - traitement chirurgical genu varum - conseil génétique - accomp. psychologique - suivi grossesse

Spinal cord compression (pseudo-chiari)

Neurosurgical decompression indication
-Clonus and hyperreflexia majoration
-Hypotonia
-central apnoea
-MRI imaging on the cervical junction



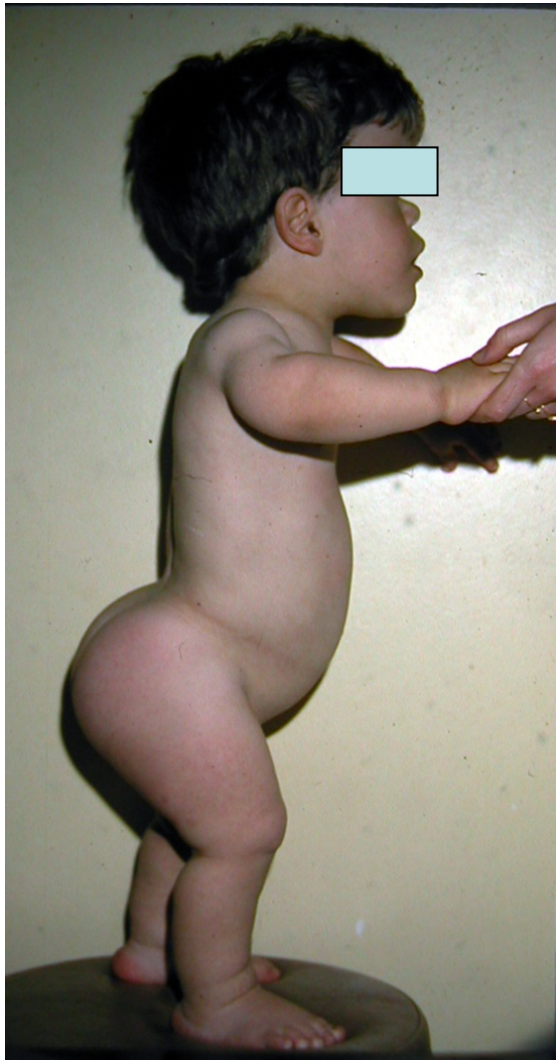
hyperlordosis

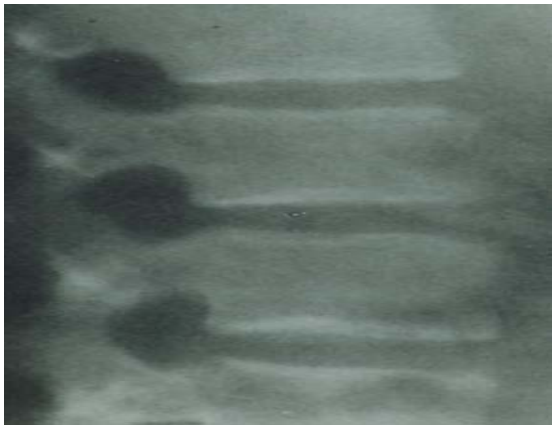
Importance of physiotherapy and postural excercices

Muscle work (abdominal, dorsal)

hyperlordosis

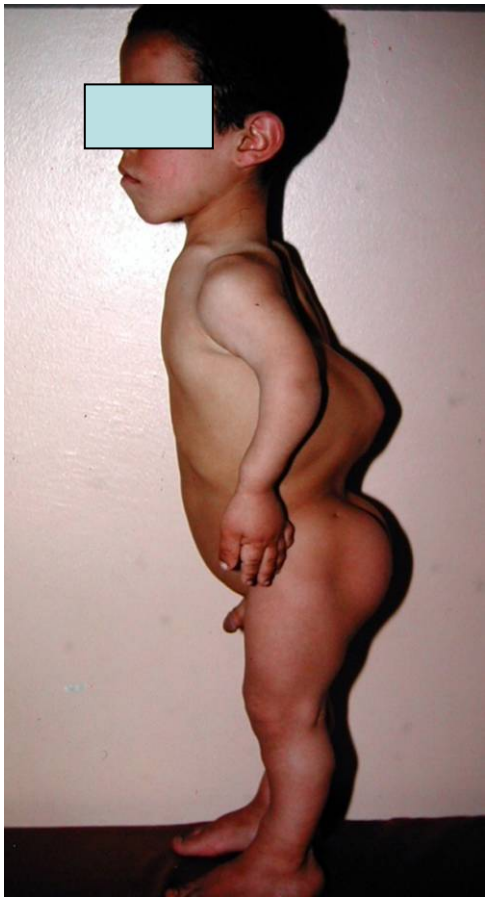
Hip flessum surgical correction

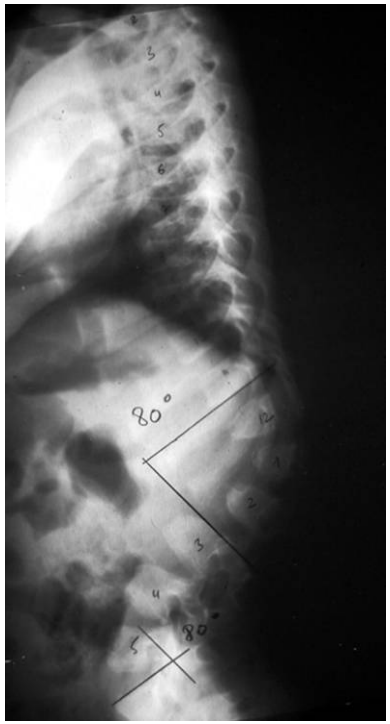


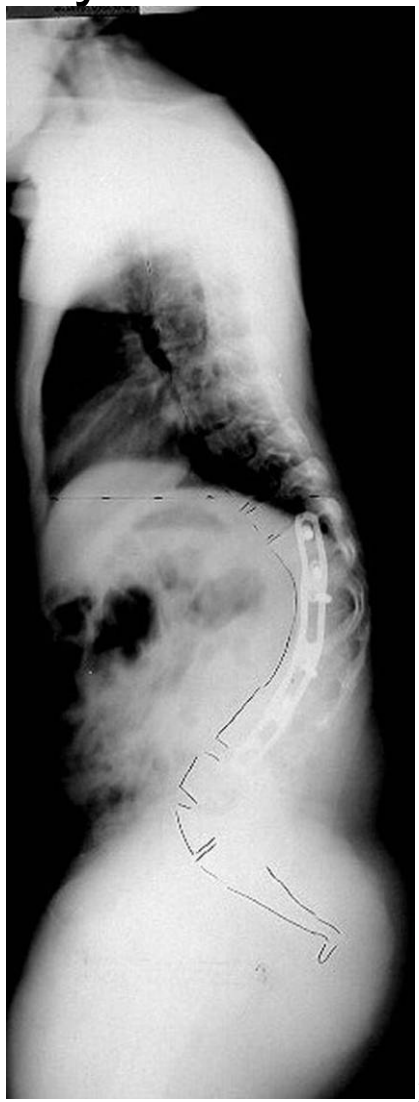


dorsolumbar gibbus

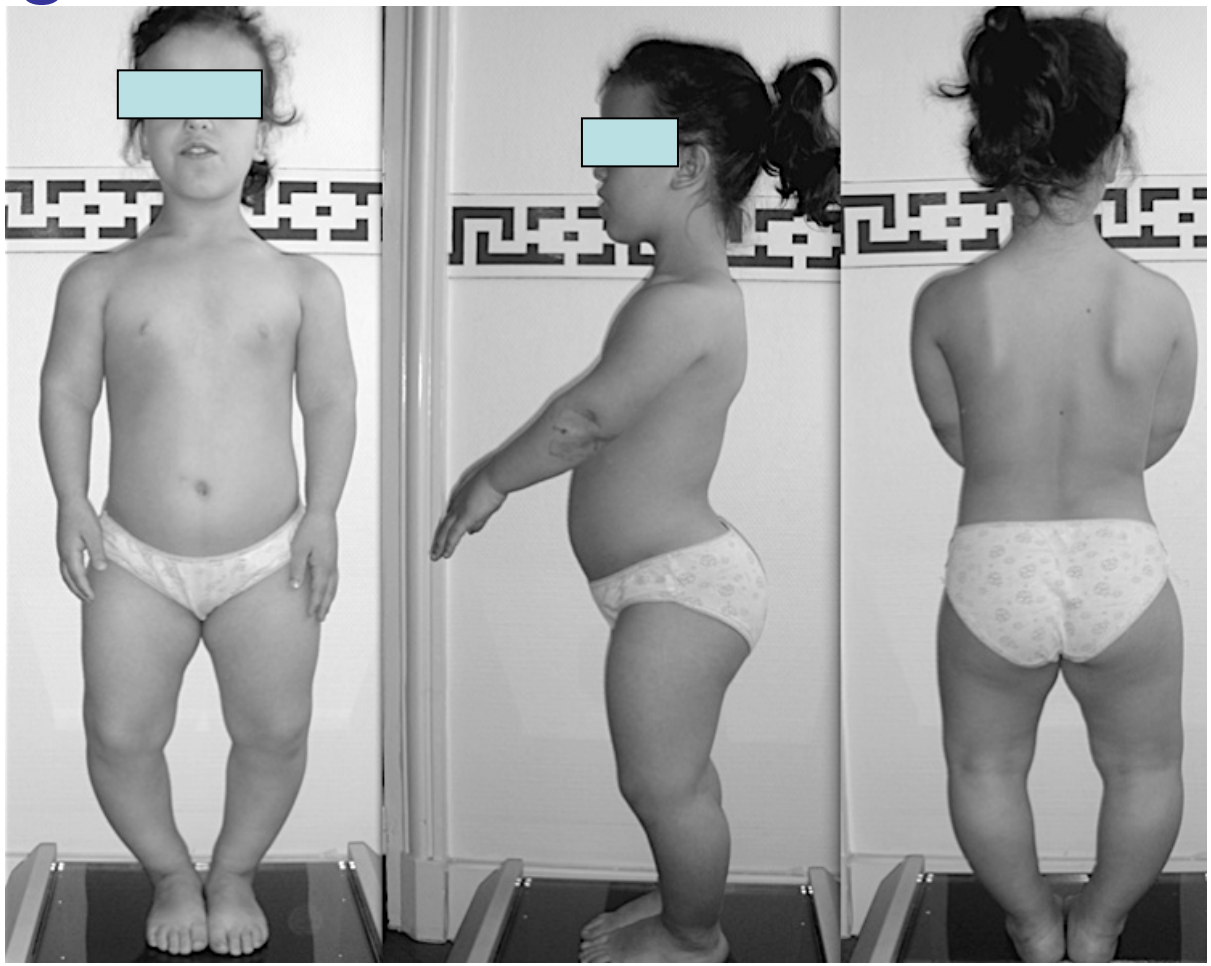
Consequence of abnormal management in infancy







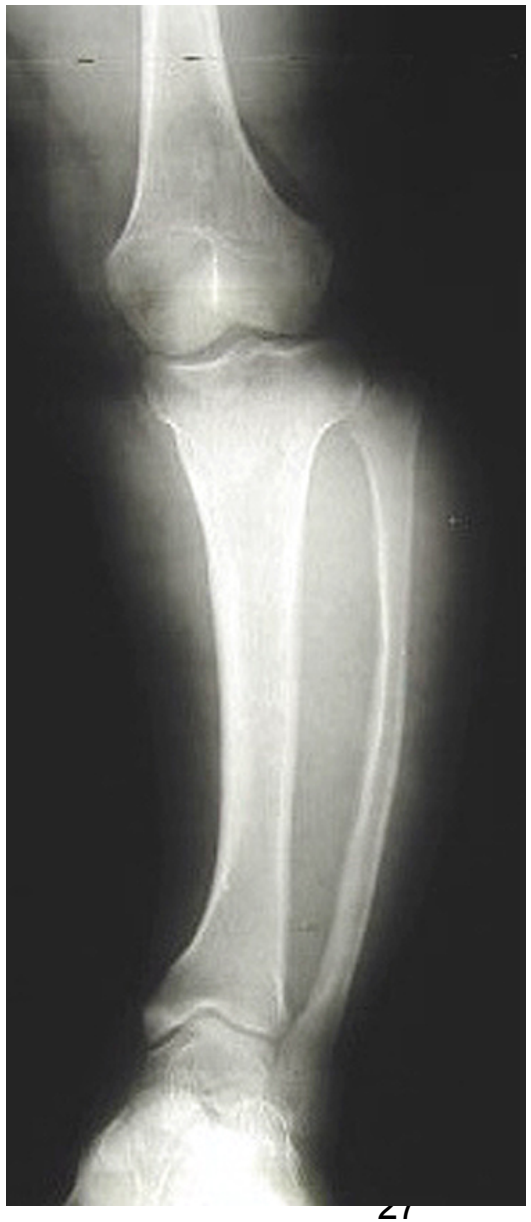
genu varum

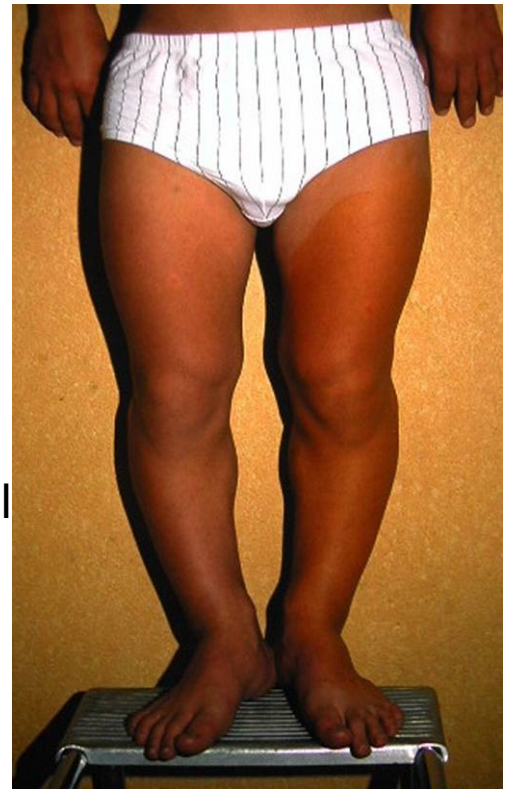


5% at 5 years, 40% at 40 years
Osteotomies
Limtation of secondary osteoarthritis

- *«Attelles » =0*
- *Assymetrical piphysiodese =0*
-

Surgical correction after 7-8 years
If patient asking

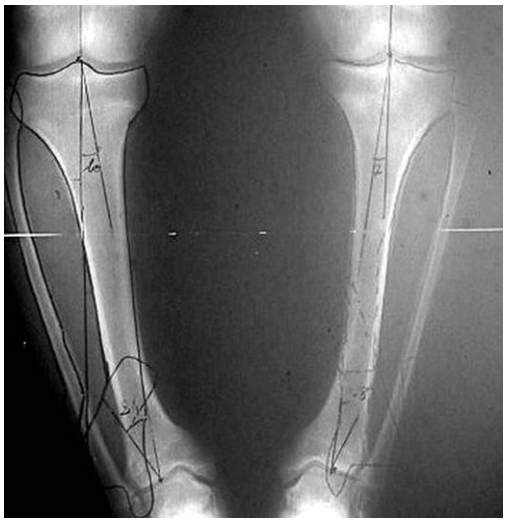


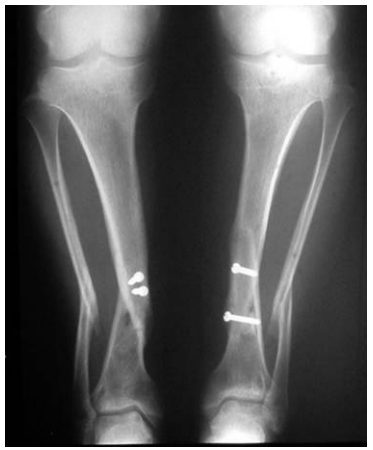


Functional and esthetic improvement

-in case of too early
Recidive risk

-In case of too late
Gonathrosis risk

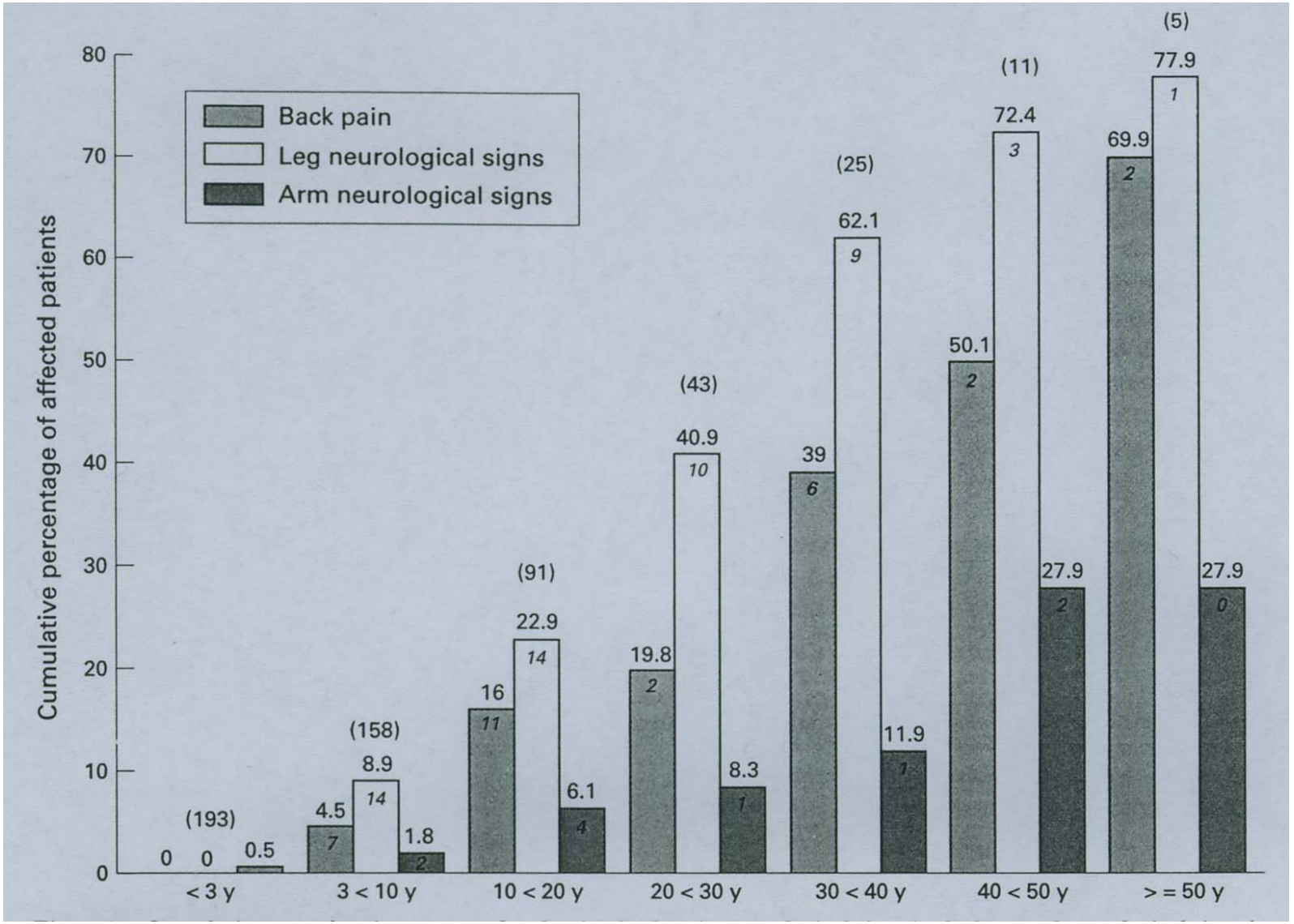




Don’t forget adult managment

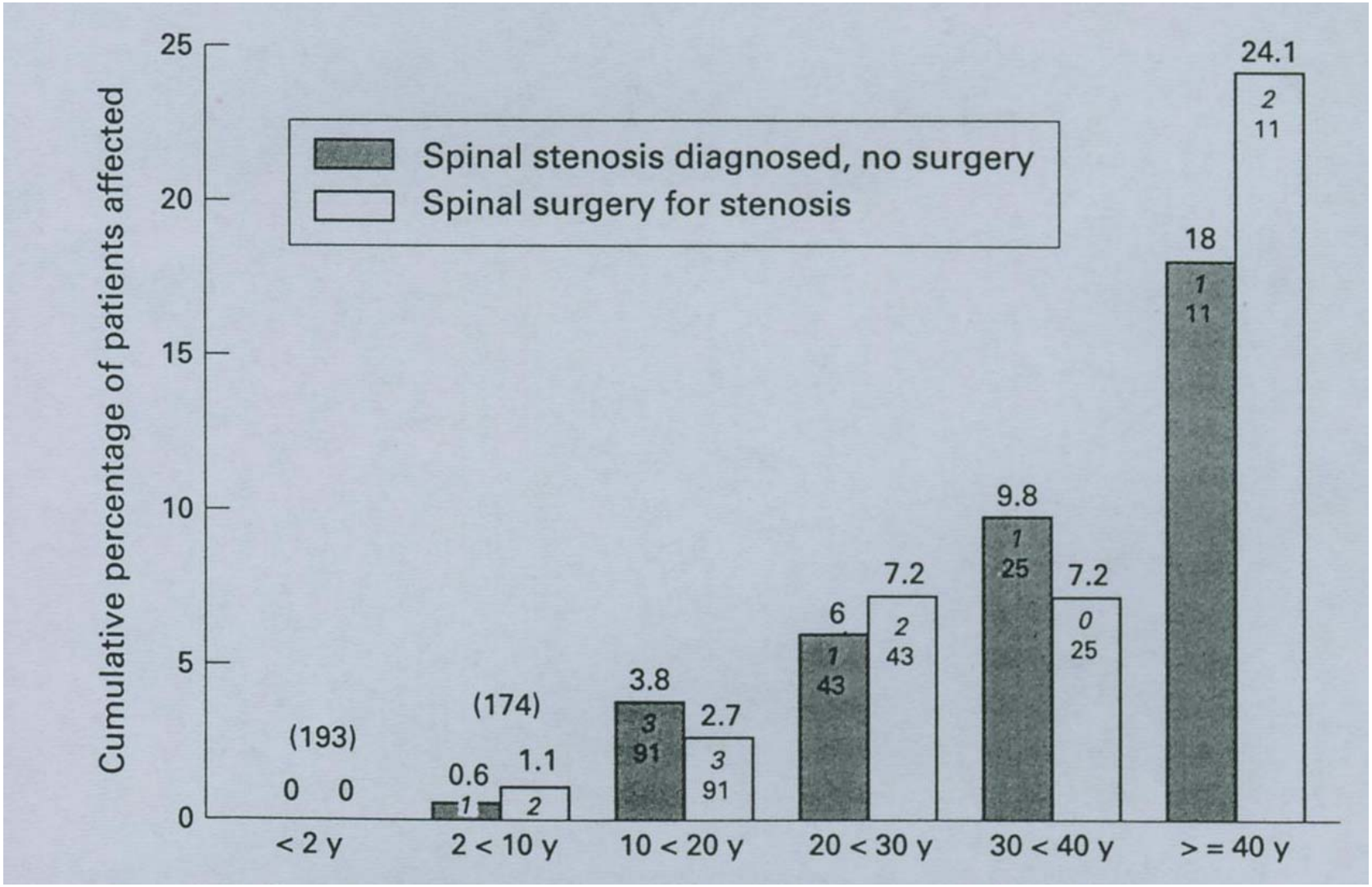
- Lumbar spine
- Legs deformations (tibial bowing)
- Hearing loss
- Sleep apneoa
- Obesity
- Metabolic complications
- Psychological support
- Genetic counsellinf
- Pregnancy

Spinal stenosis



Hunter 1998

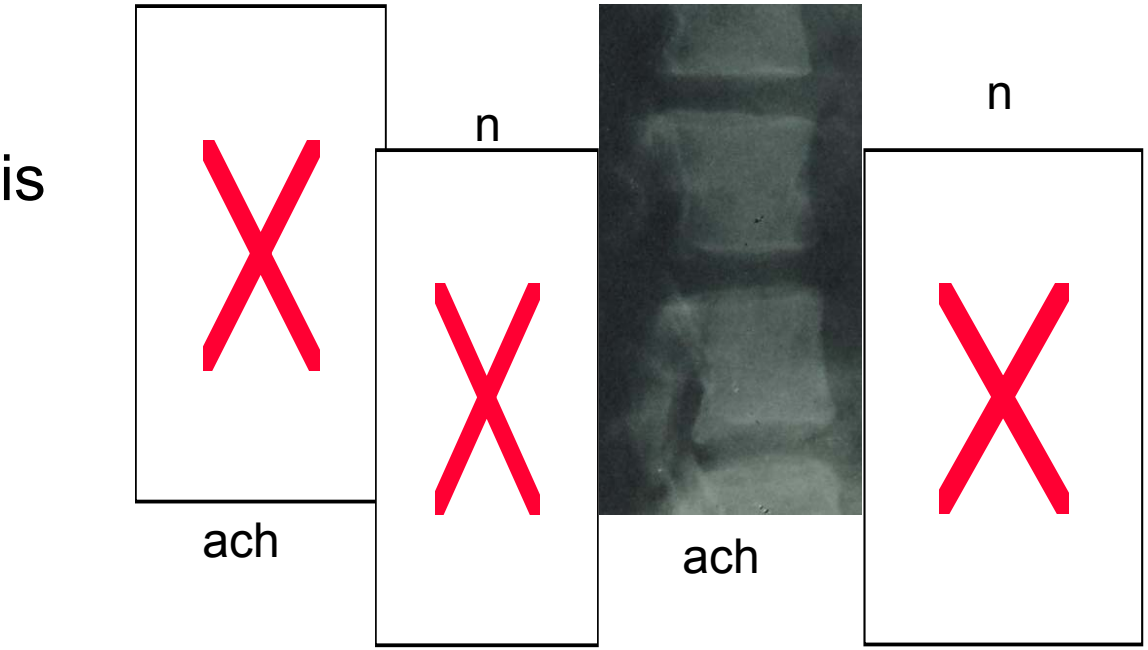
Spinal stenosis

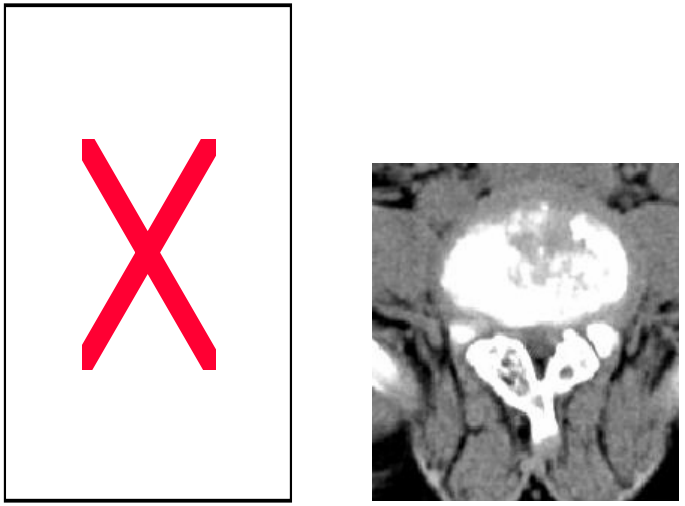


Hunter 1998

Spinal stenosis factors

- Short pedicles
- Persistent kyphosis
- hyperlordosis





Lumbar stenosis management prevention+++

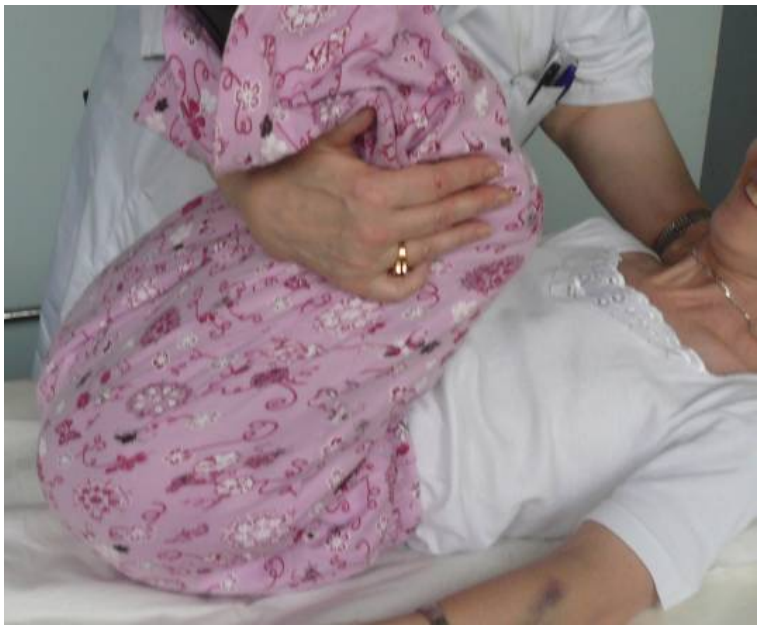
- Obesity > epidual lipomatosis
  - Dietary management
  - Physical activities
- Thoracolumbar kyphosis of the children

Lumbar stenosis management treatment+++

- antalgiques
  - Non steridien antiinflammatoires
  - Epidural and articular infiltrations
- Physiotherapy
- Surgical spinal laminectomy (by surgeons familiar with ACH

physiotherapy

1. Hip mobility
2. Muscular exercices
3. 2-3 per week; series of 15
4. Detailed prescription



Exemple: « kinésithérapie »

- Faire pratiquer par un kinésithérapeute
  - Rééducation du rachis lombaire et des membres inférieurs
    - Travail postural délordose lombosacrée
    - Rétroversion pelvienne active
    - Renforcement musculaire du tronc
    - Entretien articulaire coxo-fémoral et fémoro-tibial
    - Étirements musculaires des psoas et droits fémoraux
    - Apprentissage d'une autorééducation

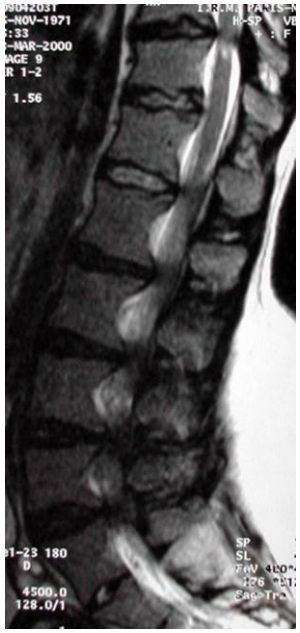
Lumbar traction

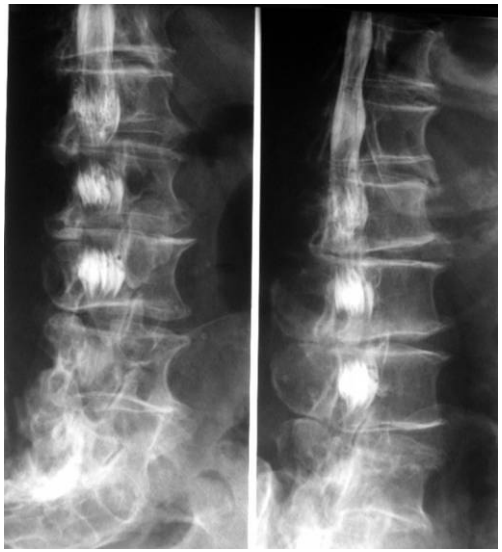
- Modalités
  - Dorsal decubitus anti-lordosis
  - Table + 10°
  - Intensity : body weight x 0.5
  - Duration : 30 to 60 minutes
  - Fqce : 5 /1-4 semaines

- Indications
  - Chronic persistant (radiculo-)lombalgies

Laminectomy indication

- abnormal neurologic examination
  - Sensitive defect
  - Sphincterien signs
  - paralysis
  - Increased reflexes and clonus
- Abnormal imaging
  - MRI
  - TDM
  - (Saccoradiculography)





Laminectomy

- Delicate surgical procedure
  - Hyperlordosis increases difficulties
  - « fraisage »
  - Prudent internal resection for neurologic liberation
  - Vascular risk
- Results
  - Less efficient on lumbar pain and sensitive abnormalities
  - Regression of motor signs, radiculalgy
  - Increased walk perimeter

Laminectomy complications

- aggravation neurologic troubles (transitory +++)
- Major accidents rare but possible
- Spinal ischemia…paraplegia

Always look for cervical stenosis before anesthesia…

ORL Complications

- Respiratory obstruction
- Differents mechanisms
- Complications
  - Mortality (sudden death)
  - Cognitive difficulties
  - Pulmonary hypertension, heart complications
  - Gastroesophageal reflux
  - Apnea

Diagnostic

- Clinical examination
- Sleep video
- ORL endoscopy (anatomy and dynamic)
- Polysomnography

Obstruction Treatement de

- Corticoïdes locaux, traitement du RGO
- ORL: amygdalectomie + adénoïdectomie ± turbinectomie inférieure ± agrandissement du cavum aux dépens du vomer
- Neurochirurgien: dérivation ventriculo-péritonéale, décompression du foramen magnum chez l'enfant
- Ventilation non invasive (VNI): apnées nocturnes non réglées par les mesures thérapeutiques précédentes
- *Trachéotomie ± ventilation assistée nocturne ou permanente:*
  - *Obstruction haute permanente non réglée par les traitements précédents ou en attente de ceux-ci*
  - *Obstruction nocturne avec VNI inefficace ou impossible pour des raisons techniques*
  - *Insuffisance respiratoire sévère nécessitant une ventilation prolongée*

Media otitis

- Children (25%) and adults (conductive hearing loss in 40%)
- Midface underdevelopment
- Small pharynx
- Tonsils and adenoid large for the available space
- Tonsillectomy, ventilation tubes
- Tympanoplasty: be careful to veinous dilatation (jugular golf

Others

- Anesthesia
  - Prudent
  - Intubation risk (cervical extension, narrow larynx)
  - Peridural and rachianestesia / lumbar anatomy

Métabolic complications

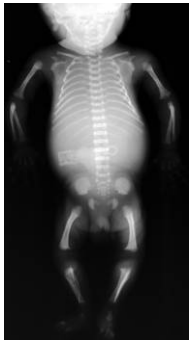
- Obesity
  - Articular
  - Obstructive sleep apnea
  - Cardiovascular problem

- Increased risk for heart disease (*Wynn et al 2007*)
  - 25 -35 y
  - life expectancy decreased by15 years compared with general population
- Psychological difficulties
  - Normal intelligence
  - Social, education and professional insertion difficulties

Genetic and molecular aspects

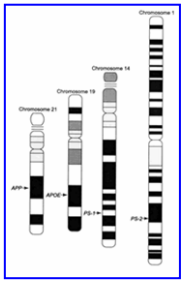
Clinical studies

Patients cohort



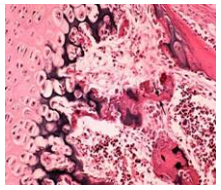
Cartography

Gene localisation & identification



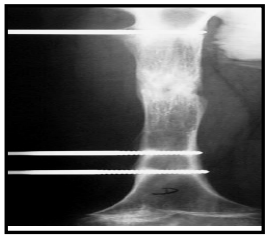
Signalling pathways

Gene roles and functions



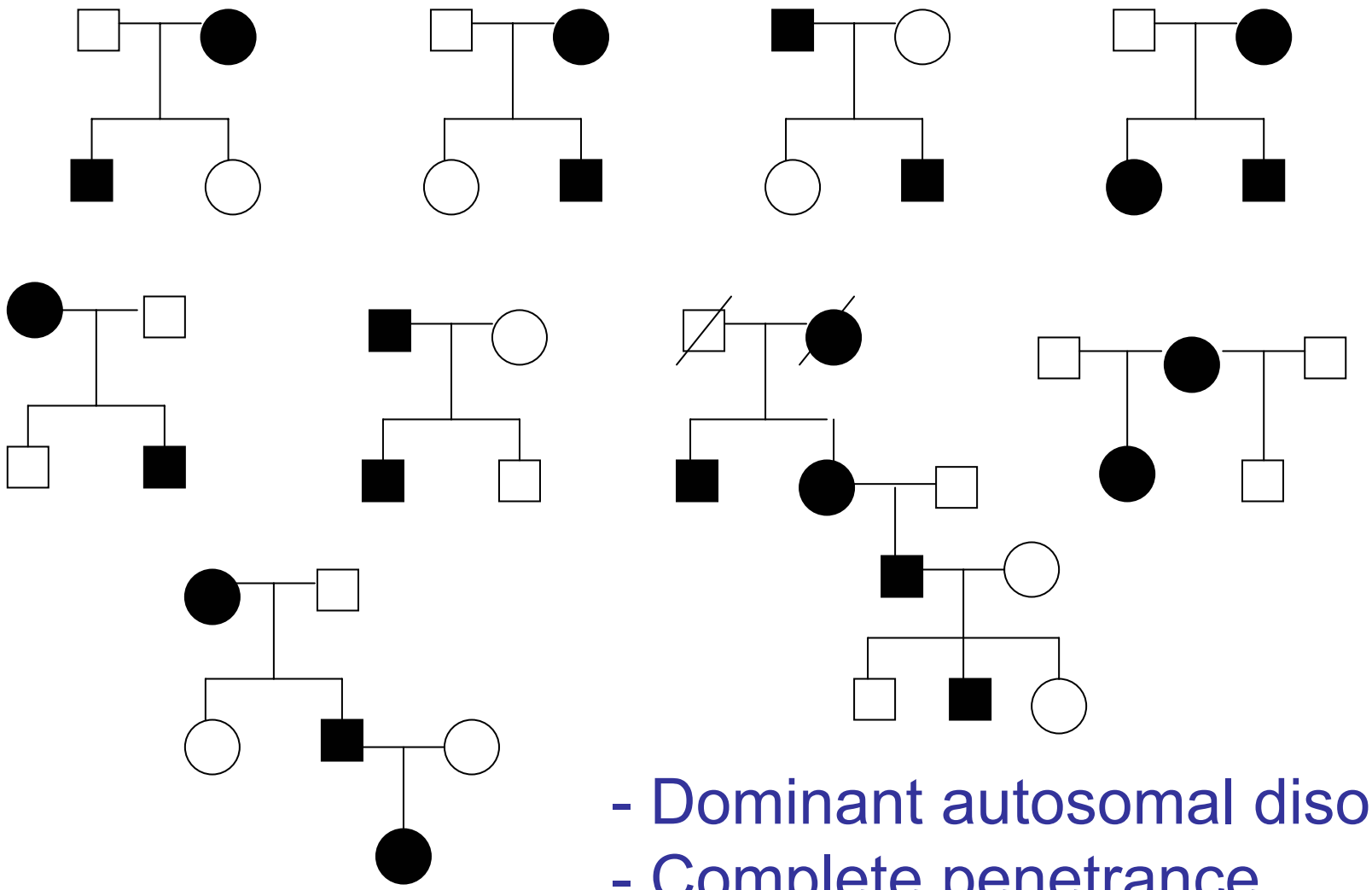
Pharmacology

Molecules



Patients cohort ⟶ cartography, gene localisation

1994: 4p16.3

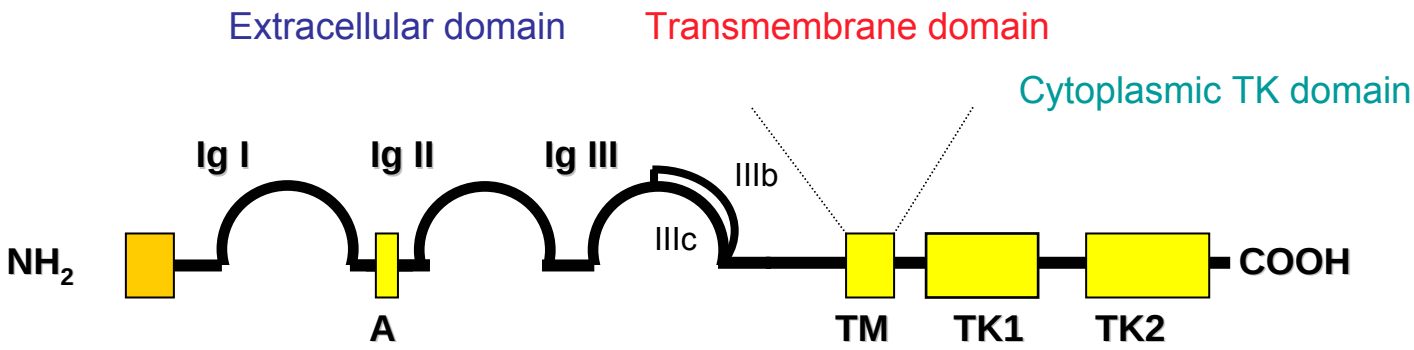


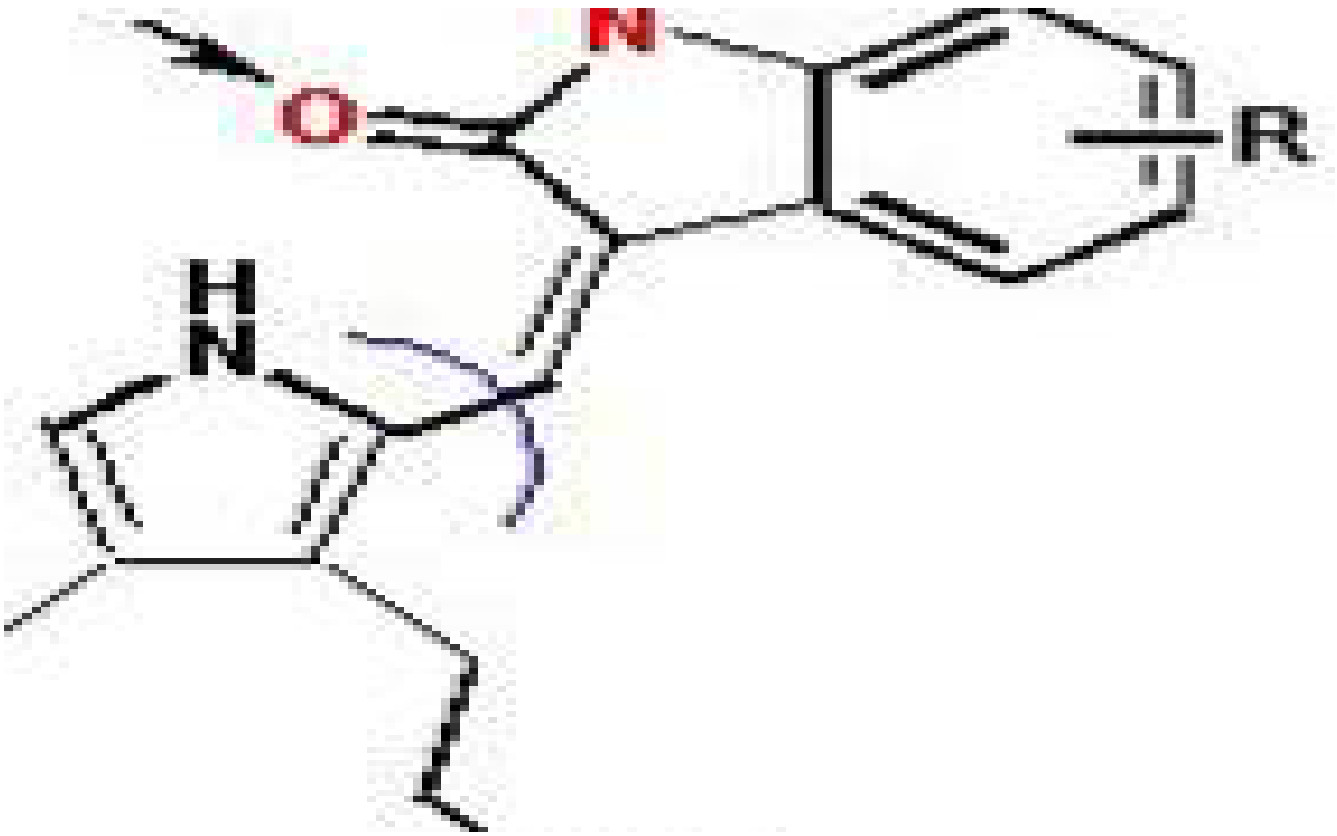
- Dominant autosomal disorder
- Complete penetrance

patients cohorts ⟶ gene identification

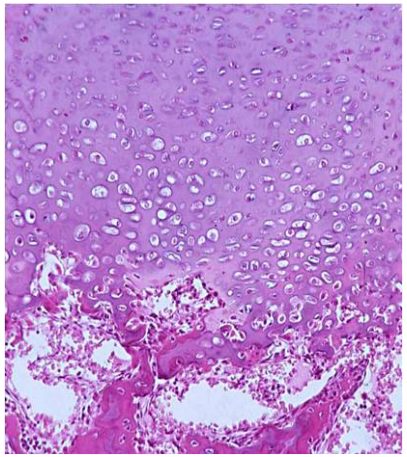
1994: Fibroblast Growth Factor Receptor 3 (*FGFR3*)

(Receptor with tyrosine kinase activity (RTKs))

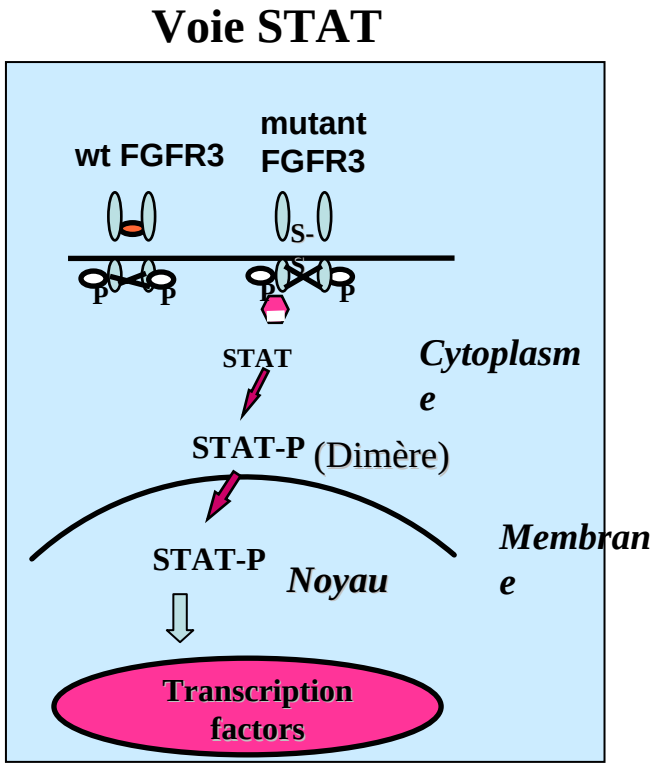



N
O
R
H
N

FGFR3 and bone growth



Severe disorganization of the growth plate



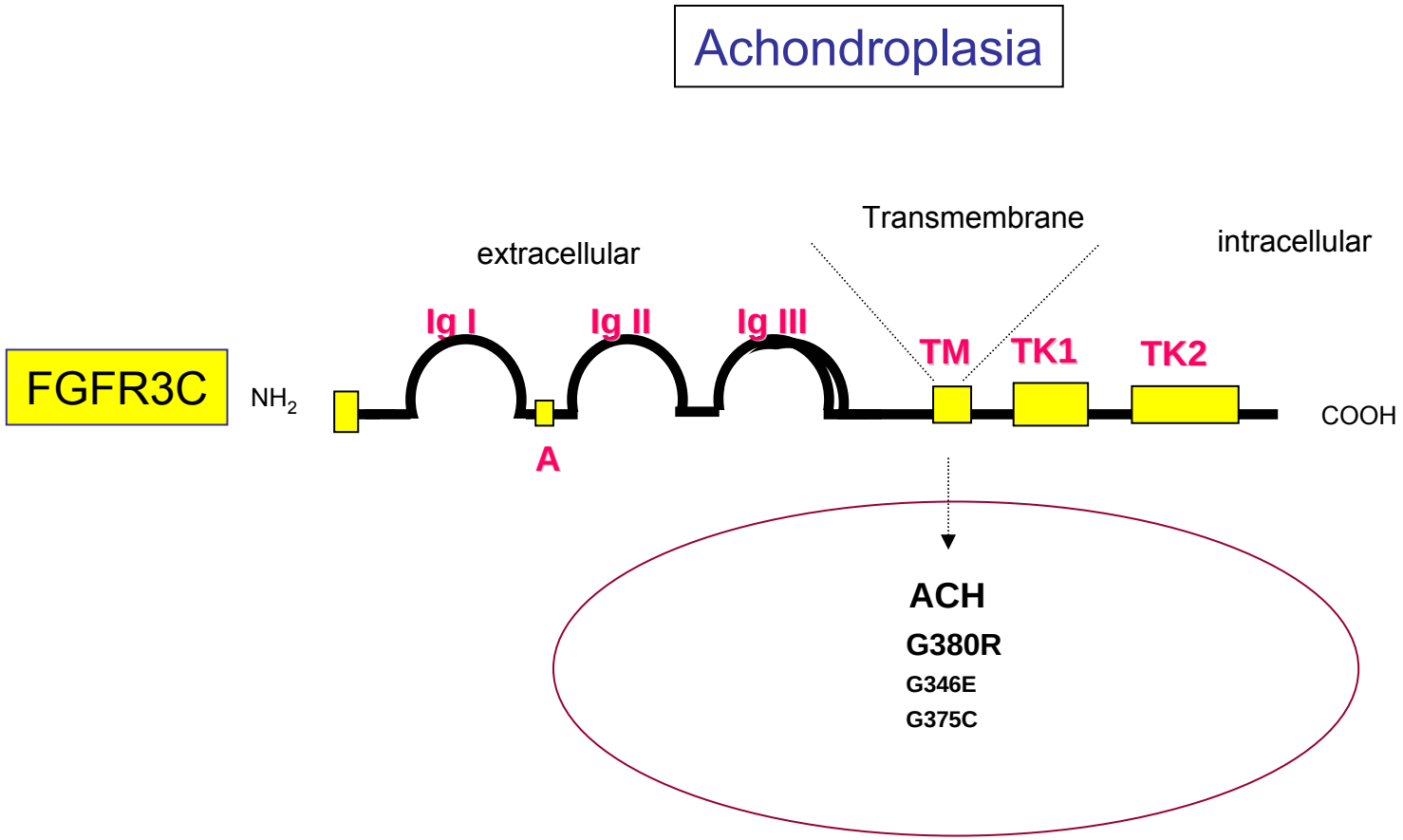
FGFR3 mutations: STAT pathway activation

FGFR3: negative regulator of the bone growth

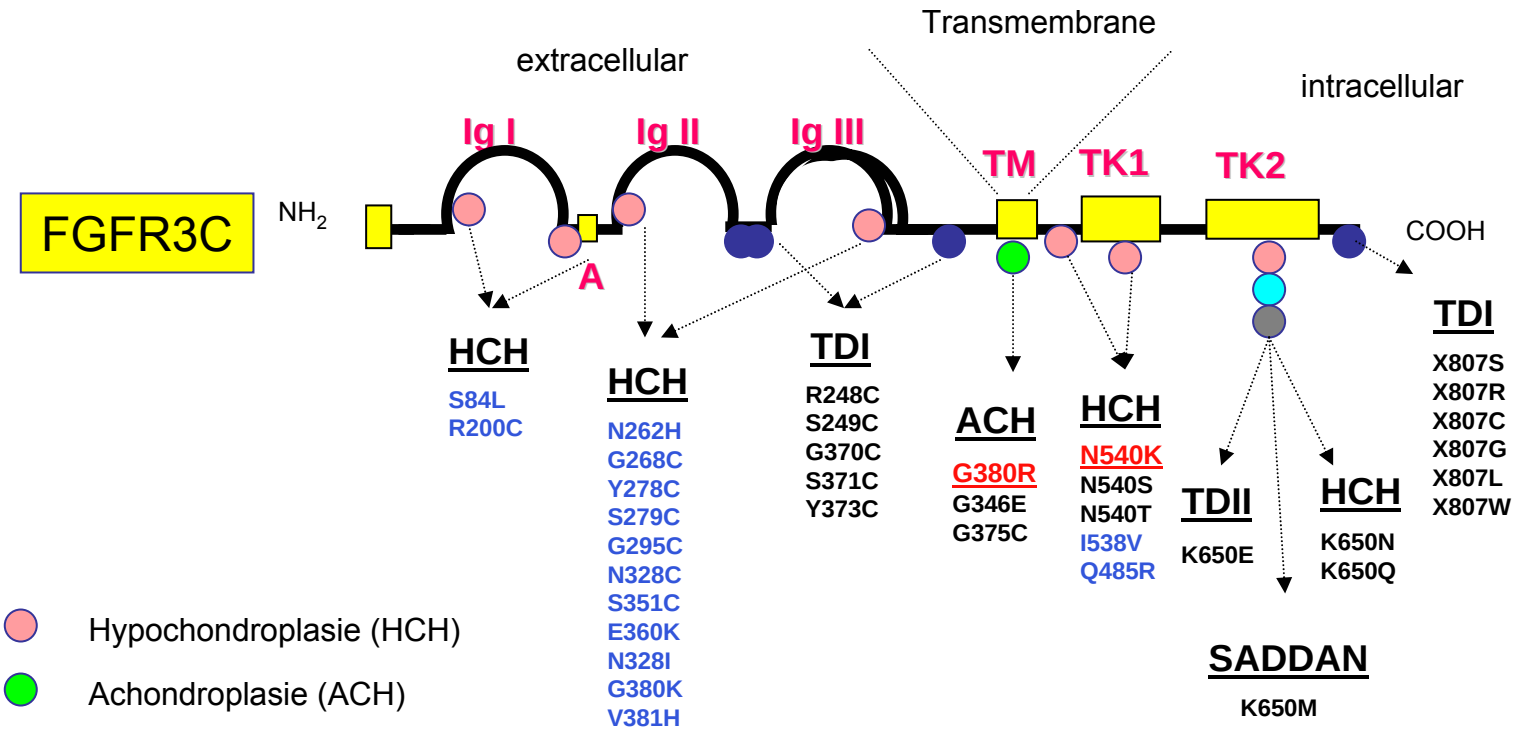
ACH/TD/HCH : - Growth plate disorganization

- Premature differentiation of the chondrocytes

- De novo mutations in 98%



Hypochondroplasia | Achondroplasia | Thanatophoric dysplasia



- Hypochondroplasie (HCH)
- Achondroplasie (ACH)
- Nanisme thanatophore type I
- Nanisme thanatophore type II
- Severe achondroplasia with developmental delay and acanthosis nigricans

(Heuertz 2007)

Gene identification → functional studies

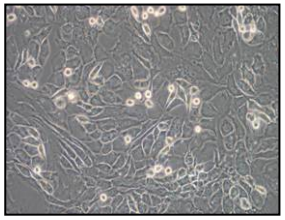
Human

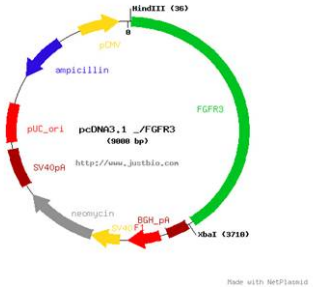
Molecular

Mouse

Chondrocytes lines

immortalized cell FGFR3 wt/M





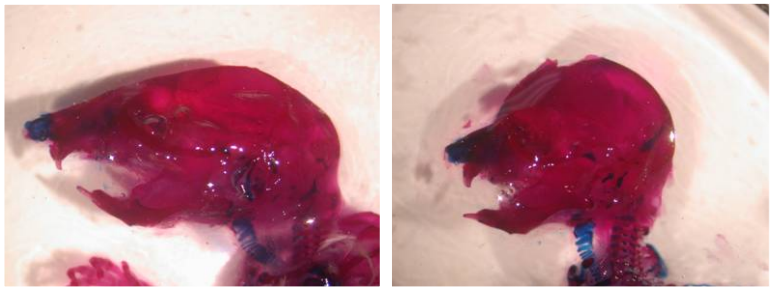
Functional studies

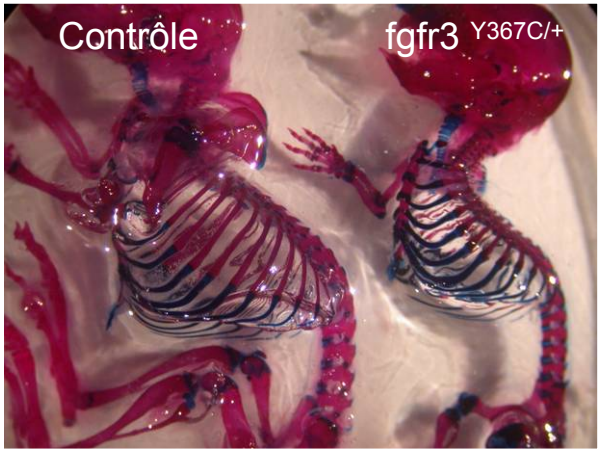
Pharmacology

Murin model fgfr3

✓**Knock in (Y367C) TDI**
✓**Phenotype similar to human**

Contrôle fgfr3 $^{Y367C/+}$

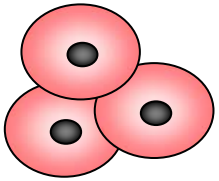




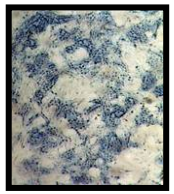
(L. Legeai-Mallaet, S. Pannier, 2007)

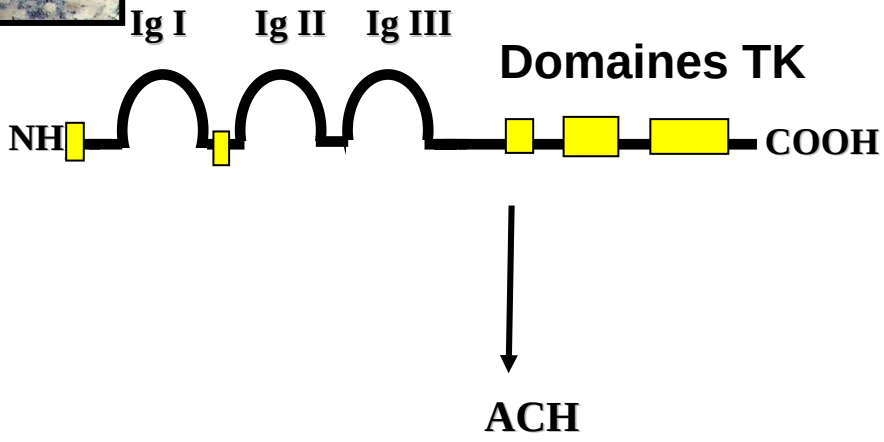
Perspectives
Tyrosines Kinases inhibitors

Human

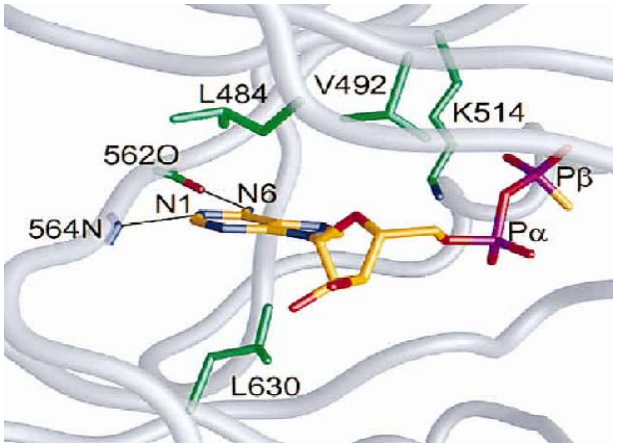


Chondrocytes lines,
WT and mutant





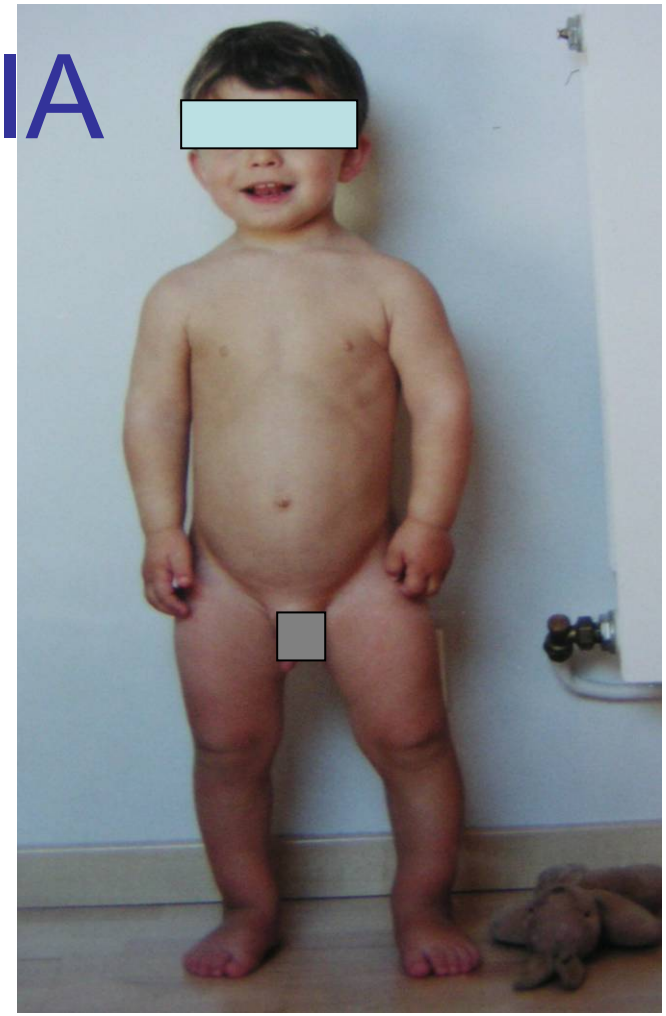
TK inhibitors



Interaction site ATP and TK domain of the receptor

HYPOCHONDROPLASIA

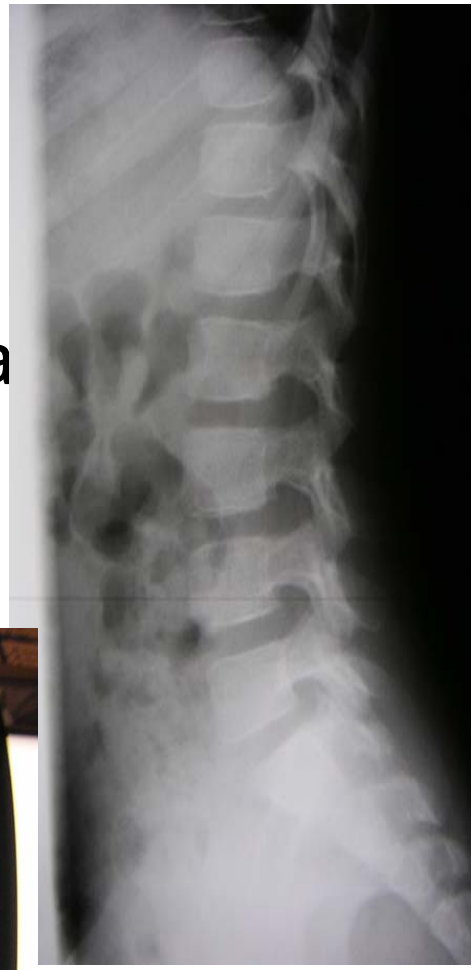
Mild phenotype

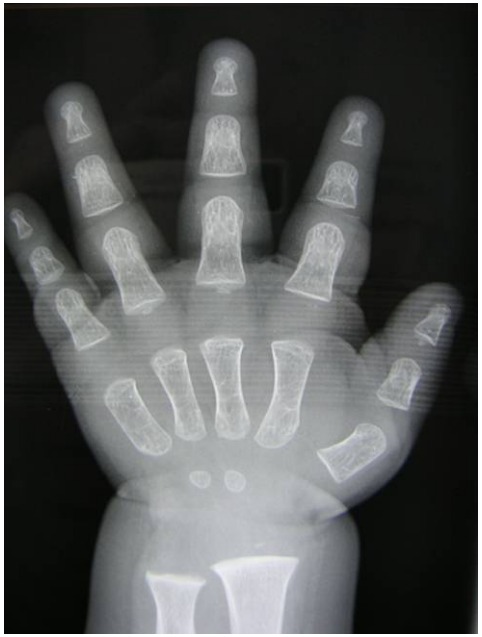


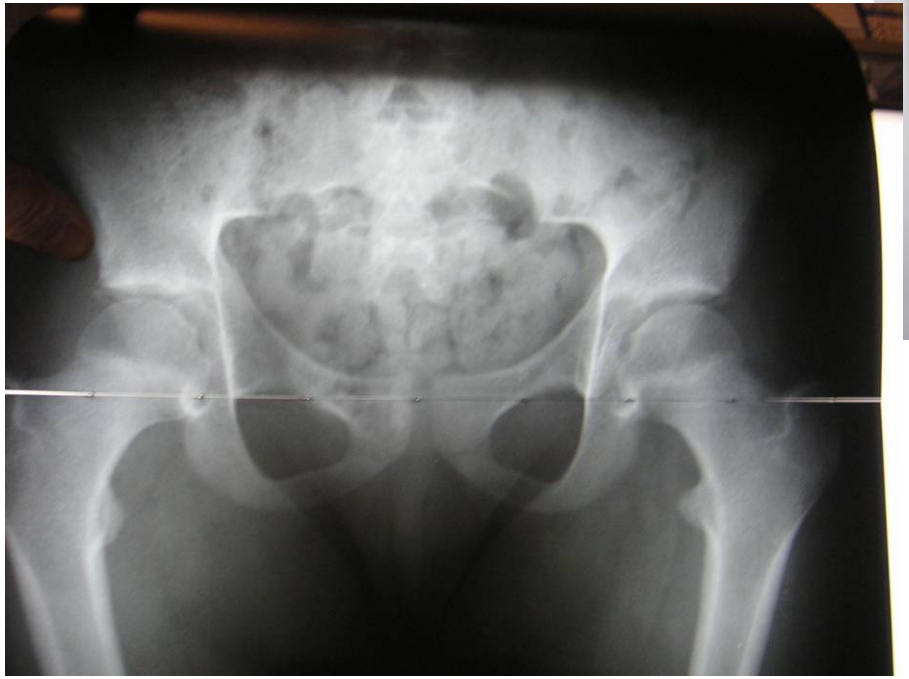
- Ravenna 1913
- Moderate short stature
- Frequency ? 1/30 000 à 1/ 40 000
- Relative micromelia
- Short hands
- Genu varum
- Adult final height variable (possible> 1m60)

Mild radiologic features

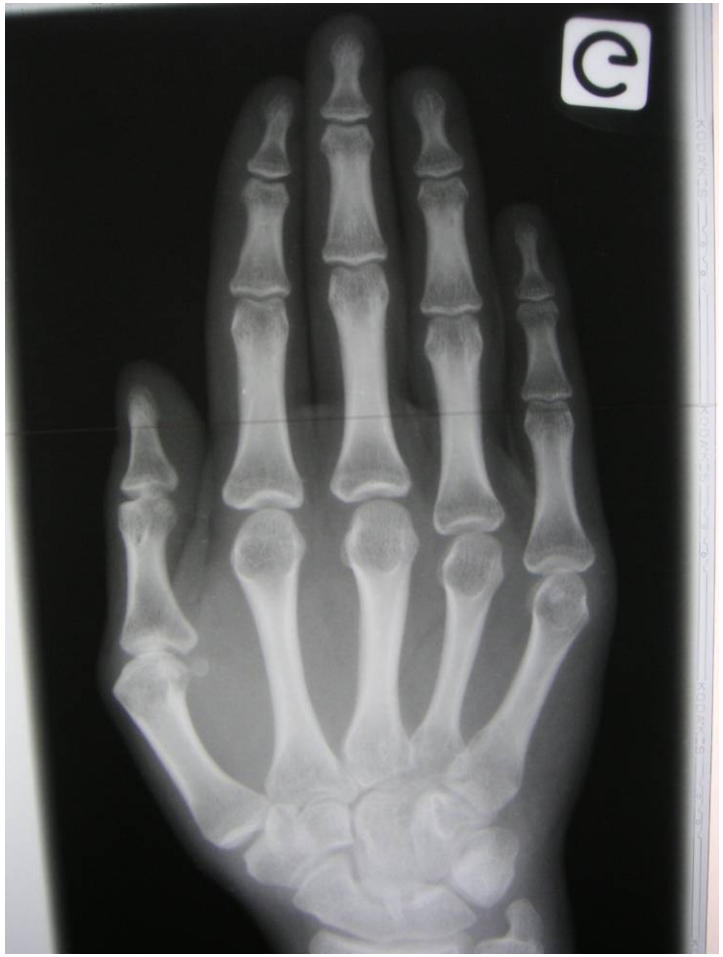
- Short femora neck
- Narrowness of lumbar vertebral cana
- Mild metaphyseal flaring
- Short hands

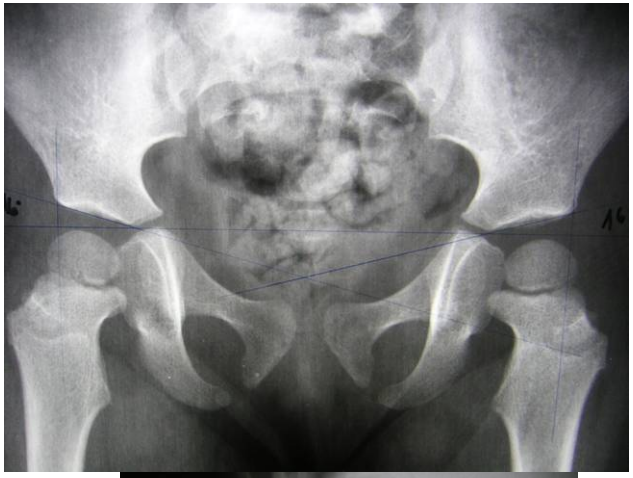


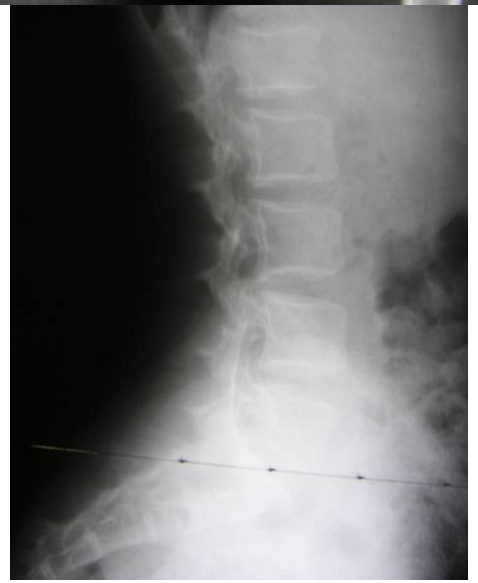


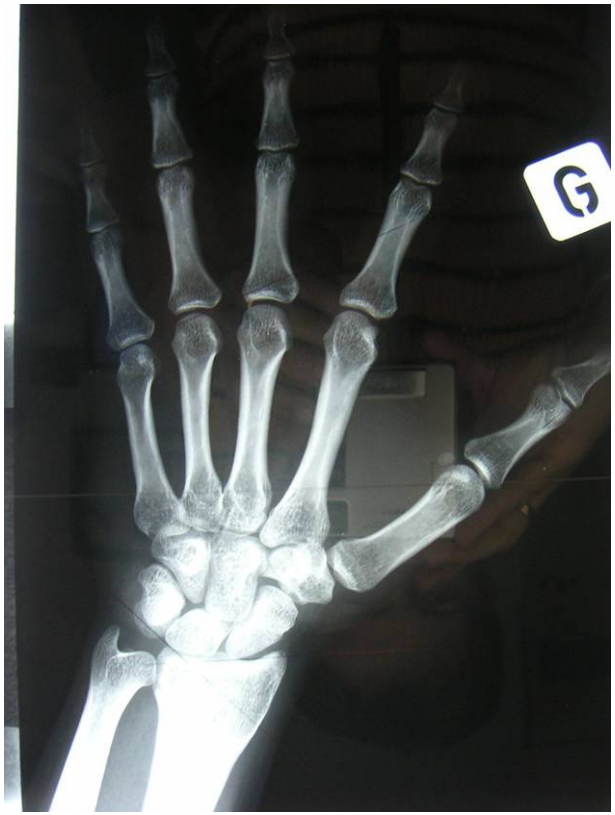


Parents often diagnosed after (because) their children





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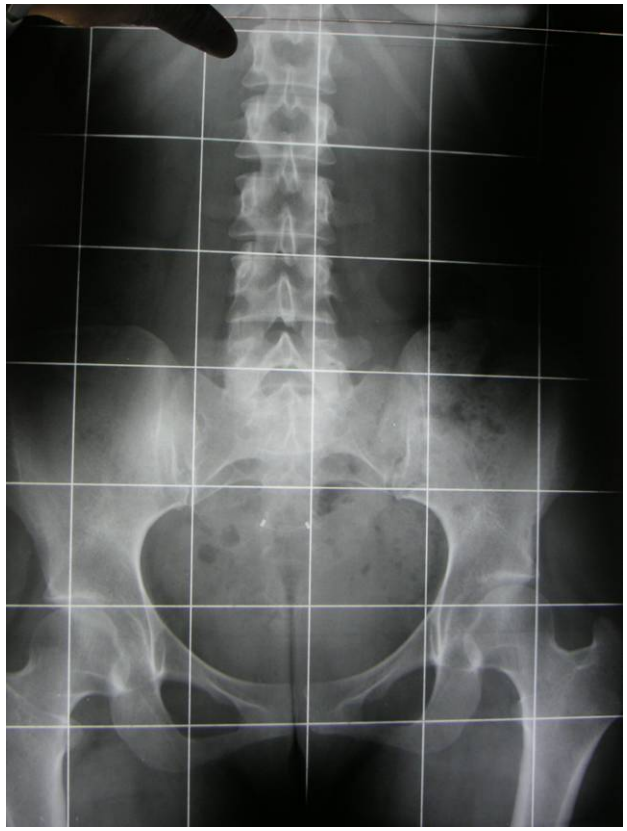
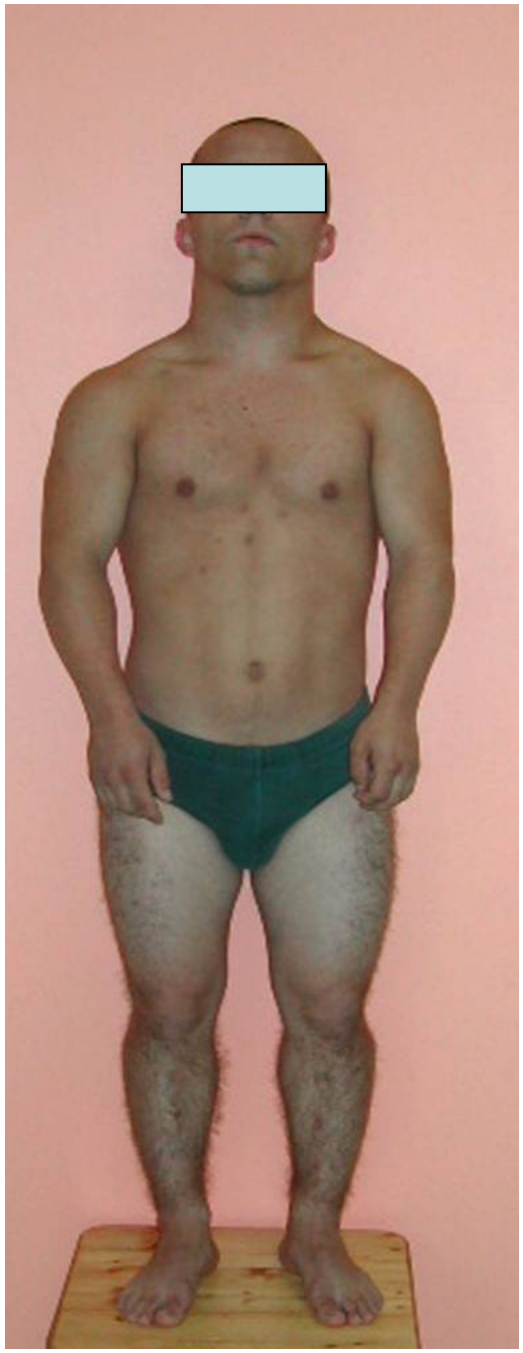




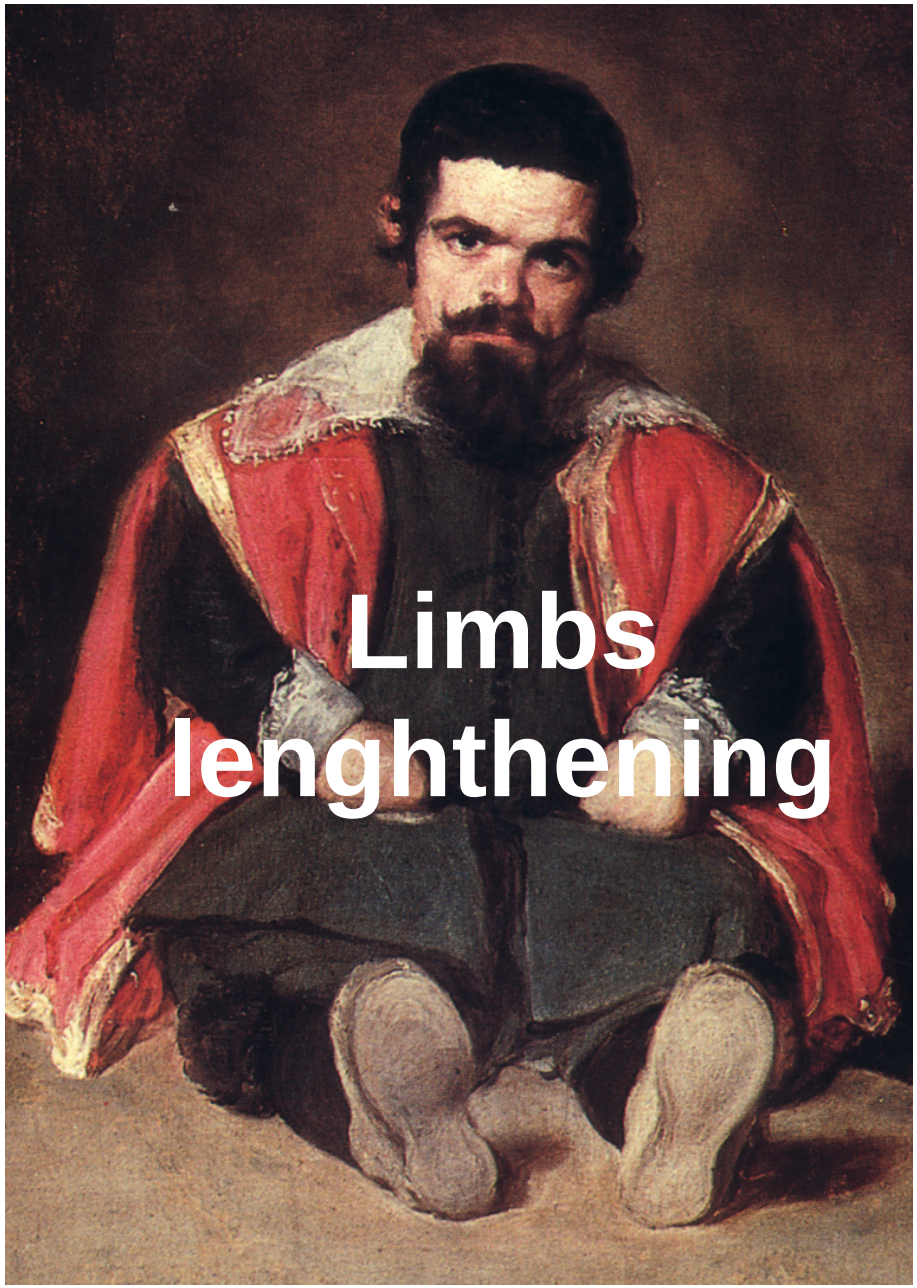
adults

Micromelia
(moderate)

height 1m35-1m65

Same rules of managment

- Legs invurvation
- Narrowness of the lumbar spine
- Limbs lenghthening
- GF Protocoles in progress (?)
- Psychological coaching
- Genetic counselling
- Molecular study


Limbs
lenghthening

Limbs lenghthening: principes

Arduous procedure, complications risks+++

1- Wait for the patient wish
Informations
Motivations

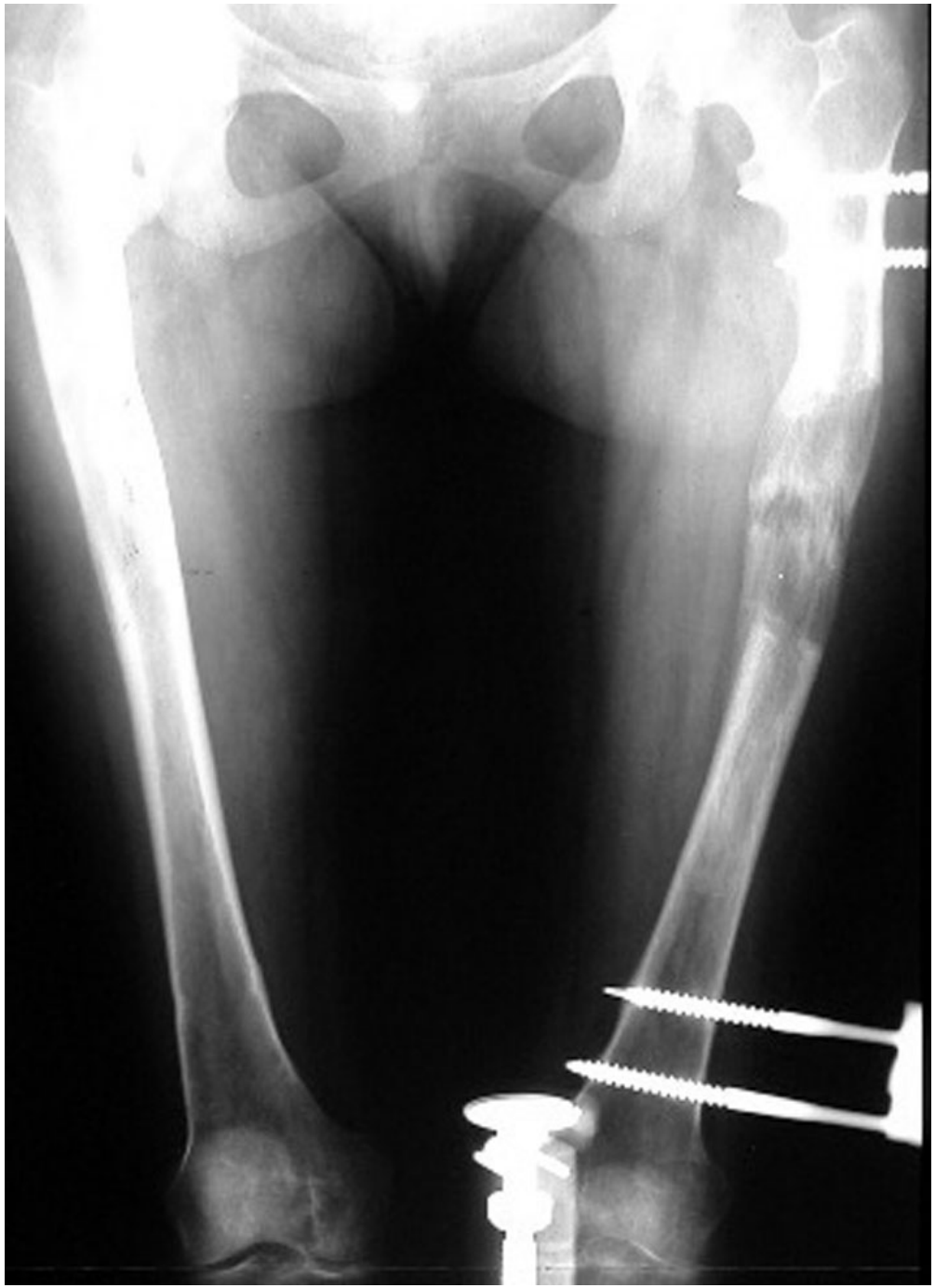
2 - Importance of a psychologist evaluation and support
No surgery if moral difficulties / pain

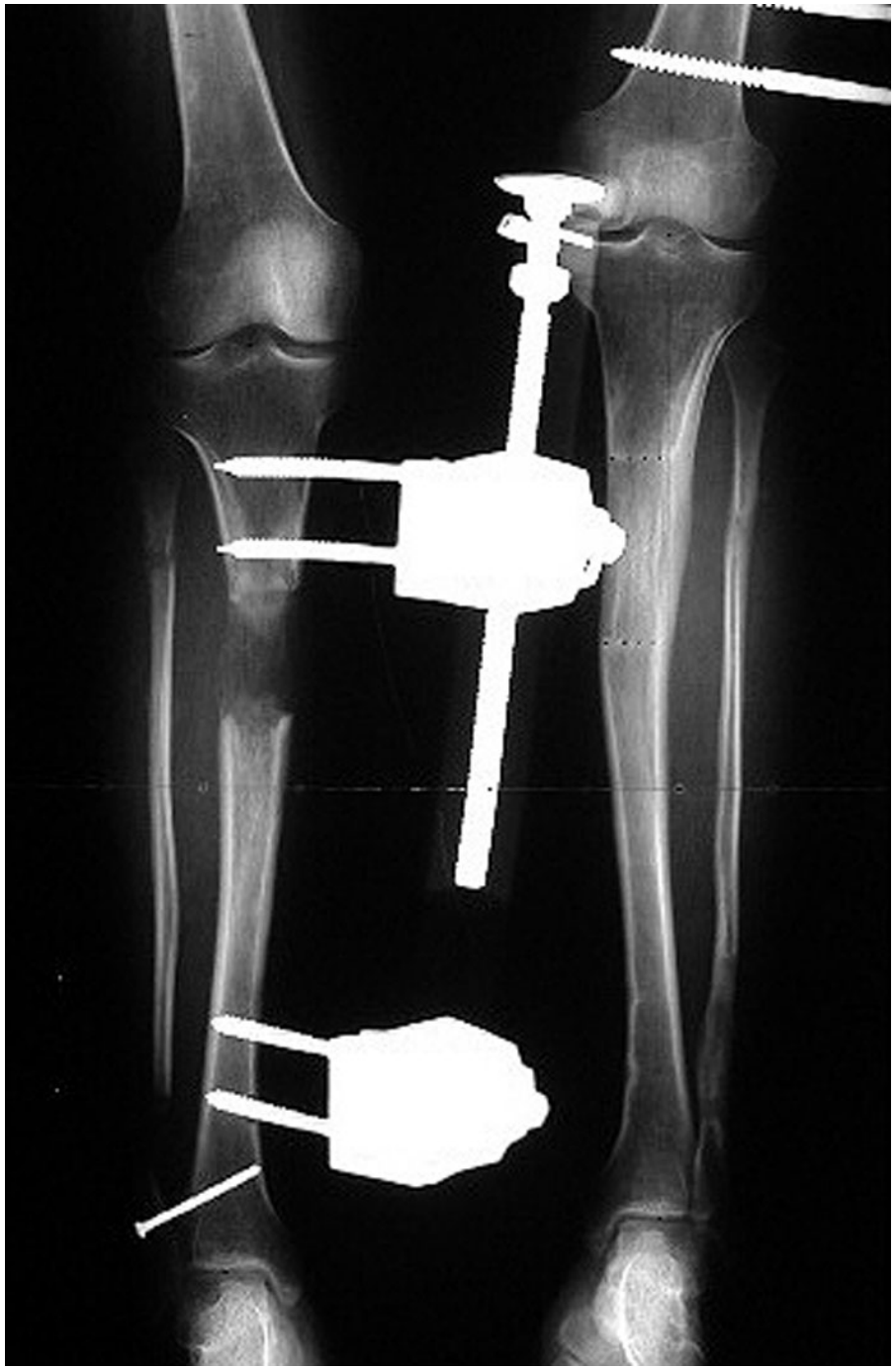
3 - Wait for a reflexion delay
Contact with other patients with limb lenghtening

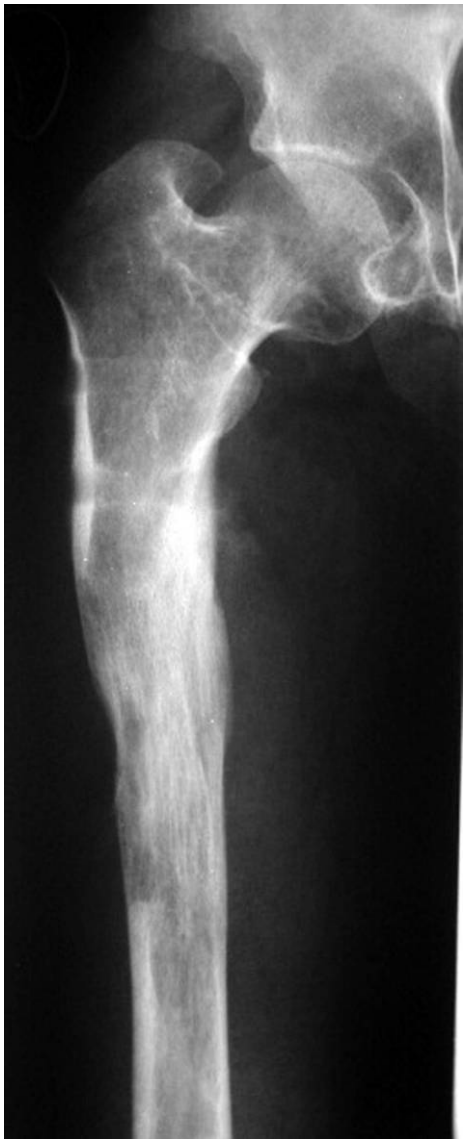
4 - No surgery
Severe forms
Neurological complications
Hip major flessum
Genu hyperlaxity

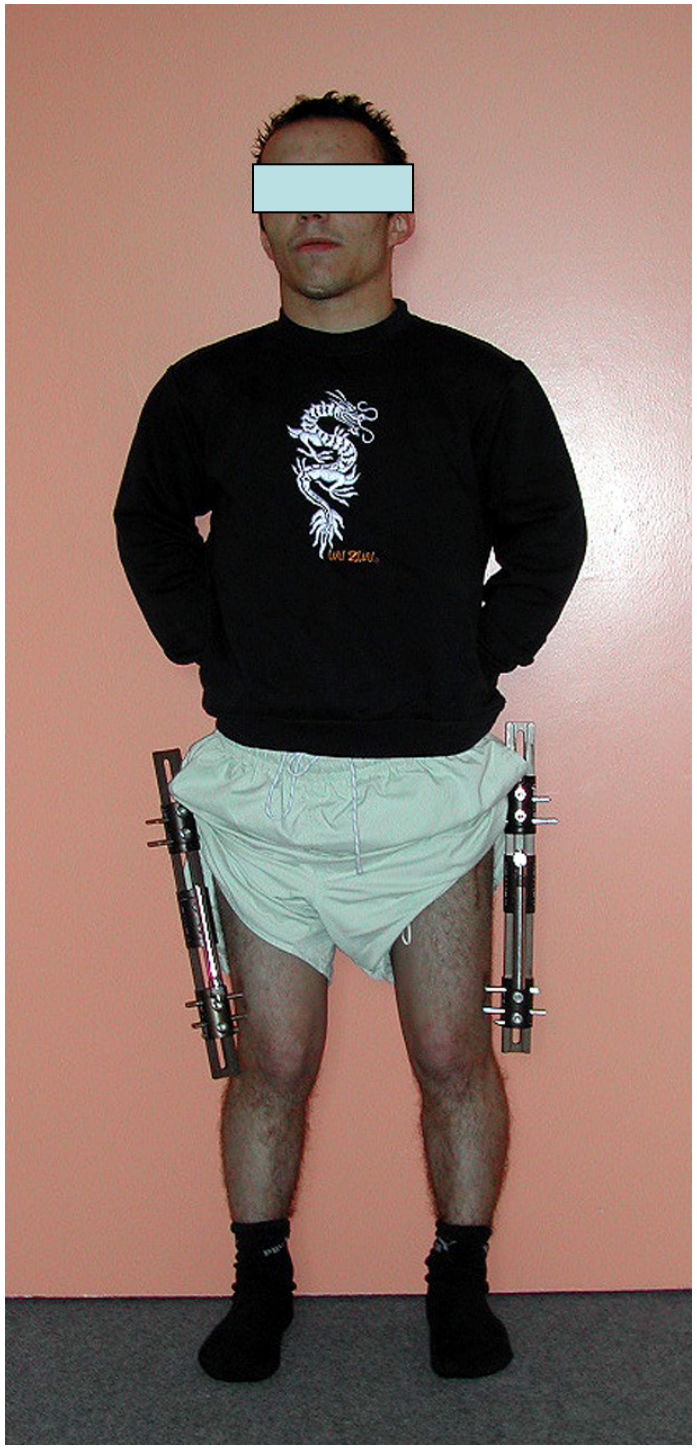
Limbs lenghthening: techniques

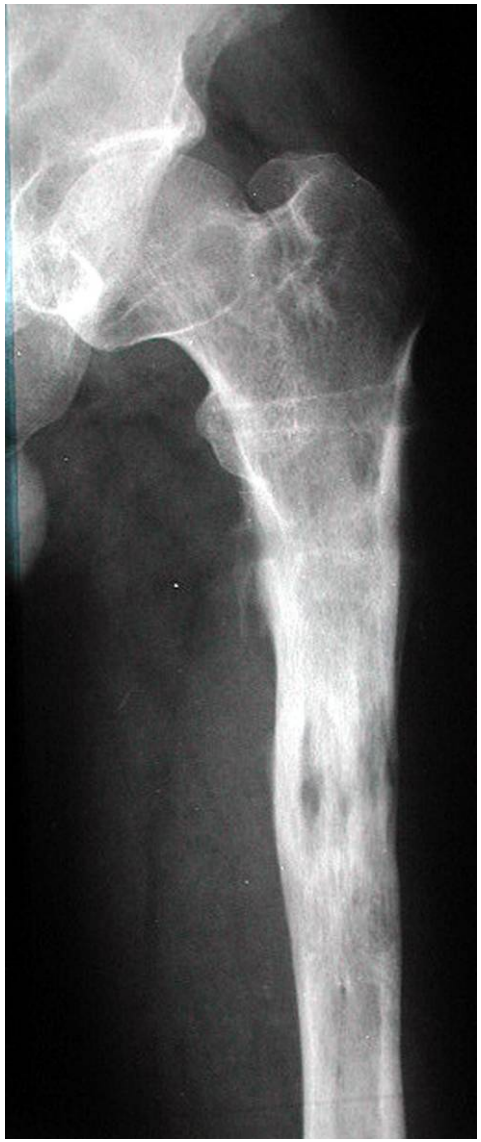
- Several procedures of surgery
  - depends of the surgeon !
  - depends of the expected lenghthening
- Centromedullar rod
- Bilateral lenghthening (no crossed)
- Lenghthening importance
  - Correlation with complications (infections, joint and soft tissue damage, pseudarthrosis)
  - Respect of body proportions

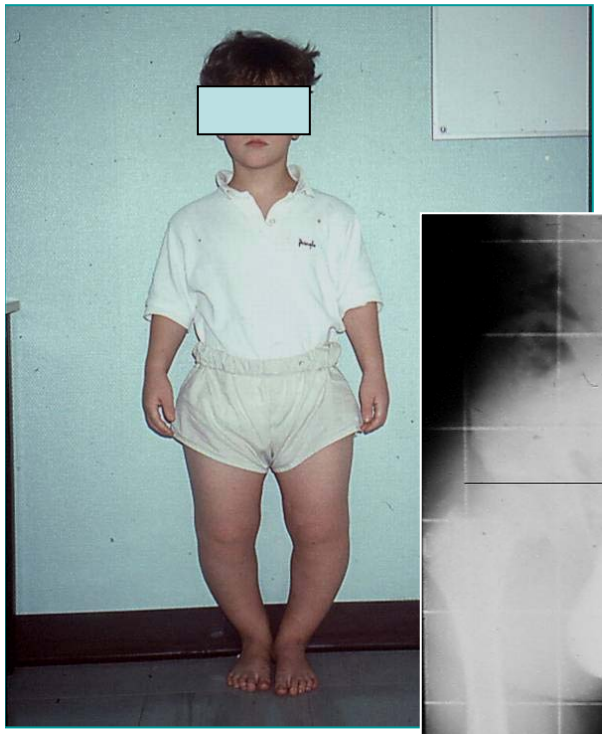


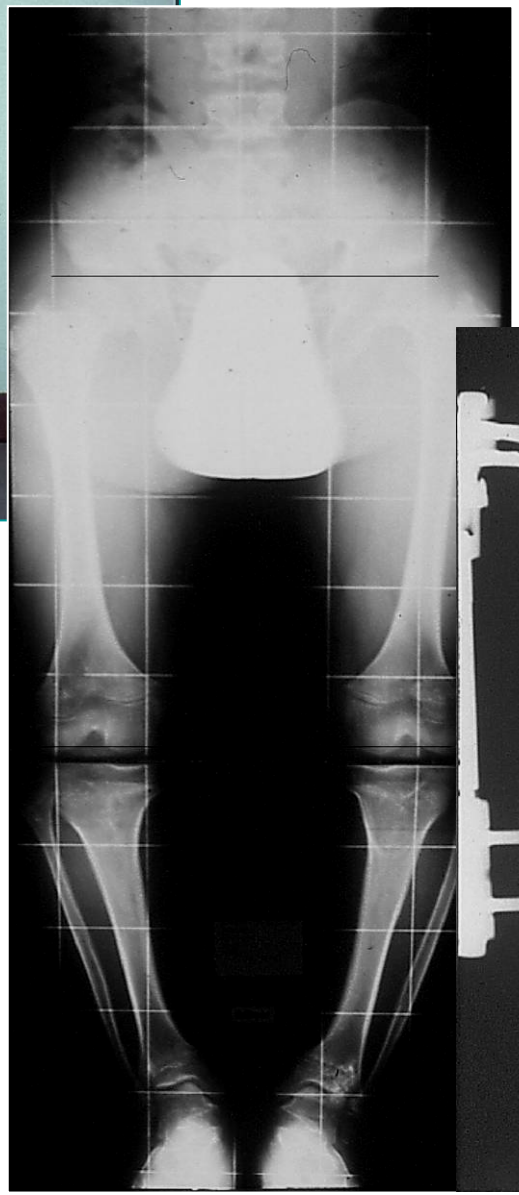


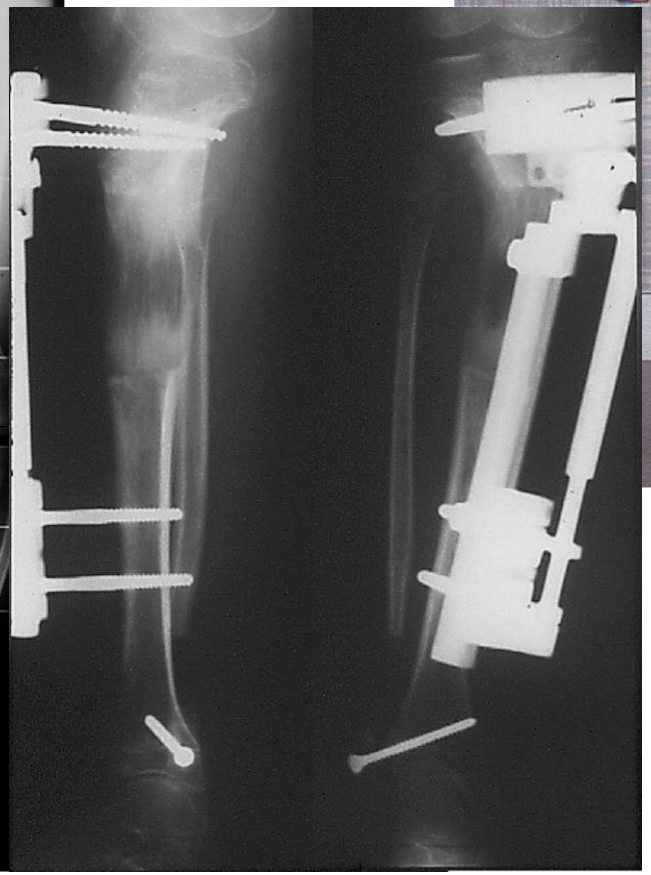


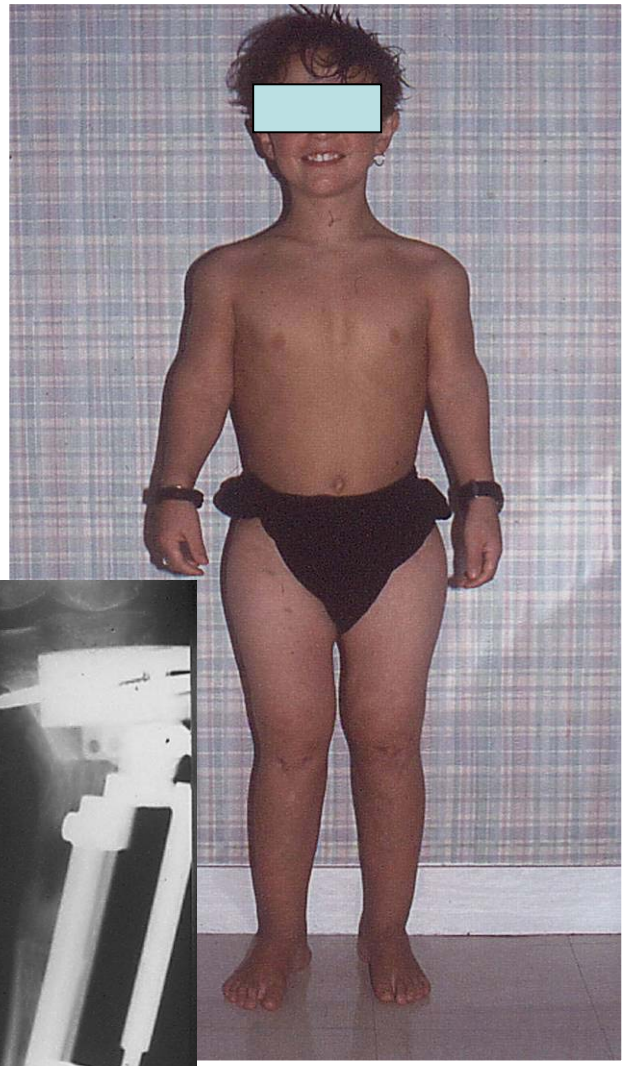


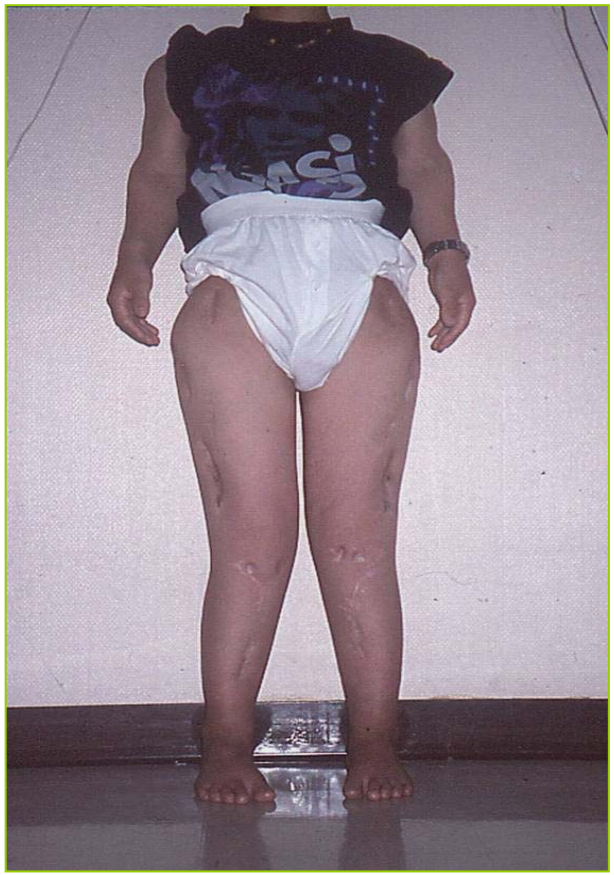


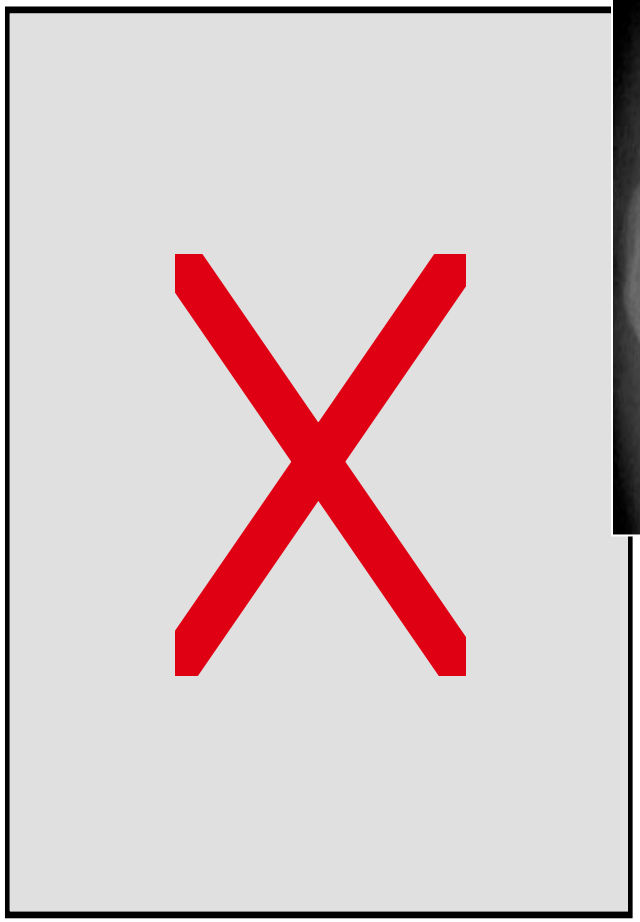


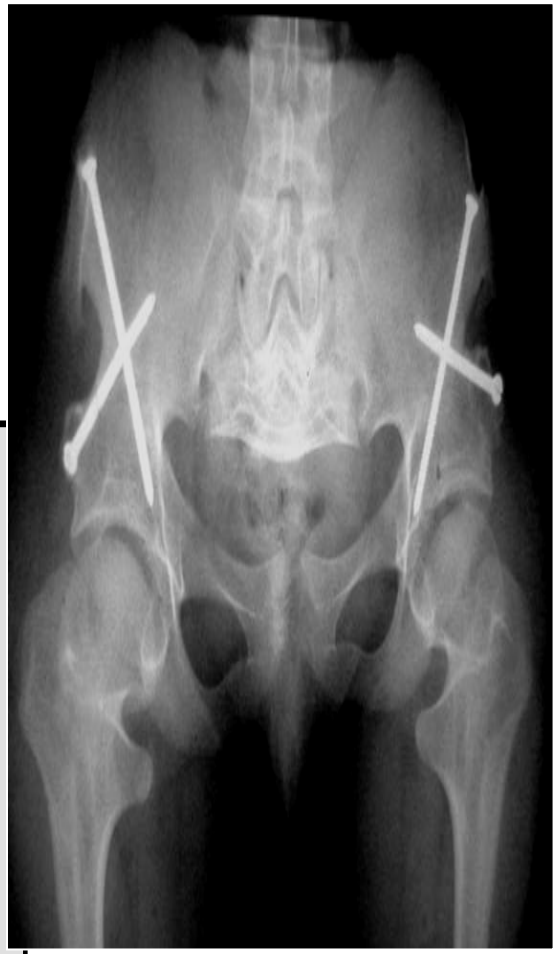




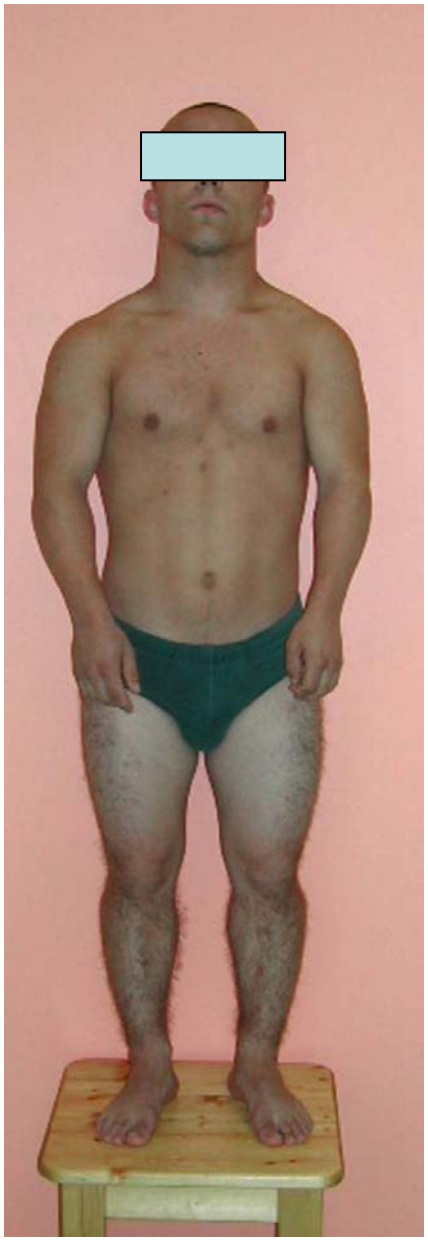


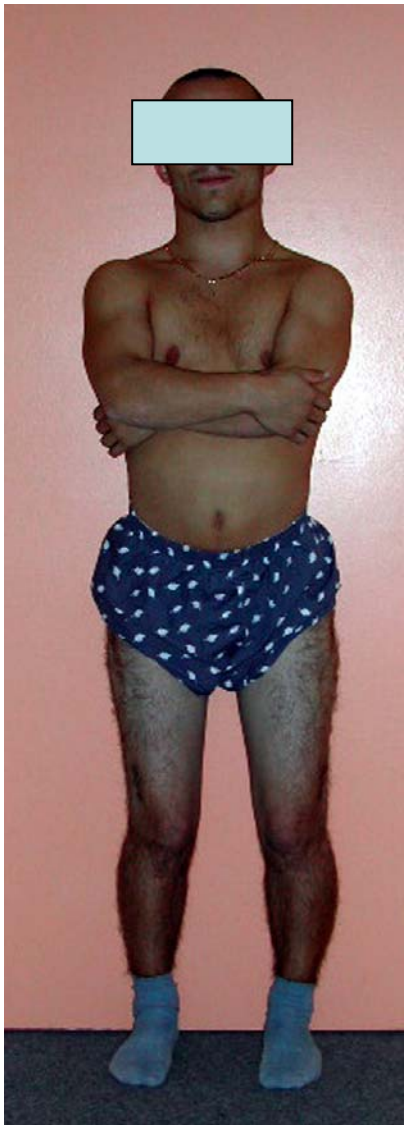






in our experience, hypochondroplasia is a better indication to such a surgery than achondroplasia





-Génétique

-M. Le Merrer
-V. Cormier Daire
-L. Legeai Mallet
-MC. Nolen
-S. Heuertz
-C. Benoît Lasselin
-E. Mugnery
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-A.Jonquoy
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- G. Finidori
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- C. Glorion
- JP Padovani
- P. Anract
- D. Hannouche

Mr Maroteaux

-Rhumatologie-R fonct

- C. Cormier
- C. Job Deslandes
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- P. Orcel
-J. Beaudreuil
- C. Roux
- V. Forin

- Anesthésistes
- Neurochirurgiens

-M. Zerah
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-S. Puget
-C. Sainte Rose
-G. Loth

-Radiologues

-K. Lambot

-Stomatos

-Pr Ginisty
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-ORL

-Y. Manach
-S. Pierrot
-V. Couloigner

-Psychologues

-MC. Nolen
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