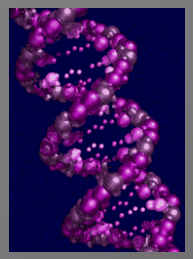


Osteogenesis Imperfecta

Geneviève Baujat

genevieve.baujat@nck.aphp.fr

Centre de Référence
Maladies Osseuses Constitutionnelles
Necker-Enfants Malades, Paris, France

BOLOGNE 13 Mai 2009

Osteogenesis Imperfecta

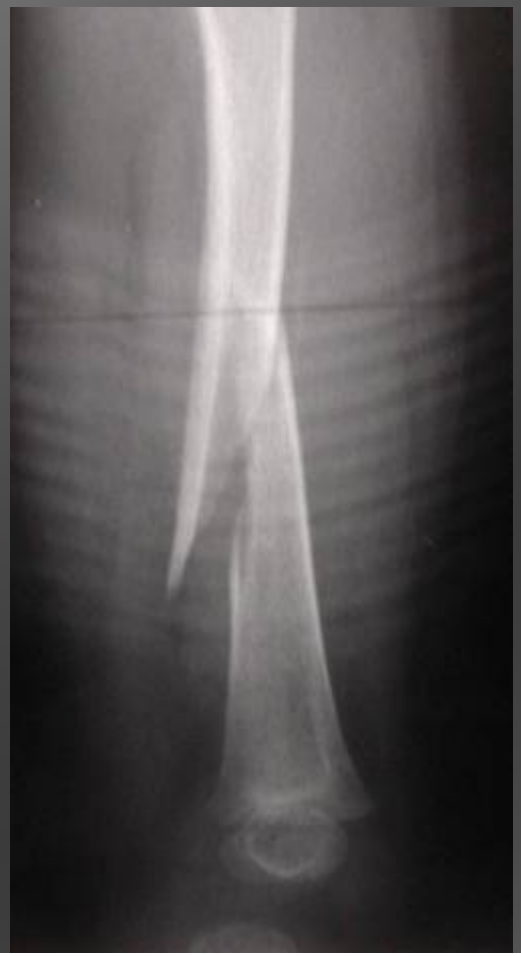
- Brittle bone disease
- Lobstein disease
- Porak and Durante disease (antenatal types)
- OI

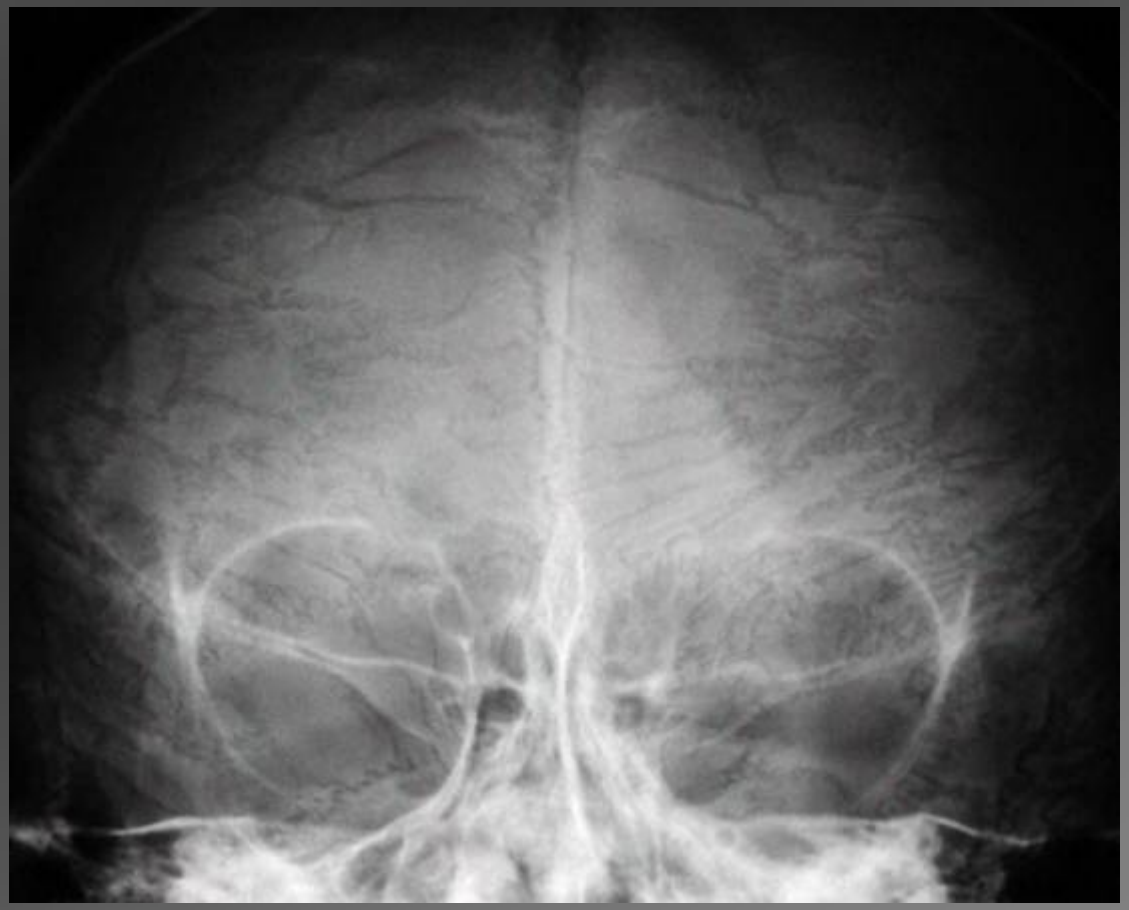
  - Heritable genetic disorder
  - Increased bone fragility, low bone mass
  - Incidence 1/10 000 births
  - Variability
  - *COL1A1, COL1A2, LEPRE1, CRTAP*

OI is a clinical & radiological disease

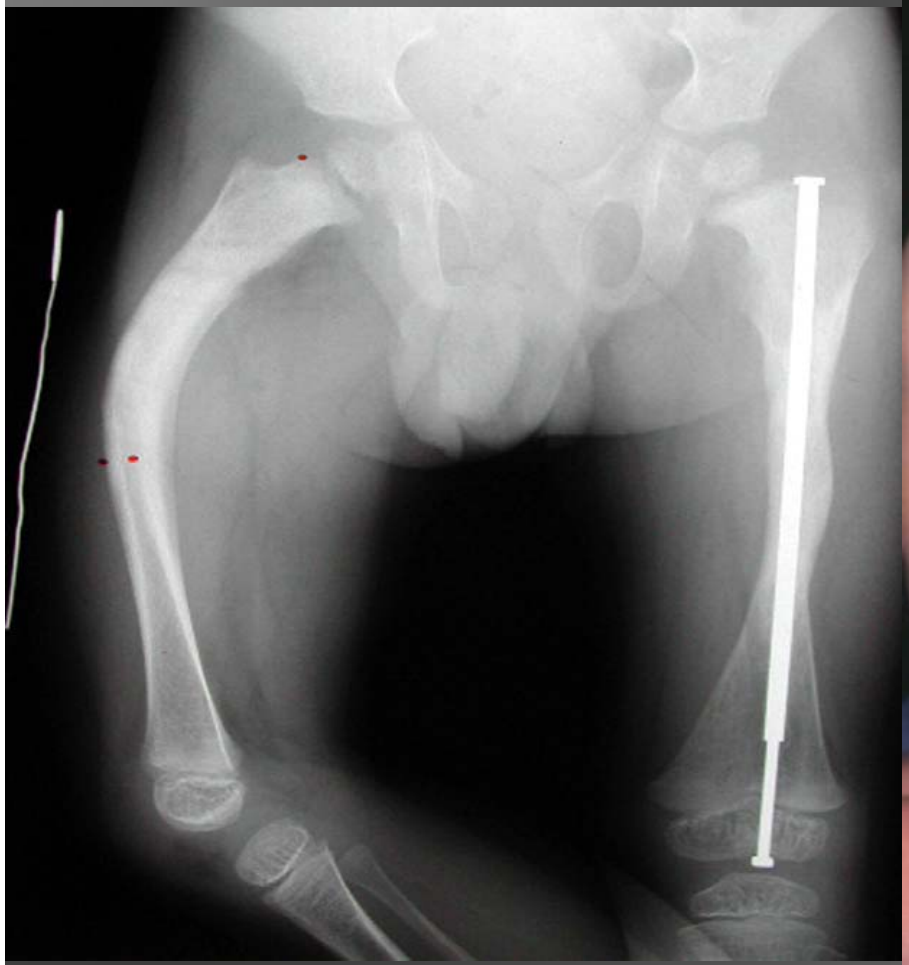
Skeletal features

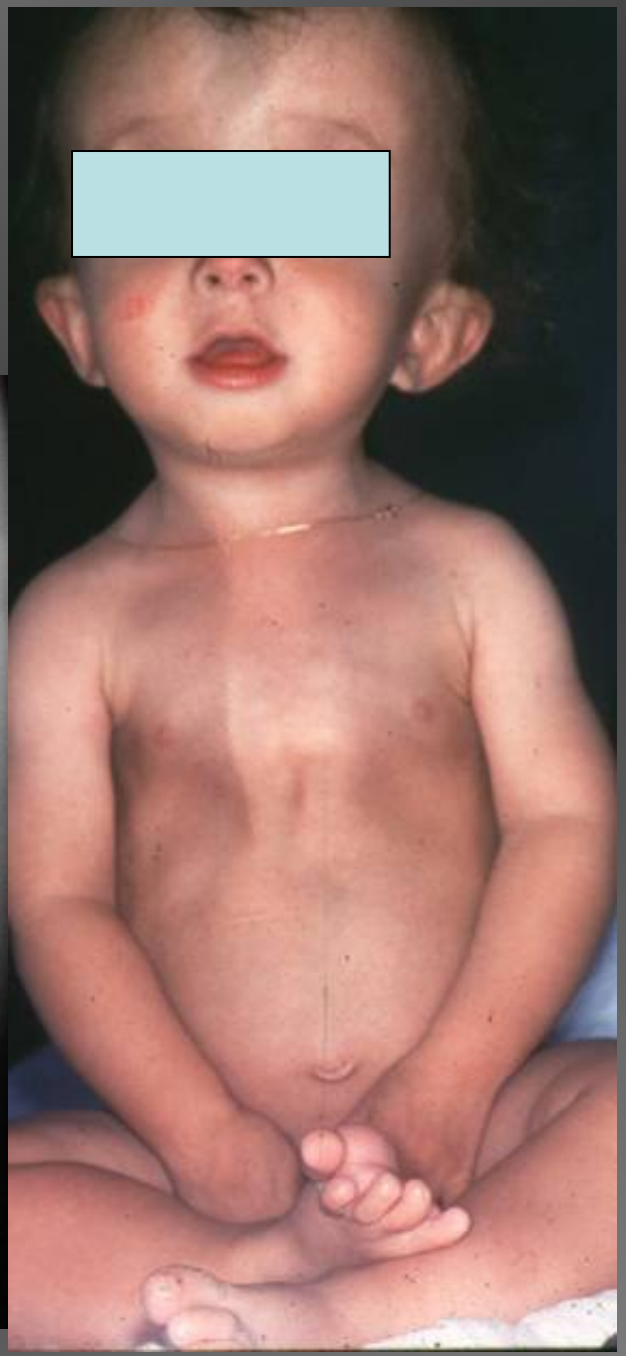
- Increased susceptibility to fractures
- Wormian bones (+/-)

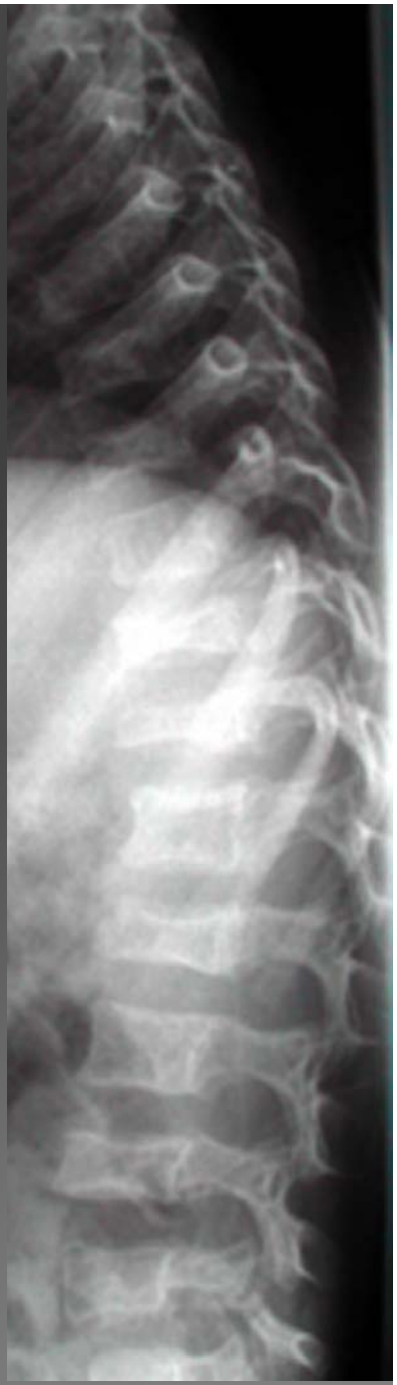




- deformities
- platyspondyly

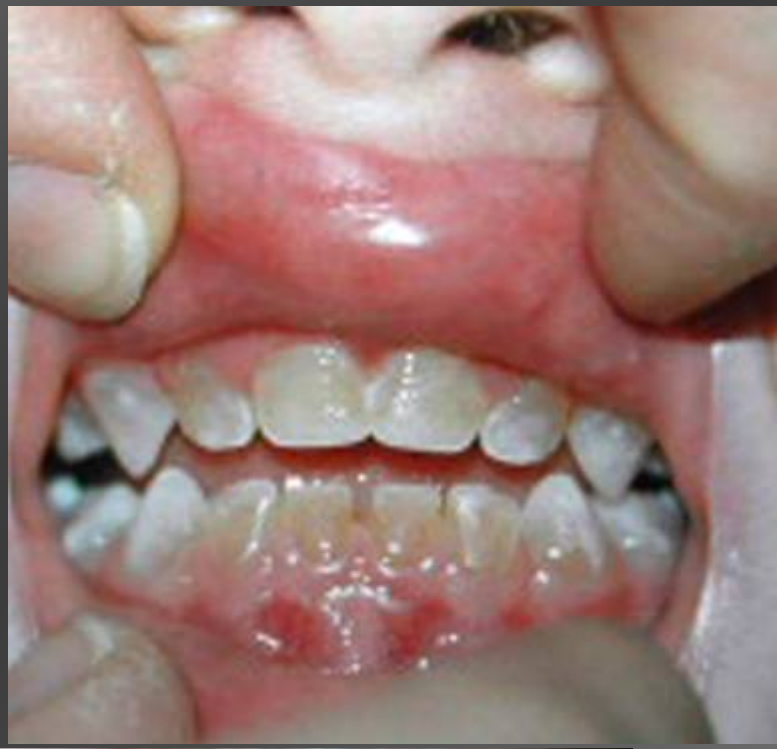






Extraskeletal features

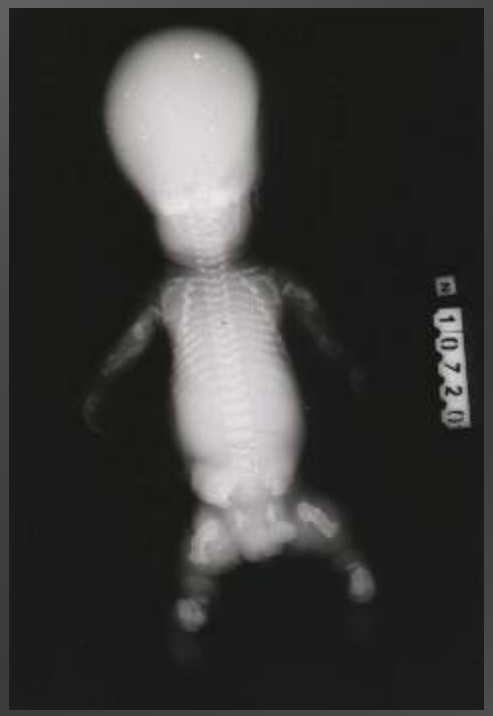
- Blue sclera
- Dentinogenesis imperfecta



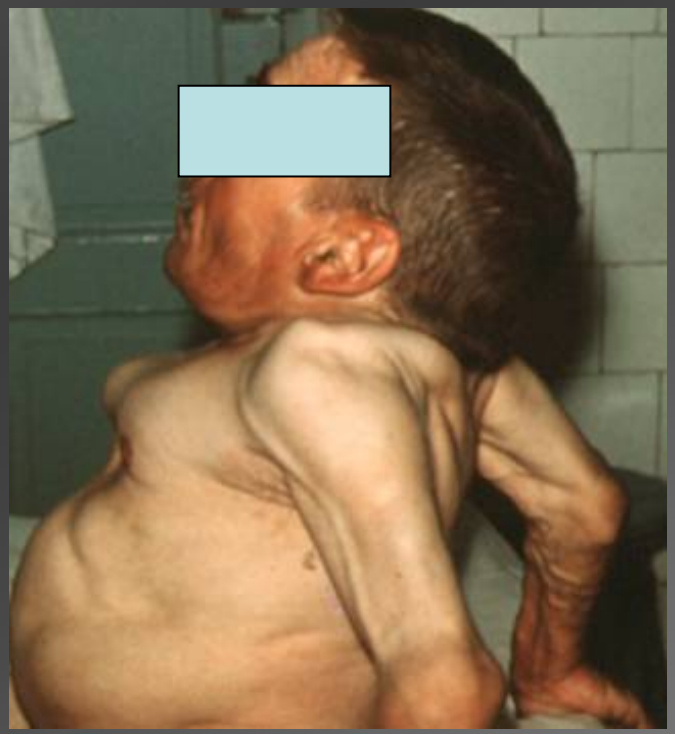
- Variable short stature
- Skin hyperlaxity
- Joint hypermobility
- Ecchymosis tendency
- Hearing loss

Severity: a continuum

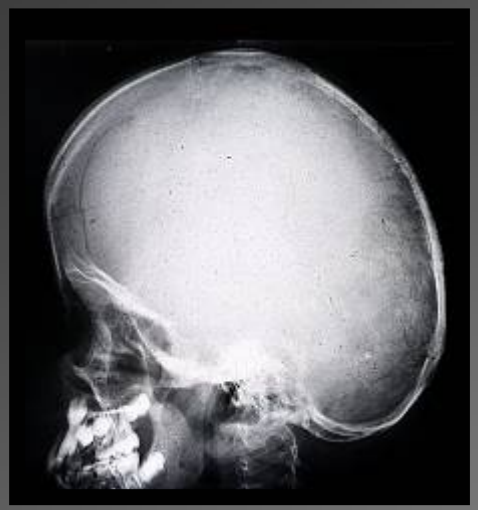
Lethal



Severe



Moderate



Sillence et al. classification (1979, 2002, 2007)

- **Type I**: mild non deforming, blue sclera (BS), stature: normal or mild short
  - IA : DI +
  - IB : DI -
- **Type II**: perinatal lethal, rib and long bone fractures at birth, low density of skull bones on radiographs; dark sclera
- **Type III**: severly deforming, greyish sclera; DI +; triangular face; very short
- **Type IV**: moderately deforming and short, DI +; +/- BS
- **Type V**: moderate short stature, mineralised interosseous membrabne, hyperplastic callus, white sclera, no DI.
- **Type VI**: moderately short; scoliosis, accumulation of osteoid in bone tissue, osteomalacia; no DI; white sclera; AR
- **Type VII**: isolat (Quebec), coxa vara, short femur and humerus; white sclera, no DI; AR
- **Type VIII**: severe, deformations

Nosology and Classification Osteogenesis Imperfecta Syndromes 2007

David Sillence
Centre for Children's Bone Health
and
Connective Tissue Dysplasia Service

Proposed Molecular Nosology June 2007

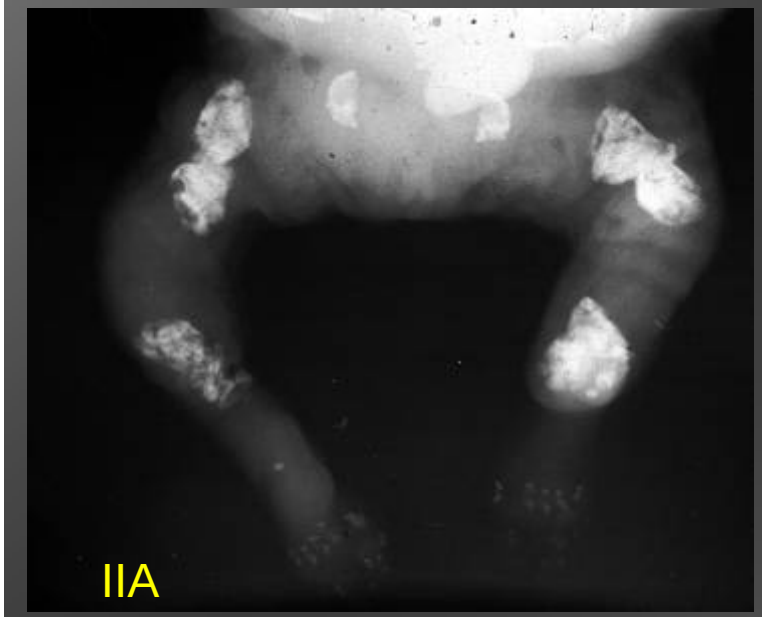
Phenotypic/ Numerical Nosology	Gene Locus	Genomic	Phenotype/Genotype
I	COL1A1	Nonsense mutations (Gly→X) fs→nonsense	Dominantly inherited OI with distinctly blue sclerae
IIA	COL1A1	Missense mutations (disrupting triple helical assembly)	Perinatally lethal OI
IIIA	COL1A1	Missense mutations (disrupting triple helical assembly)	Progressive deforming OI with normal sclerae
IV	COL1A1	Missense mutations (disrupting triple helical assembly)	Dominantly inherited OI (moderate) with normal sclerae
Disorders due to mutations in COL1A2			
I	COL1A2	Nonsense mutations (rare)	Dominantly inherited OI with distinctly blue sclerae
I	COL1A2	Multi-exon (in frame) deletions	Dominantly inherited OI and opalescent dentine
IIB	COL1A2	Missense mutations which affect triple helical folding	
IIIB	COL1A2	Missense mutations Deletions	Progressive deforming OI with normal sclerae
IV	COL1A2	Missense mutations	Dominantly inherited OI (moderate) with normal sclerae
DISORDERS RESULTING FROM MUTATIONS IN 2-DIOGENASES			
Disorders resulting from mutations in genes affecting lysyl hydroxylation			
Bruck type II	PLOD2	Missense	OI with congenital joint contractures
Bruck type I	THL1		OI with congenital joint contractures
Disorders resulting from mutations in genes regulating prolyl 3-hydroxyaltion			
IIC	CRTAP	fs→nonsense	Perinatally lethal OI with crumpled bones and beaded ribs (AR)
IIIC	CRTAP		Progressively deforming OI
VII	CRTAP	Complex missense/activation of cryptic splice	Rhizomelic progressively deforming OI (AR)
Proposed VIII (OI type III D)	P3H1/Lepre1	IVS 5 + 1G > T c.788deL C	Progressively deforming OI (AR) Founder African mutation

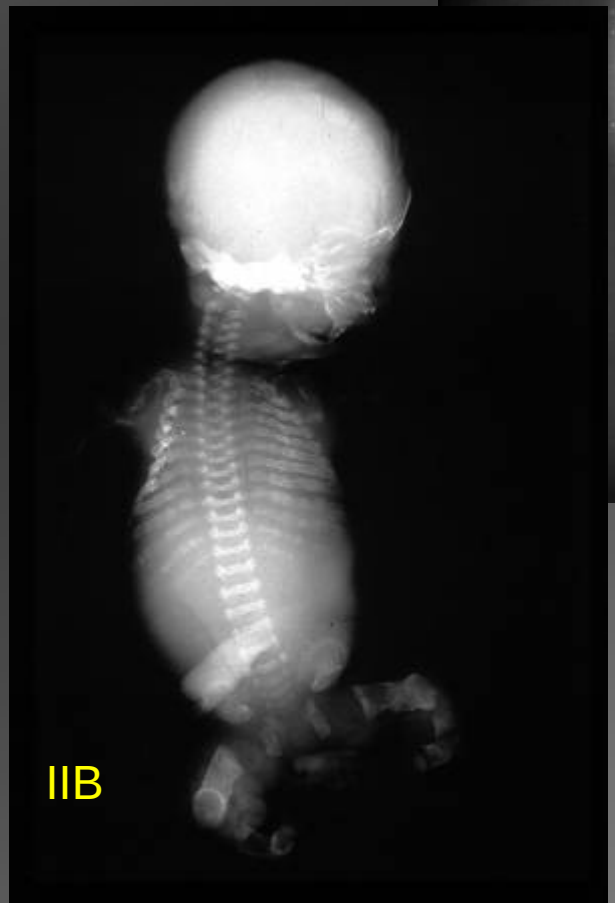
Antenatal lethal

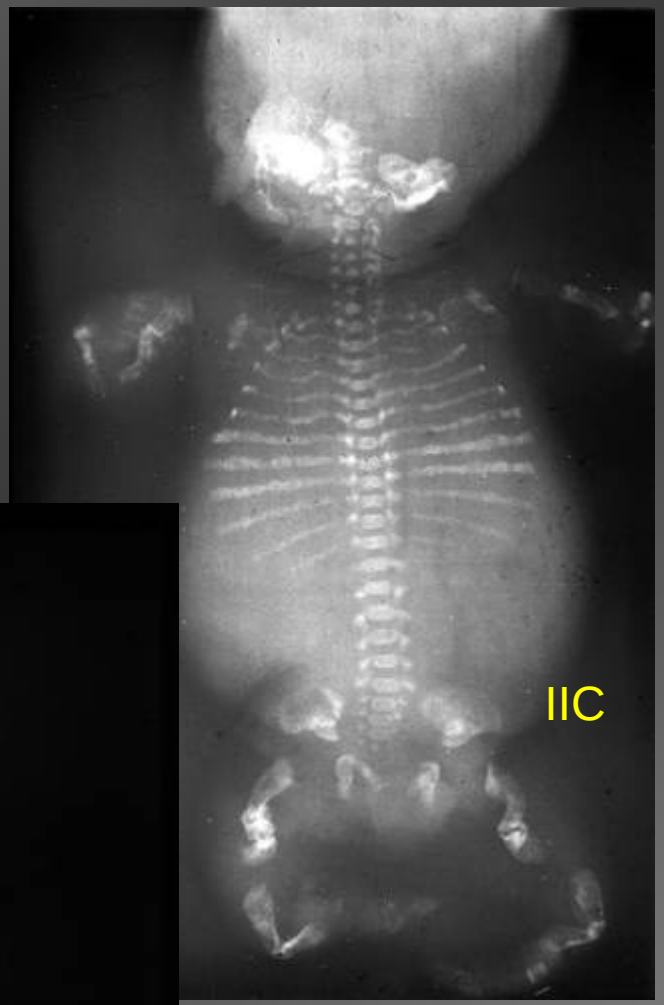
IIA : broad ribs, continuous fractures broad long bones, crumpled femora

IIB : ribs discontinuous fractures, long tubular bones, thin cortical

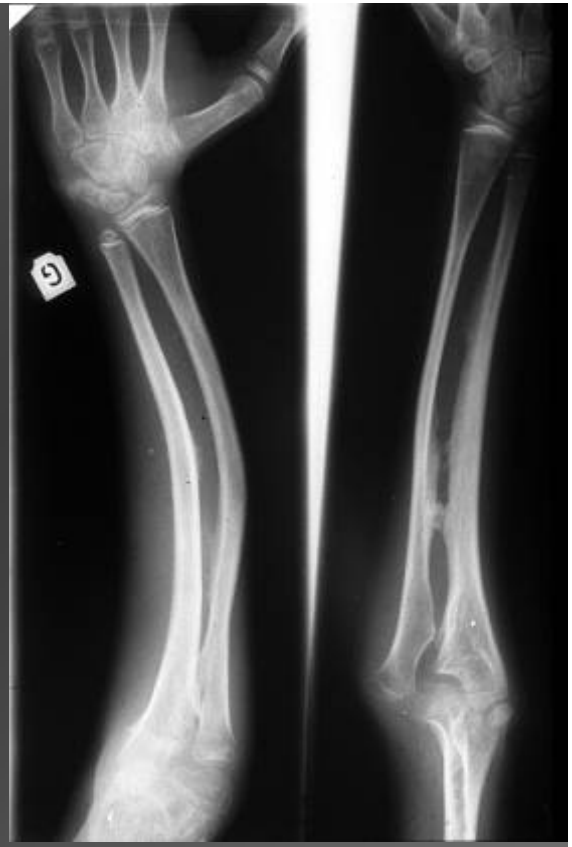
IIC : slender and twisted long bones, almost normal spine bones, discontinuous beading of the ribs







Type V



- Moderate to severe fragility
- Rare (5%)
- Calcification of the interosseous membrane at the forearm early in life
  - Limitation of movements of the hand
  - Discolation of the radial head
- Hyperplastic callus after fracture or surgical interventions (≠osteosarcoma)
- Heredity ? Seems autosomal dominant
- No evidence for COL1 abnormality

Differential diagnosis

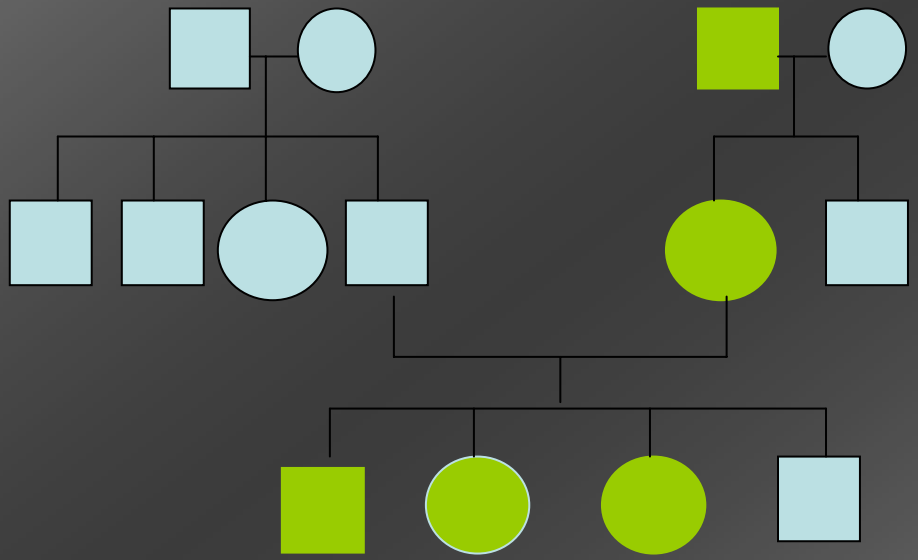
- **During pregnancy**
  - Campomelic
  - Stüve et Wiedemann
  - Femoral hypoplasia
  - hyperphosphatasia
- **At birth**
  - hypophosphatasia
  - I cell disease
  - Brück (congenital joint contractures)
  - Cole Carpenter (craniostenosis)

- **Infancy** :
  - child abuse (Silvermann)
    - 3 - 18 months
    - difficult situation
    - family history
    - X-ray absorptiometry : no range before 1y.

- childhood
  - Ehler Danlos
  - Hemopathy
  - Juvenile Paget’s disease
  - Juvenile idiopathic osteoporosis

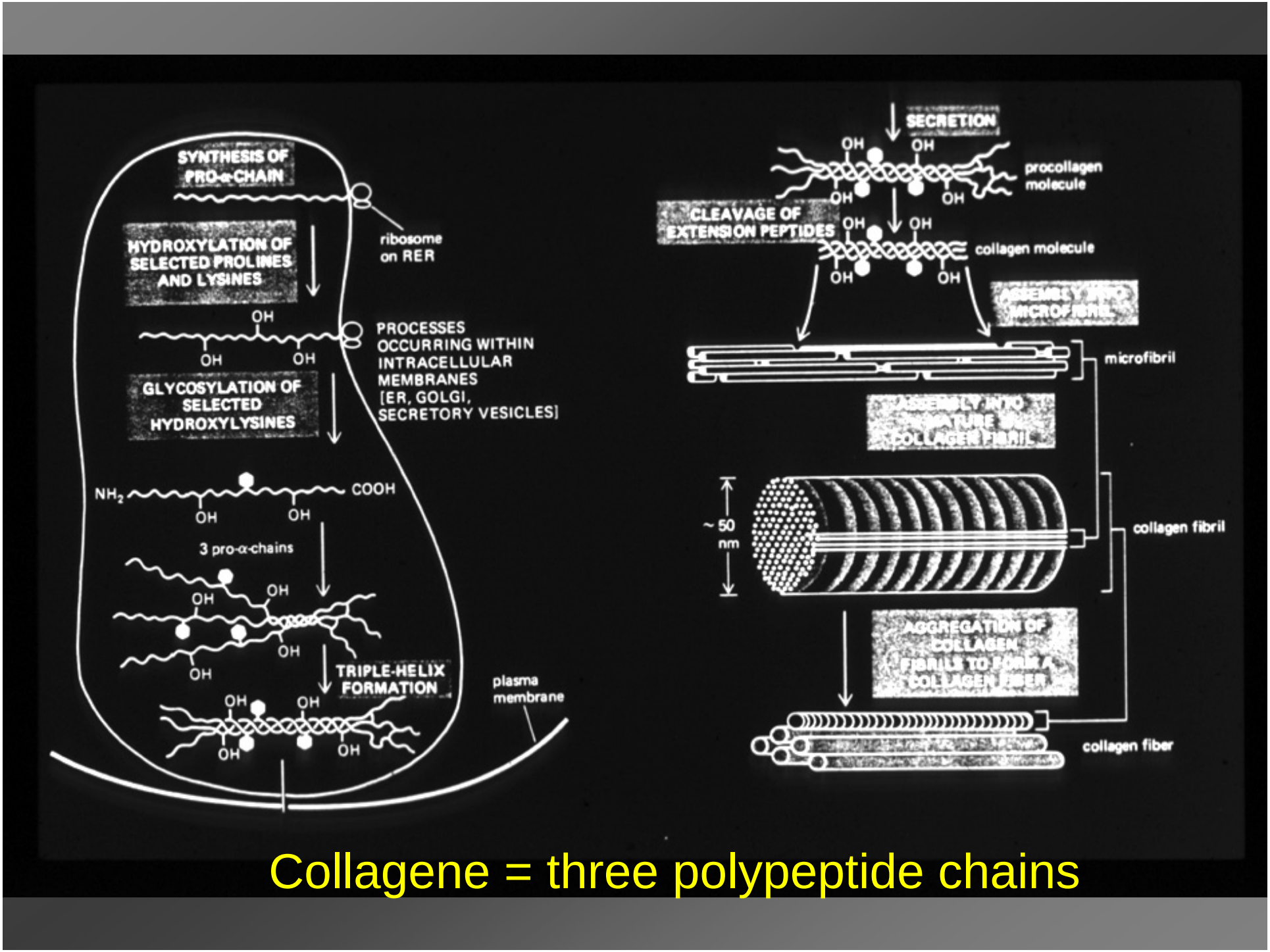
Pathogenesis

Dominant OI ++++

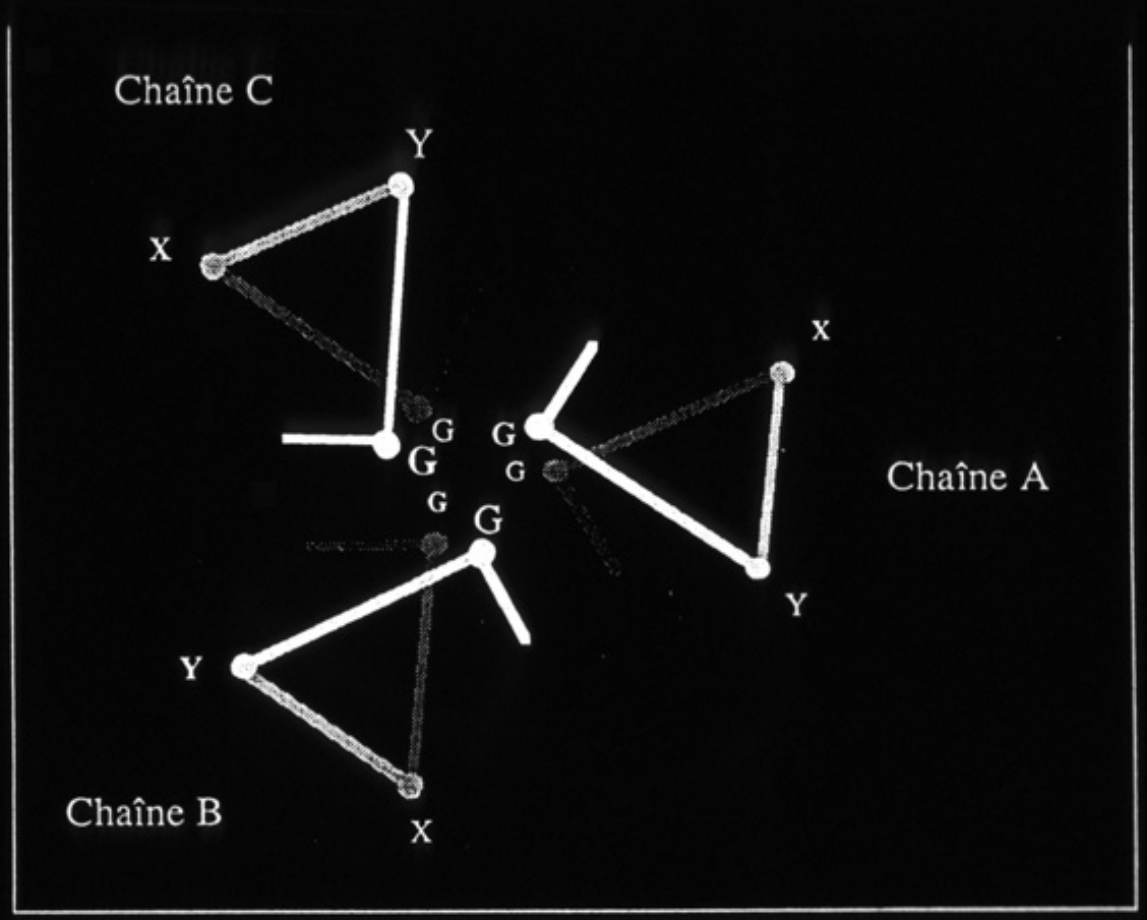


Dominant OI

- Autosomal dominant OI (> 90%)
- Heterozygosity for mutations in the COL1
  - *COL1A1* 17q21-22
  - *COL1A2* 7q21-22
- Paternal age in sporadic cases
- Recurrence: 6-10% (germinal mosaïcism)



Collagene = three polypeptide chains



Glycine residues

Figure 1. ***Représentation schématique d'une coupe transversale de la triple hélice du collagène.*** *Trois chaînes polypeptidiques hélicoïdales (A, B et C) s'enroulent entre elles pour former la triple hélice. Seuls sont indiqués les carbones α des acides aminés constituants. Les liens peptidiques sont symbolisés par les droites. Les résidus glycines (G) occupent le centre de l'hélice alors que les résidus X sont souvent de la proline et Y de l'hydroxyproline. Les tailles et l'intensité des traits et des lettres suggèrent l'éloignement par rapport au plan de la figure.*

Recessive OI

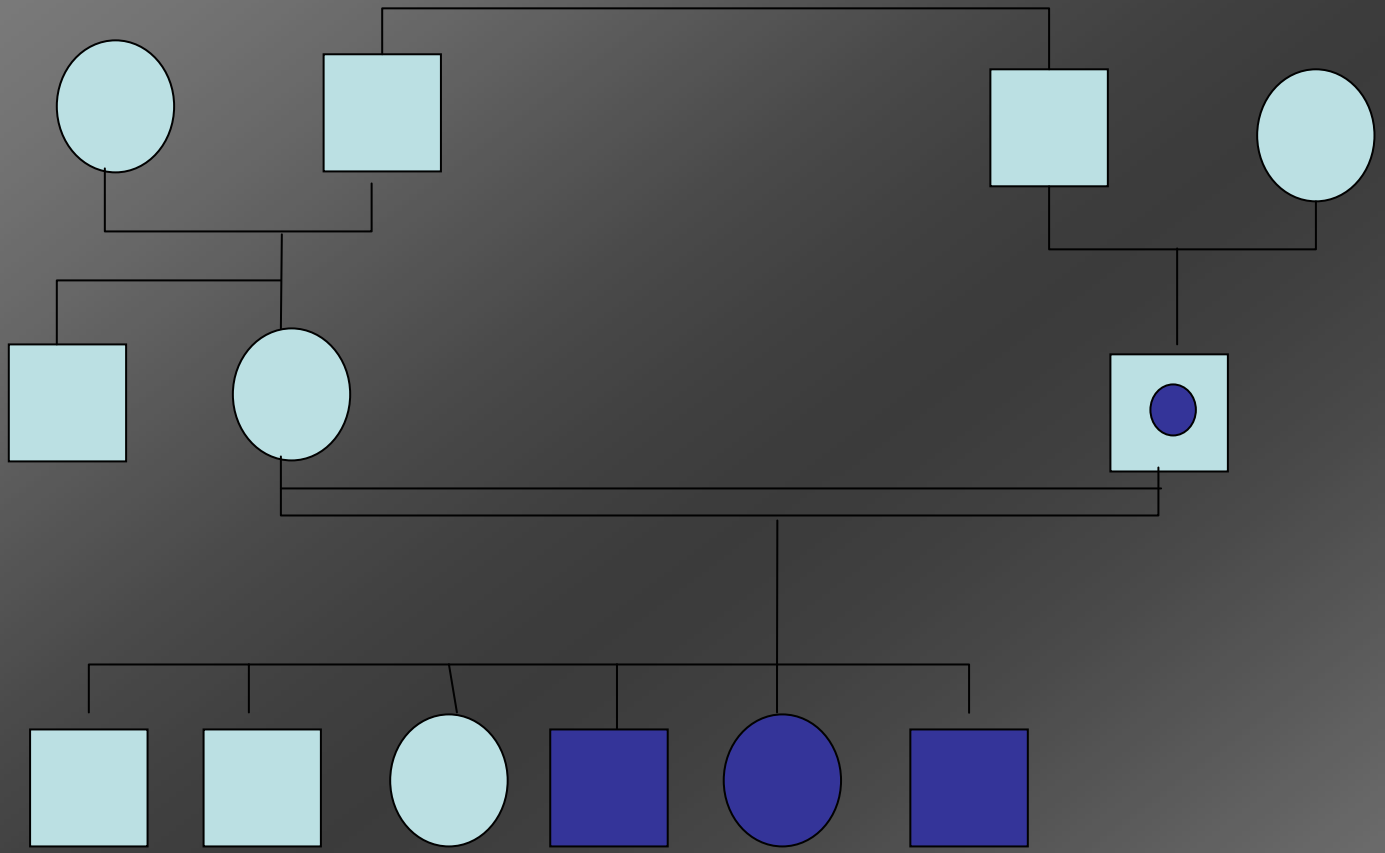
- Rares
- Exceptional observations of recessives forms with homozygosity for *COL1*

  (de Paepe et al , Hum Genet 1997,99:478-83)

  – Parents with mild OI, first cousins
  – Children with severe OI
  – Mutation *COL1A2*

- Other genes recently identified

OI: germinal mosaïcism or recessivity ?

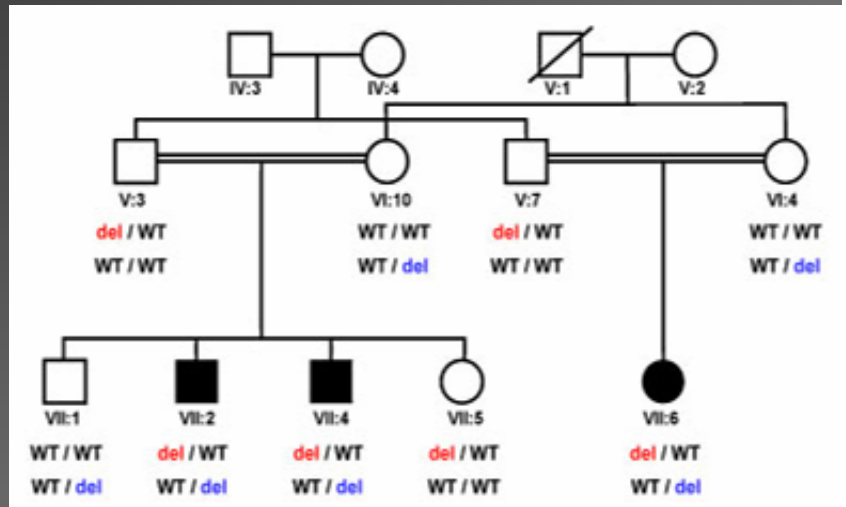


COL1A1 exon 38 -18 C>G

Osteogenesis imperfecta, ocular form

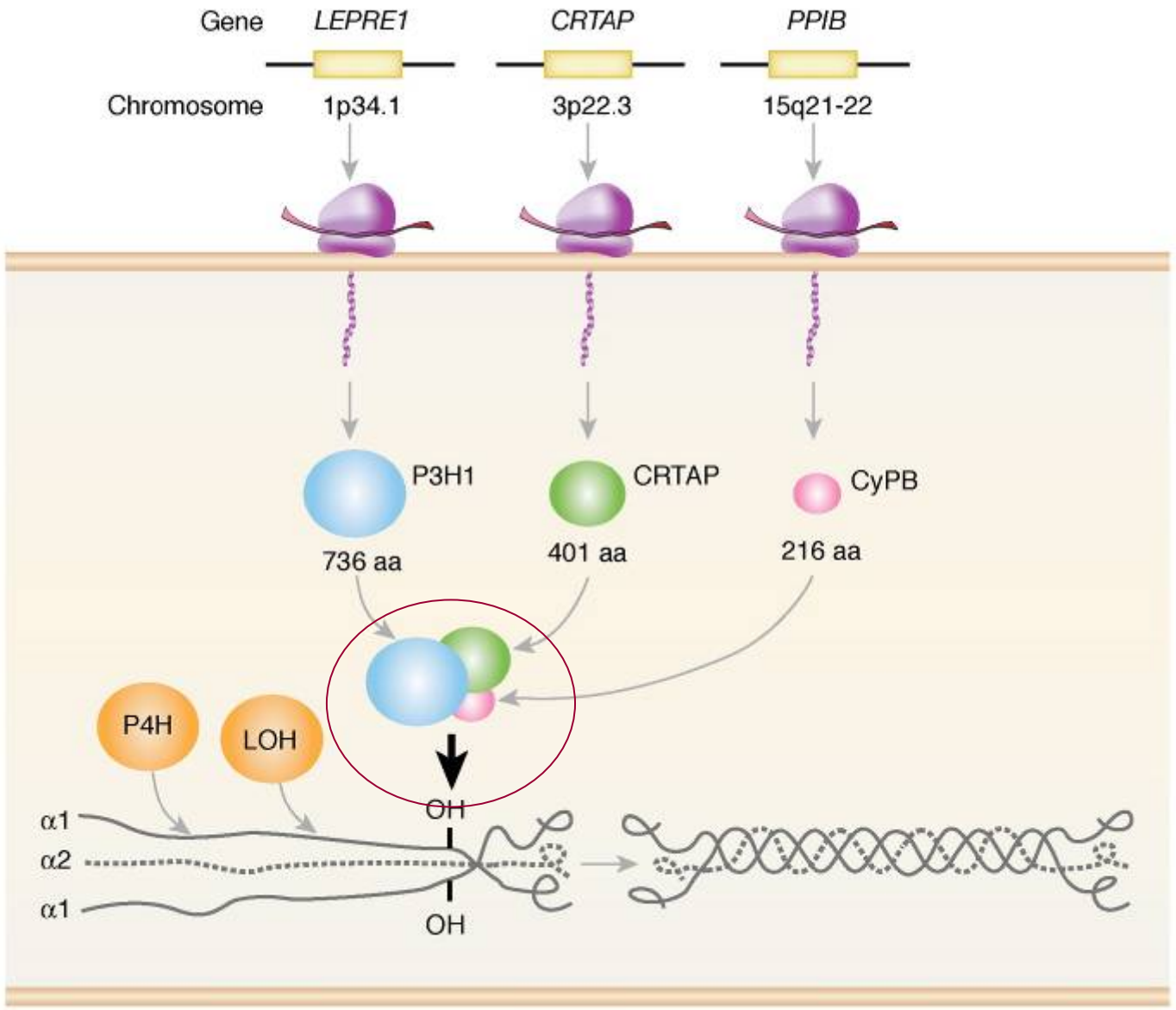
Bianchine et al Am J Med Genet , 1972

- Pseudoglioma, vitreous hyperplasia, cornea opacities, glaucoma
- Fractures
- Vertebral ostéoporosis, platyspondyly
- Short stature
- Mental retardation inconstant
- Hyperlaxity
- Heart defect (ASD)
- 11q12-q13, *LRP5*



Ostéoporosis and contractures
Bruck syndrome

- Neonatal contratures, arthrogryposis
- Fractures
- Wormian bones
- Recessive autosomal
- 2 types: Bruck I et II
- PLOD2 (3q24) and TLH1 (17p12)(?)
- Lysyl hydroxylases (linkage between collagene molecules)

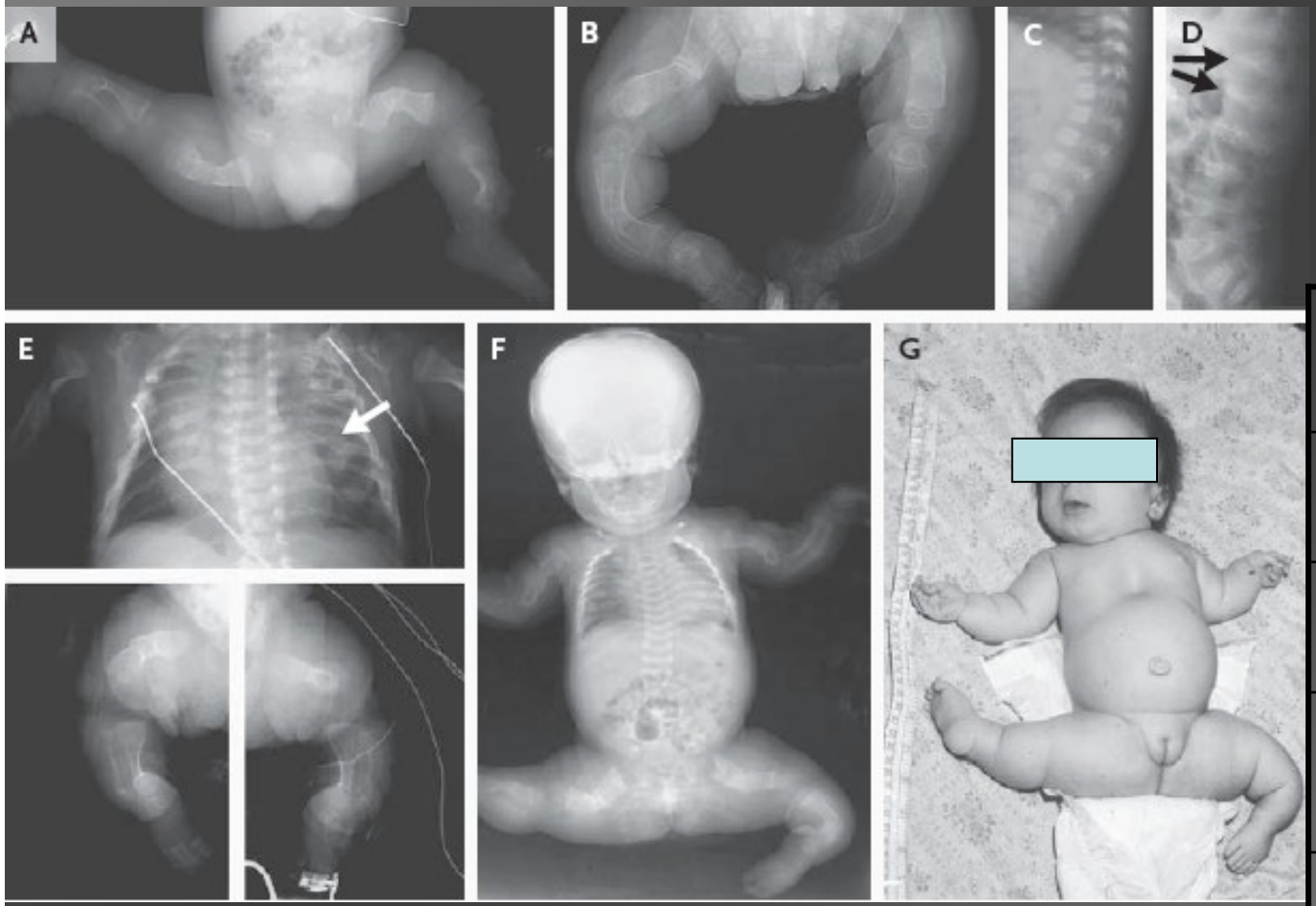


Cabral W, Barnes A, Marini J. Cell 2007

PROLYL 3-HYDROXYLATION

Proteines	Genes	Human phenotype
Leprecan	P3H1(LEPRE1)	+
Cartilage Associated Protein	CRTAP	+
Cyclophin B	CYPB	

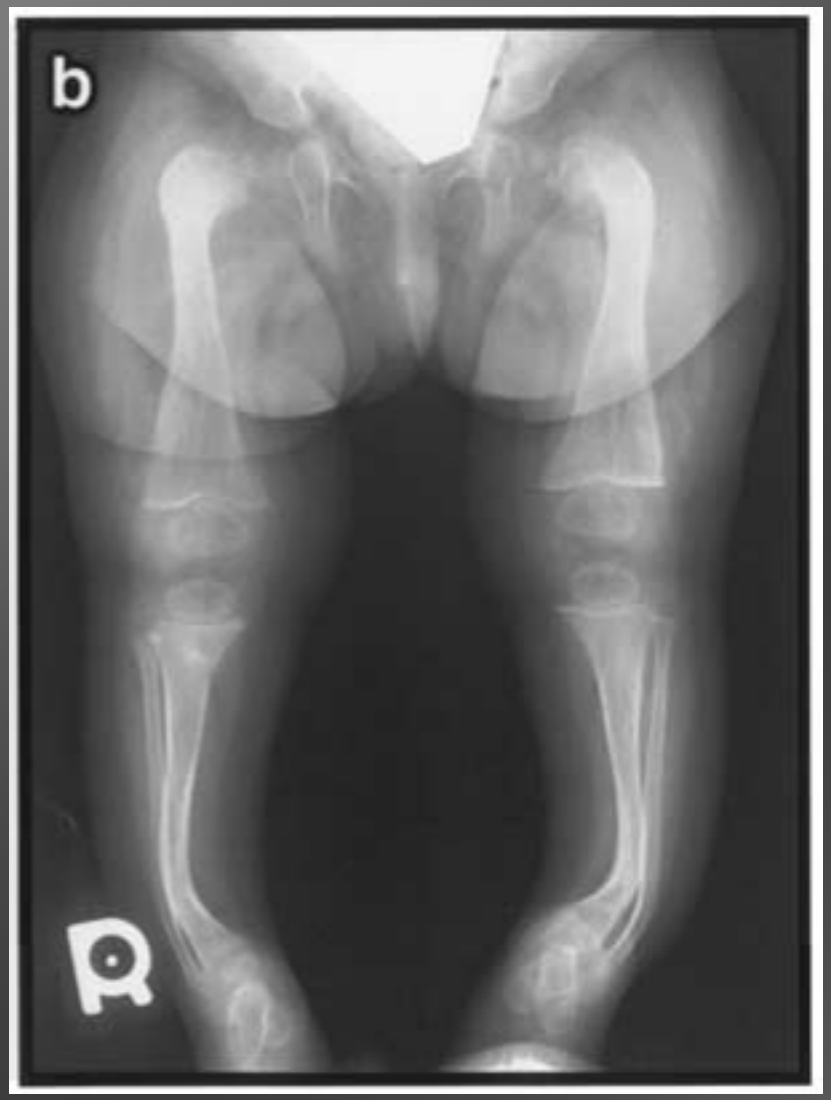
CRTAP mutations



Phenotype	Mutation
II	IVS 1 + 1G > C/ IVS 1 + 1G > C
II	Gln 276 stop/ Gln 276 stop
II	Met1 → ile / 16-nt duplication nucleotide
II	G.879 del T / c879 delT
VII	G.472-102 / C > G

Barnes A, et al. N Eng J Med 355:2757, 2006

Osteogenesis Imperfecta Type VII

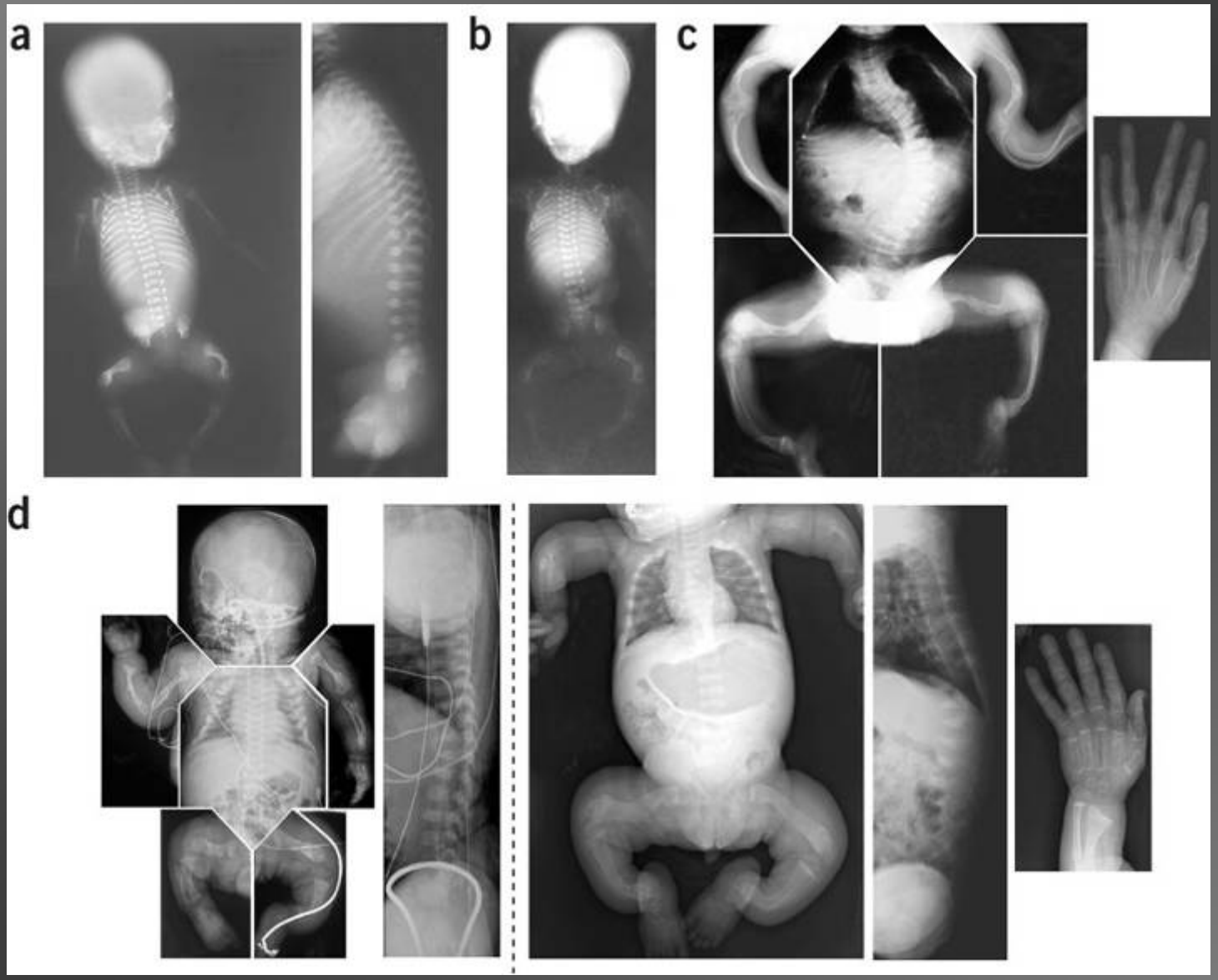


Ward et al, Bone 2002; 31:12-8

- Quebec (Canada)
- autosomique recessive
- bone fragility
- rhizomelia, coxa vara
- White sclera, no DI
- Histology ≈ OI type I
- 3p22-p24.

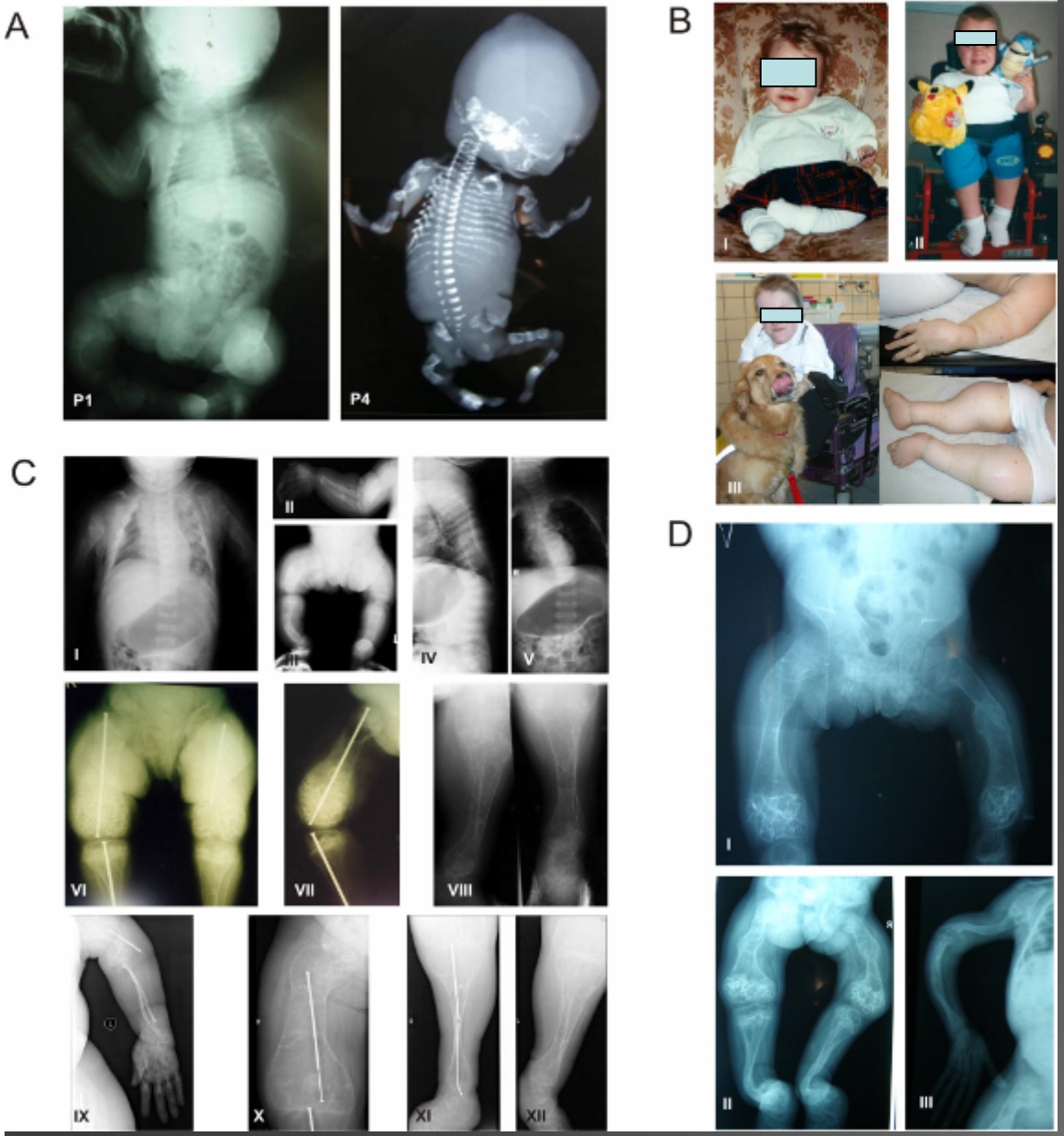
CRTAP mutation

Leprecan mutations



Cabral et al, Nat Genet 2007

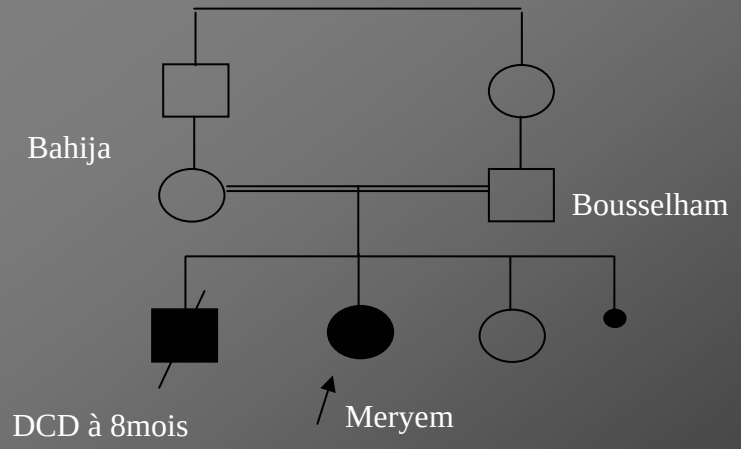
Fig 1



Willaert A et al JMedGenet 2008

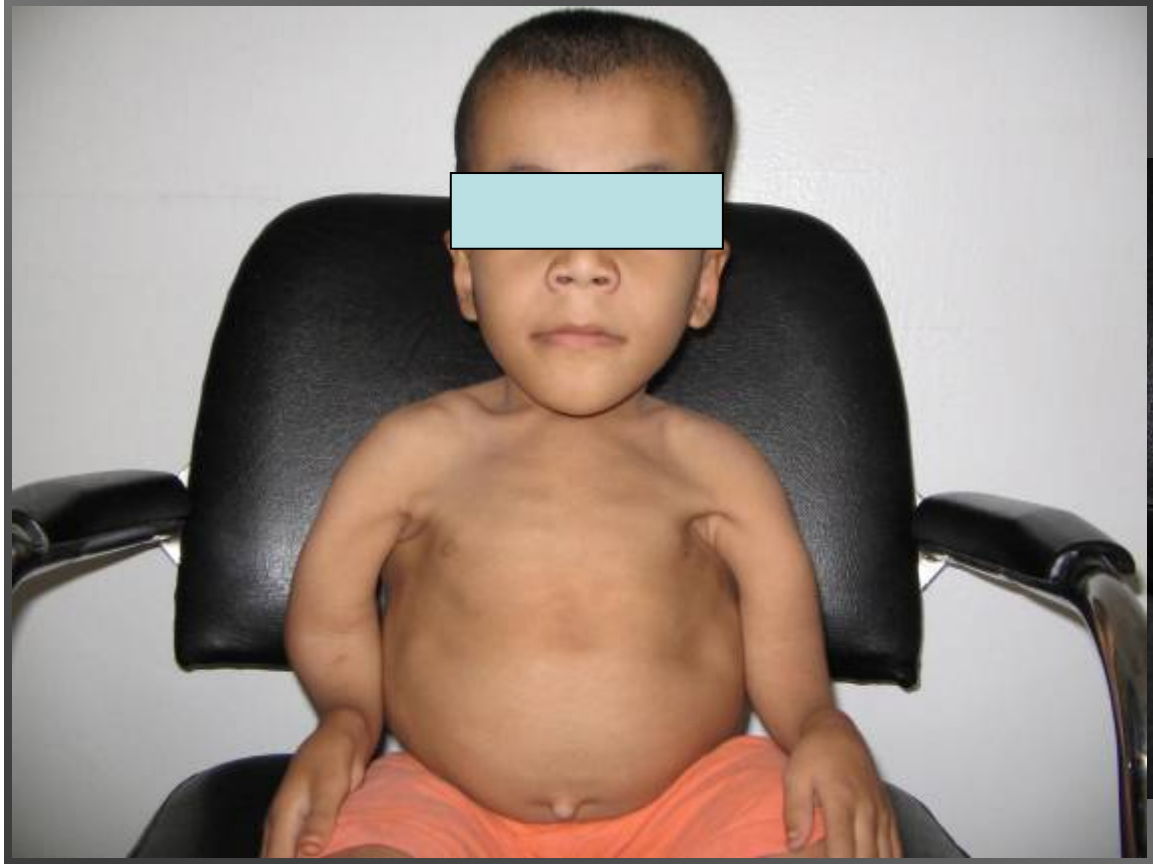
LEPRECAN mutations

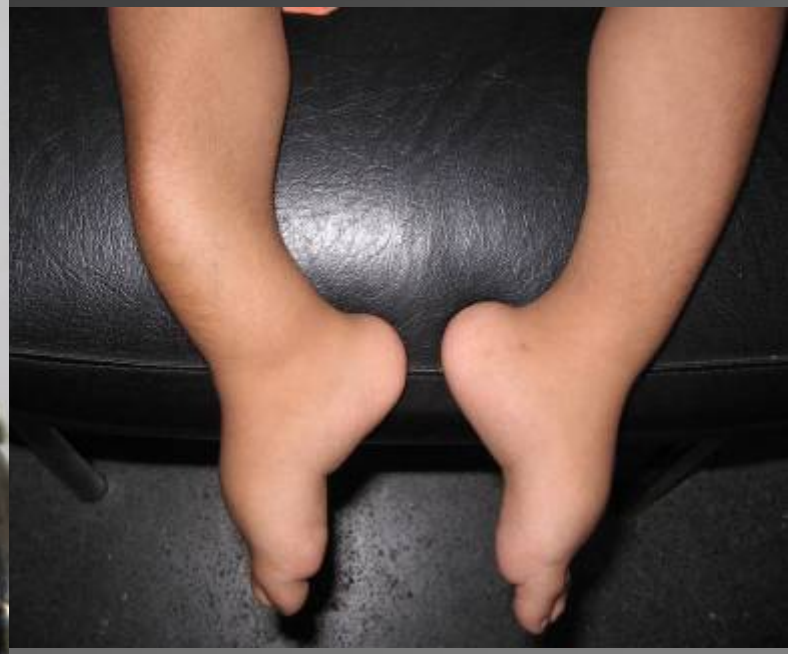
- At birth
  - no distinct sign
- Infancy
  - metaphyses flaring,
  - pop corn epiphyseal aspect
- Adolescence
  - narrow diaphyses
  - severe osteoporosis

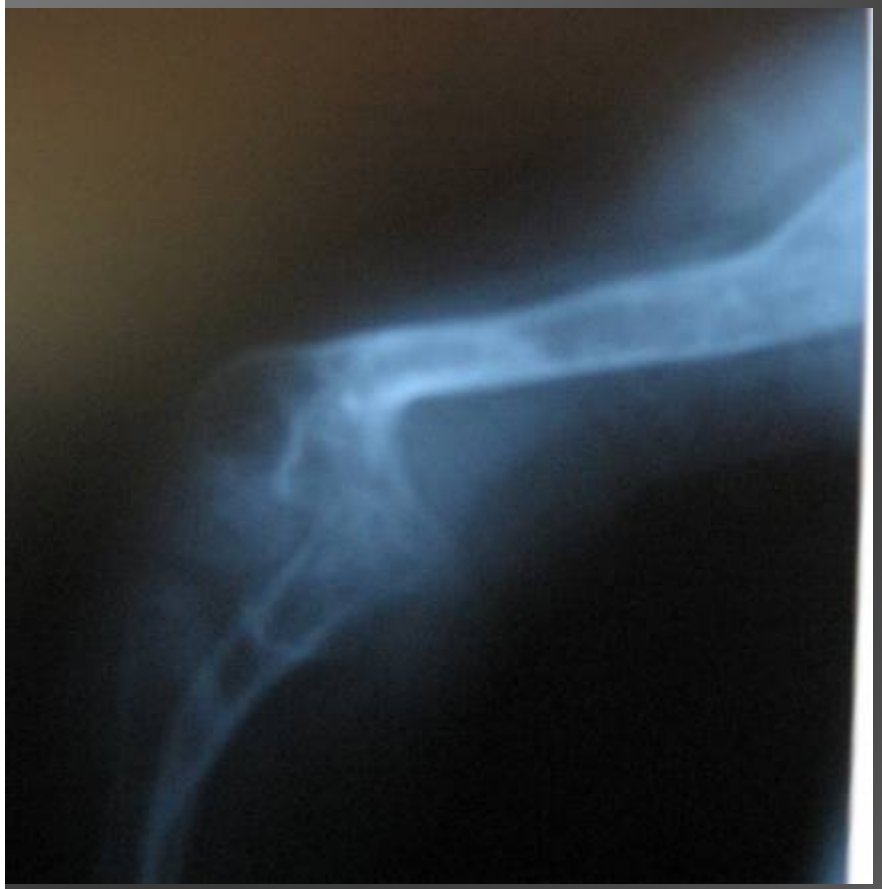


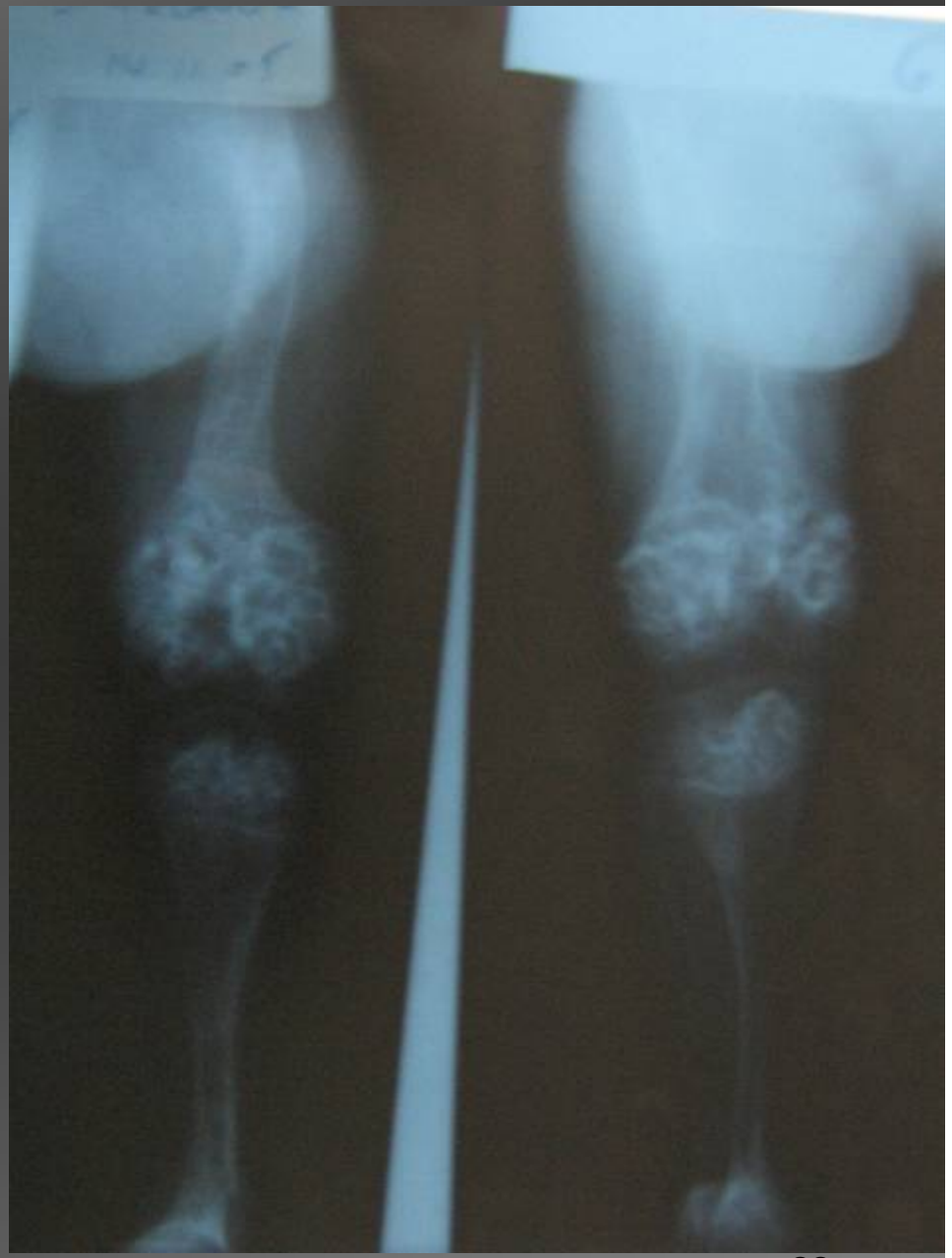
Mutation homozygote
Leprecan

Dr Leila Refai (Maroc)









Arguments for a recessive OI

- Recurrence in consanguineous parents
- Extraskeletal signs (ocular, extremities)
- Severe cases
- 10% of OI

Willaert et al, Mariani et al 2008

OI, experience of Necker Hospital

(Dr AS LEBRE,
anne-sophie.lebre@nck.aphp.fr)

103 patients (2006-2008)

- 68 mutations of COL1A1/ COL1A2
- 1 mutation of CRTAP
- 1 mutation of LEPRECAN
- 15 patients without mutation (clinical reevaluation)
- 20 patients in progress

Molecular analysis

- *COL1A1* et *COL1A2* direct sequencing
  - 3 to 6 months
  - 80 – 90 %
- Indirect familial analysis
  - *COL1A1, COL1A2 , LEPRE1, CRTAP*
  - Polymorphic markers
- Chips project

Indications

- Accepted
  - OI patient with severe disease and prenatal diagnosis reflexion
  - Parents with severe OI child and PND request (germinal mosaïcism risk)
- Discussed
  - Confirmation of diagnosis in moderate cases, child abuse cases.
  - Genotypes-phenotypes correlations
- Every collagen analysis has to be done through a genetic consultation
  - Limits, implications of the test

Management and treatments

Non medical management

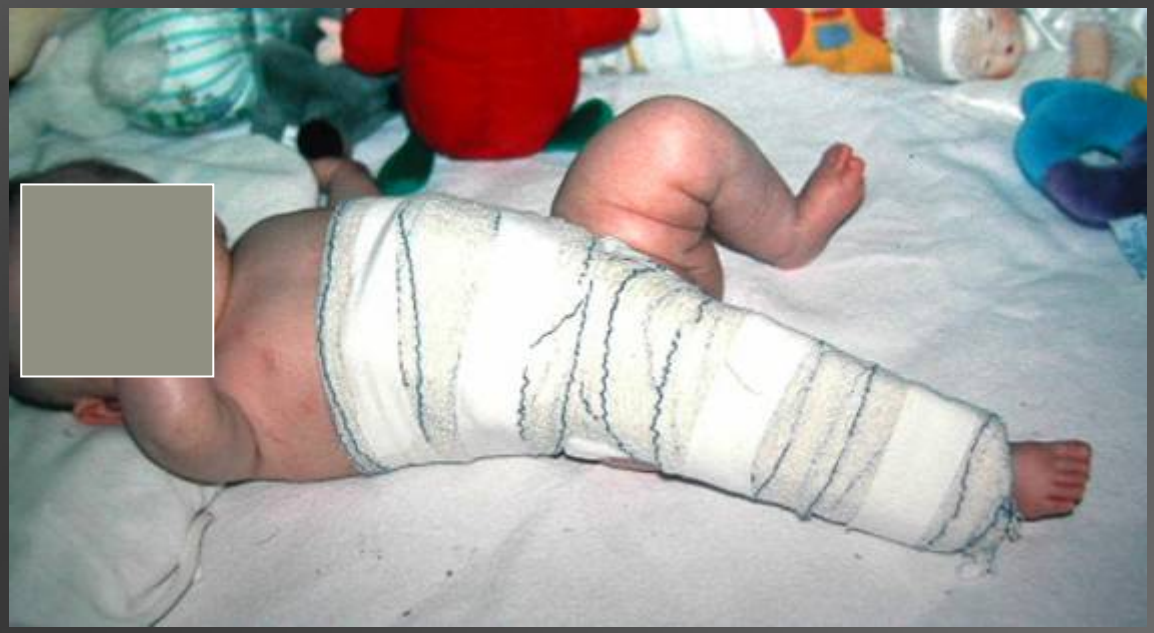
- Physiotherapy
- Rehabilitation
- Orthopedic surgery
- Psychological follow up (patient and family)

Medical Management

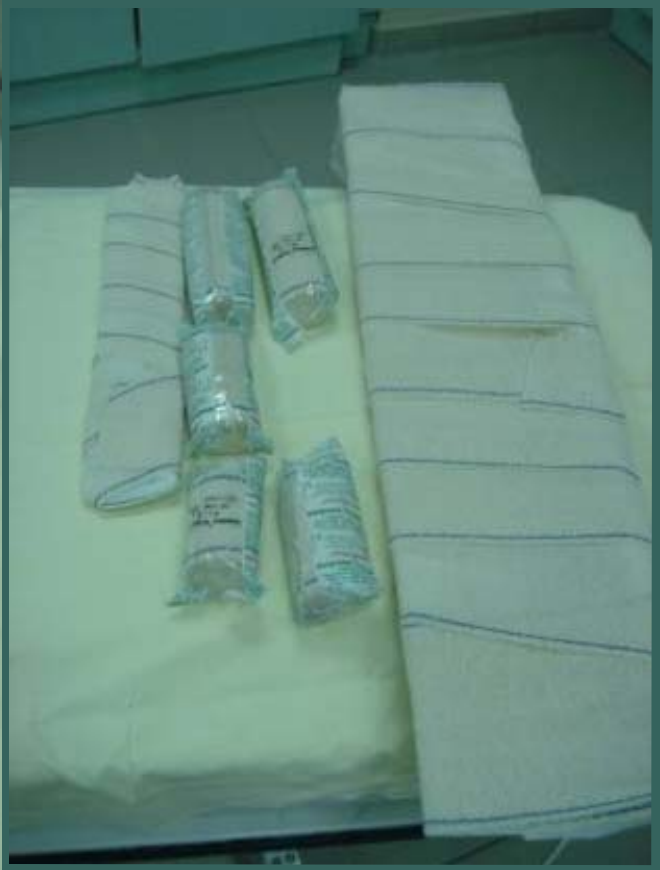
- Systematically
  - D vitamine (prevention, 100 000 UI /3-6 m)
- Severe forms
  - Bisphosphonates
- Projects and others
  - GH / OI

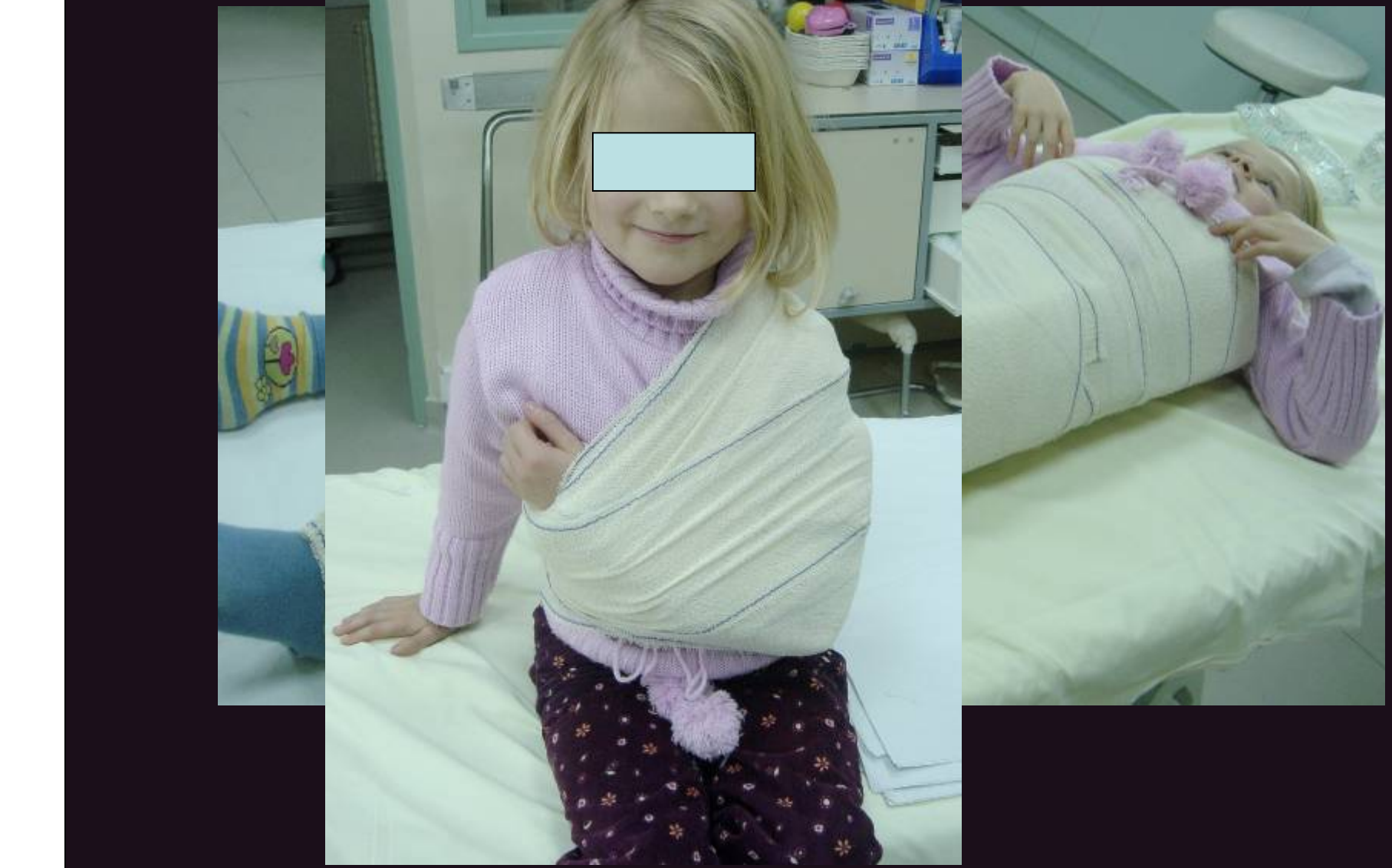
Parental education

Immobilization « home made»

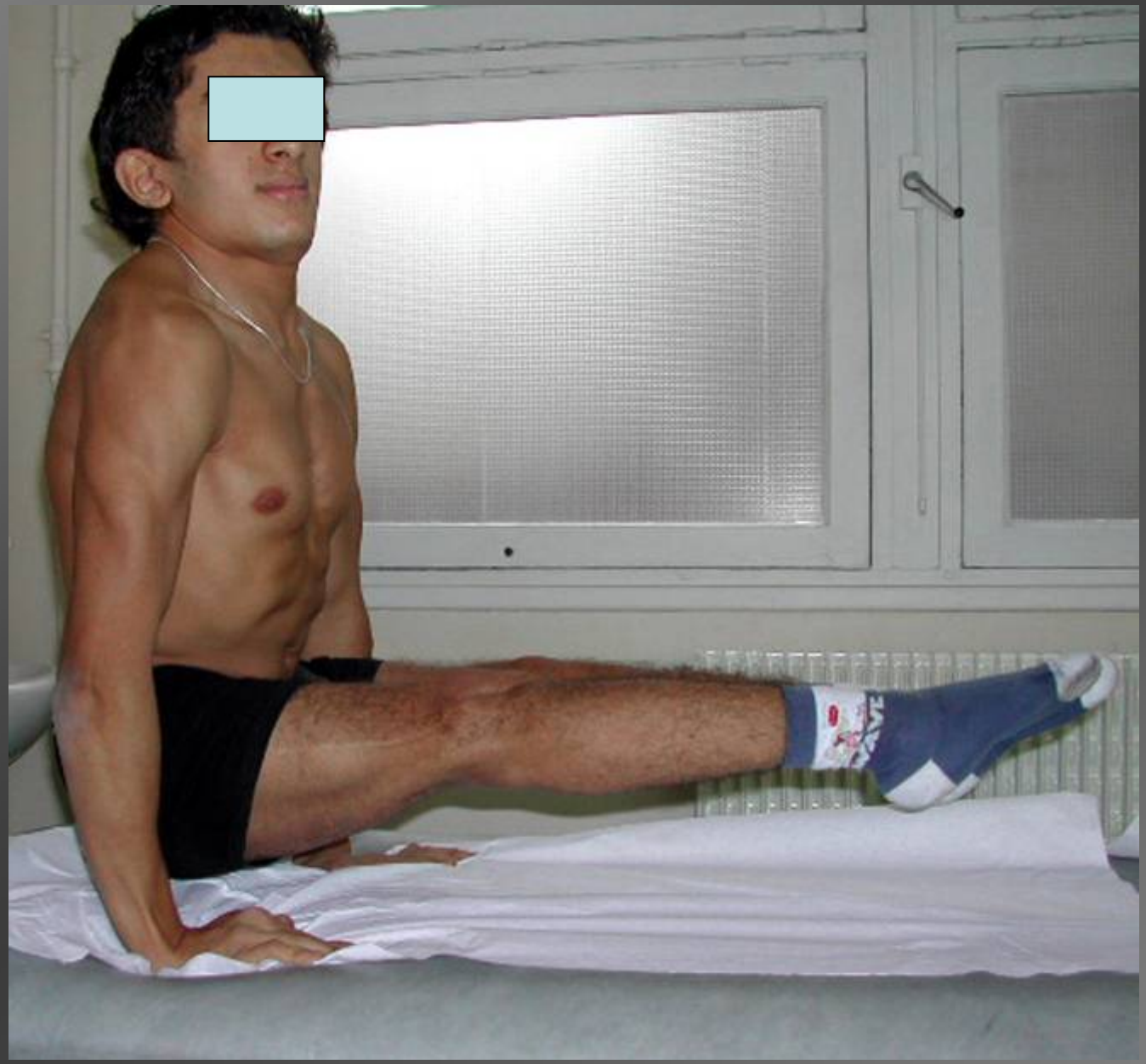


« analgesic package »





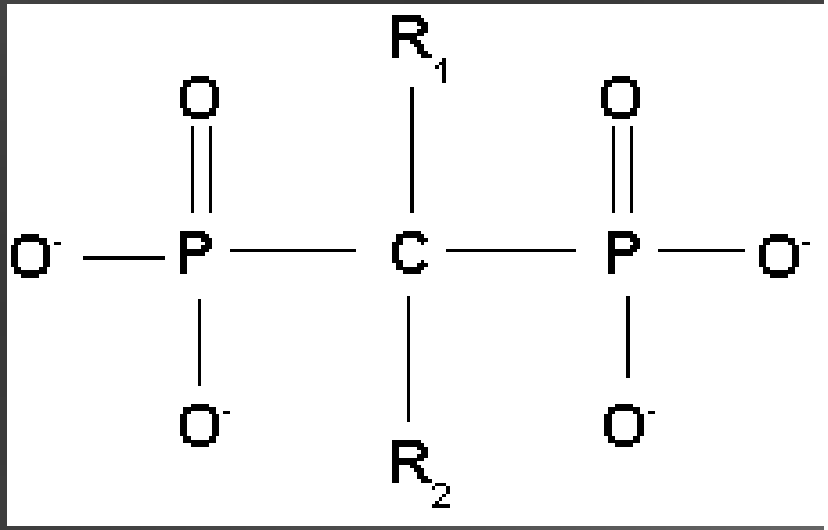
Physiotherapy



Bisphosphonates

- Polyphosphates (1930): inhibition of calciums salts cristallisation (industry, washing powder)
- Bisphosphonates (> 1970)
  - osseous antiresoptive action
  - Inhibition of osteoclasts function (interference with mevalonate pathway of cholesterol biosynthesis in osteoclasts)
  - First evaluation in OI: Devogelaer (1987)

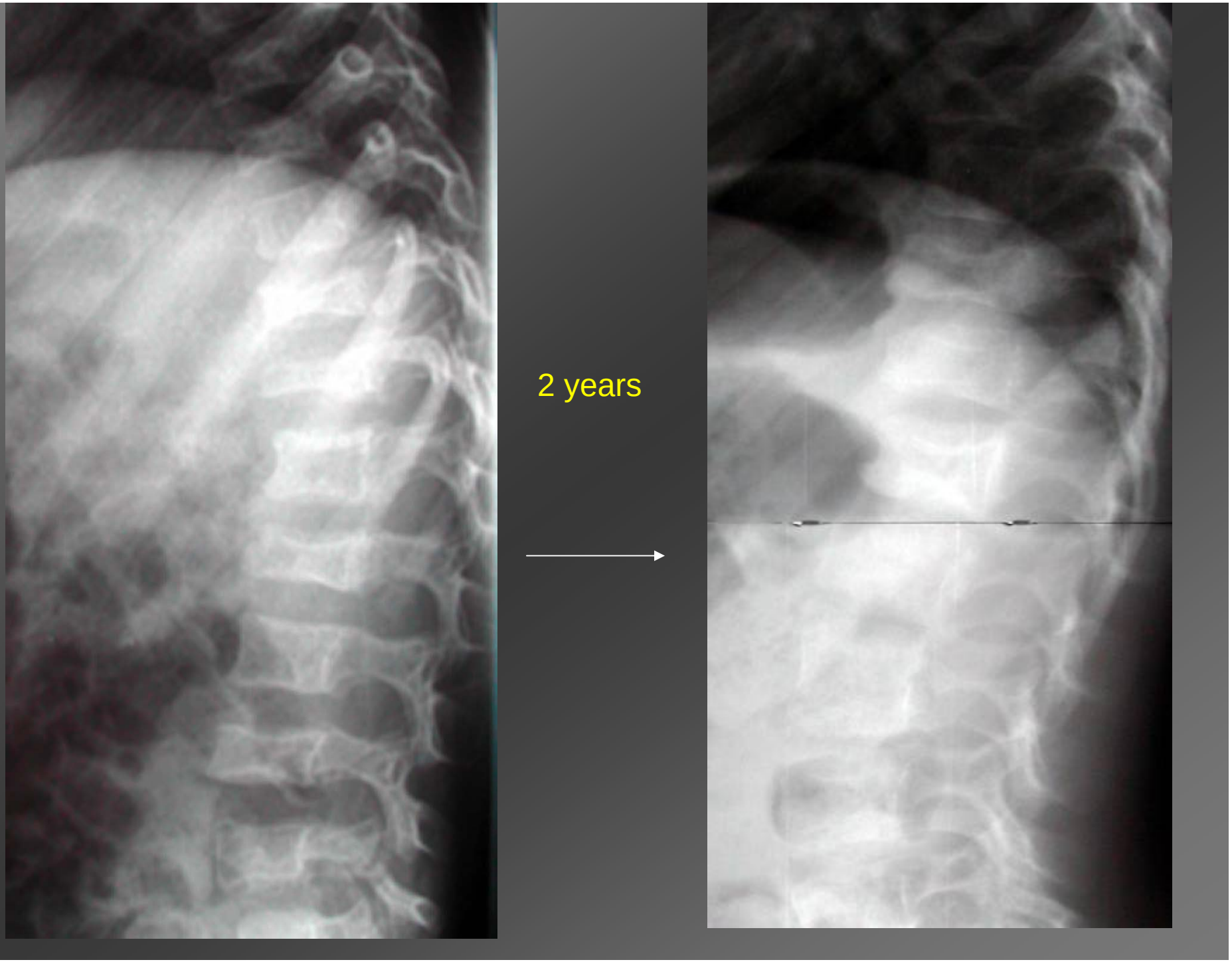
BPs: chemical structure



- Basal structure P – C – P
- Chain R2
  - OH / H / Cl
  - Bone hook
- chaîne R1
  - 0 to 2 N
  - Osseous resorption potential (power)
- Several generations
  - 0 N: étidronate, clodronate, tiliéronate
  - 1 N: pamidronate, alendronate
  - 2 N: zolédronate

Bisphosphonates and OI

- Rapid decrease in chronic bone pain
- Increase vertebral bone-mineral mass (density and size)
- Enhance cortical thickness (not on trabeculae)
- Reduce fracture rate
- Improve mobility


2 years

But limits

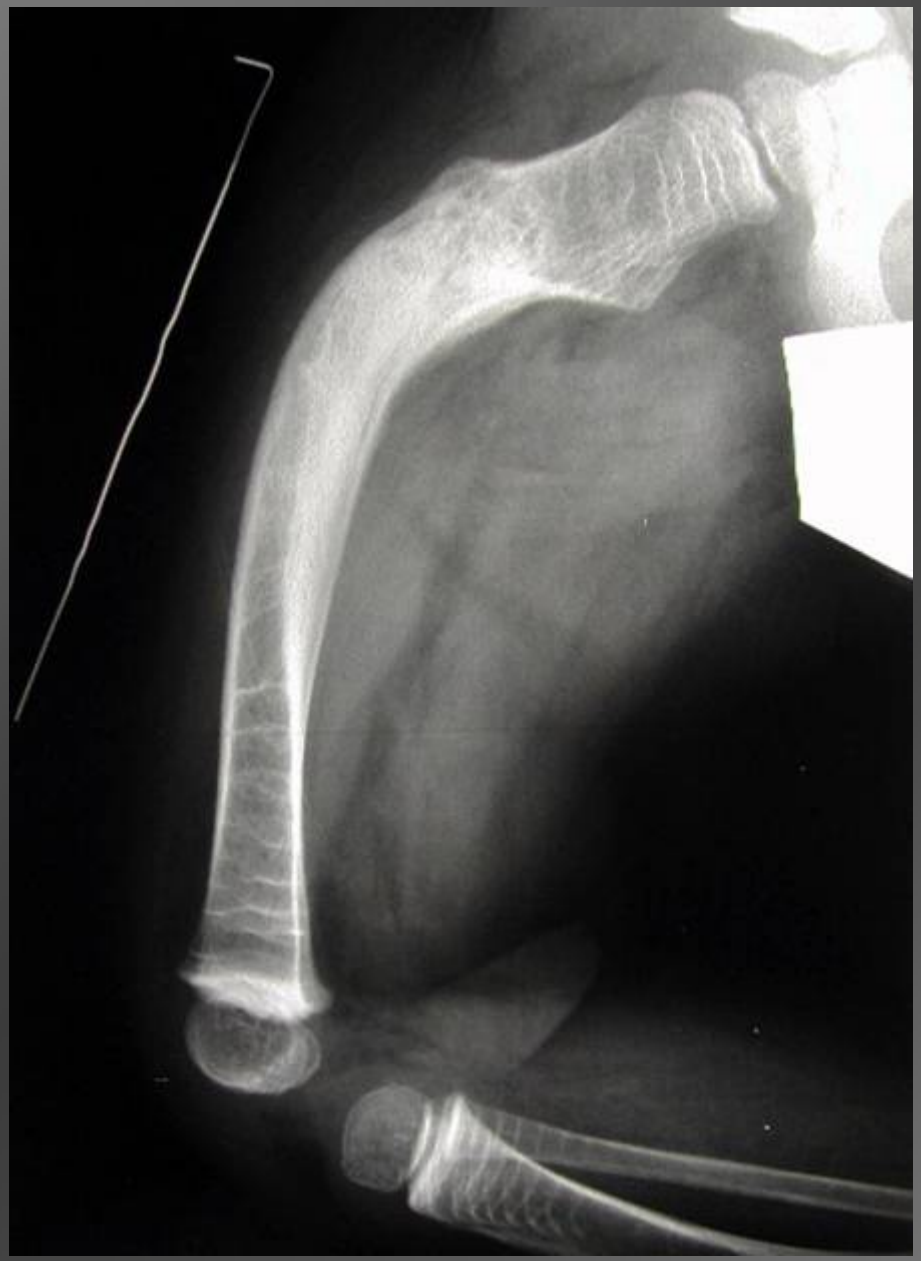
- safety
  - during administration
    - influenza like reaction (fever, rash, vomiting)
    - hypocalcemia
- long term effects ?
    - persistance in bone tissue for many years
    - shaped metaphyses, metaphyseal lines

    - alteration osseous consolidation/ fracture repair
    - uveitis
    - osteonecrosis of the jaw (no case in children)

    - high mineral density with osteopetrosis

Unresolved questions

- oral or intravenous ?
- longitudinal bone growth alteration ?
- optimal treatment duration
- consequences on future pregnancies of treated women ?



Bisphosphonates indications

- > 2 fractures / year
- vertebral compression fracture
- long bones deformities
- basilar impression
- acetabular protrusion

Montral pamidronate protocol
(Glorieux)

- Pamidronate (Aredia), intravenous
- Baseline evaluation (serum, urine, Xrays, BMD)
- dosage (max. 60 mg/day)
- annual dose 9 mg/kg
- age
    - > 2y.: 0.5 mg.kg/d/ x3days /2 months
    - 2 – 3y.: 0;75 mg/kg/d/ x3 days /3 months
    - >3y.: 1 mg/kg/d / x3days /4 months
- calcium, D vitamin*
- dilution in saline

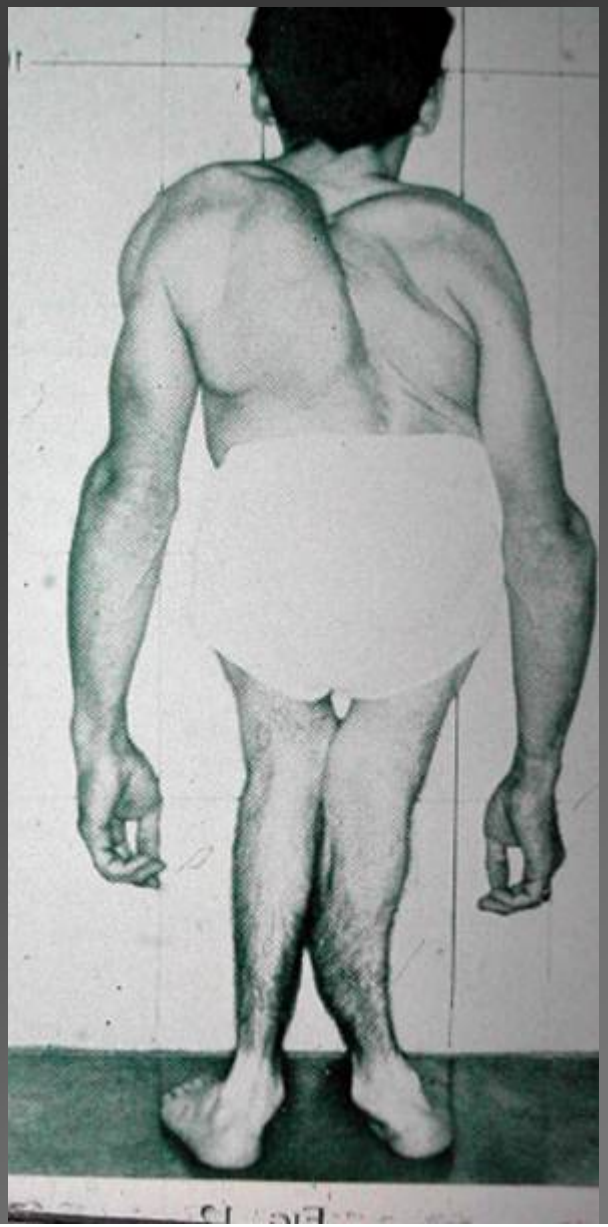
Socioeducative management

- Communal life integration
- Creche, nursery
- School integration and adaptation
  - Transports, schoolbag, physical activities
  - Playtime and break safety
- Social recognition, ALD
- occupational facilities and adaptation

orthopedic surgery

Orthopedic management particularities

- fractures
- strengthening of long bones
- scoliosis



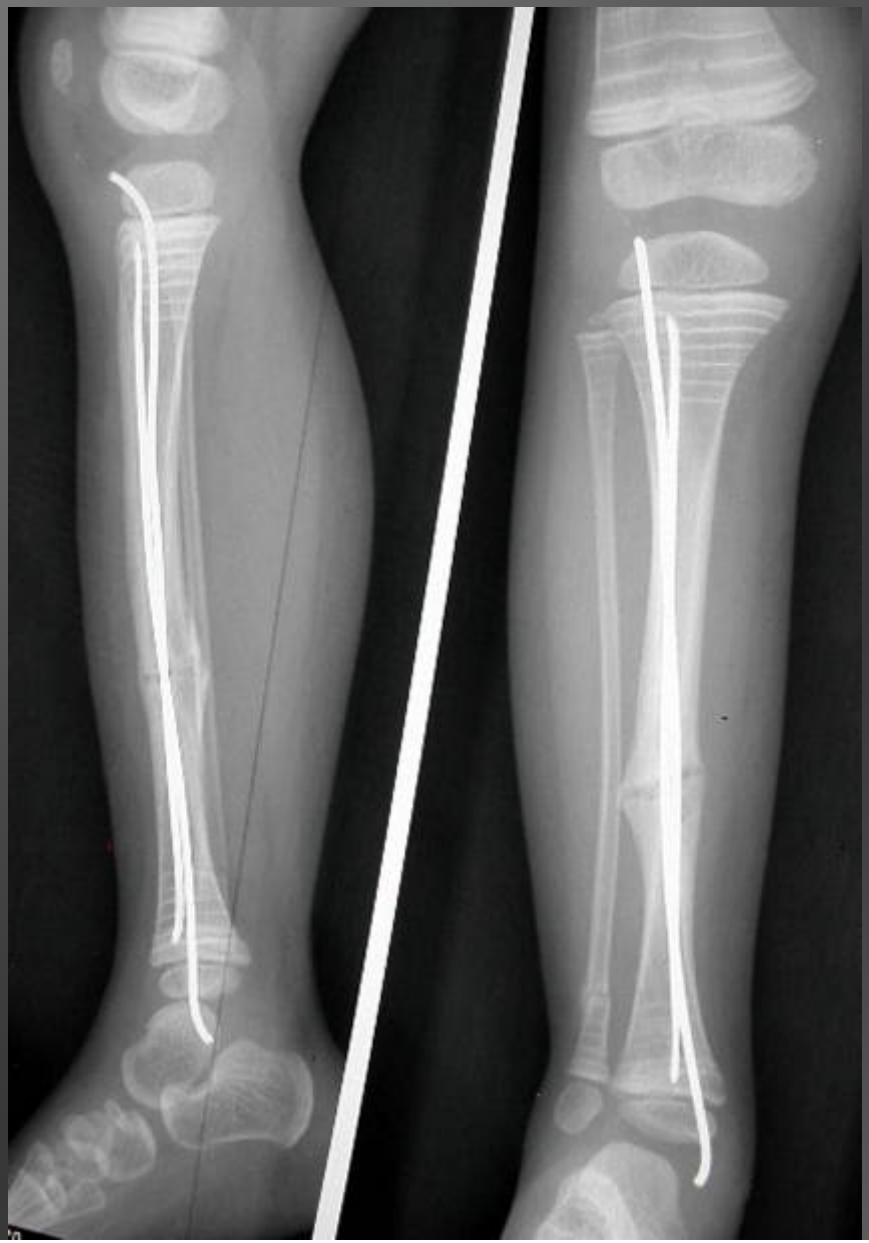
Fractures

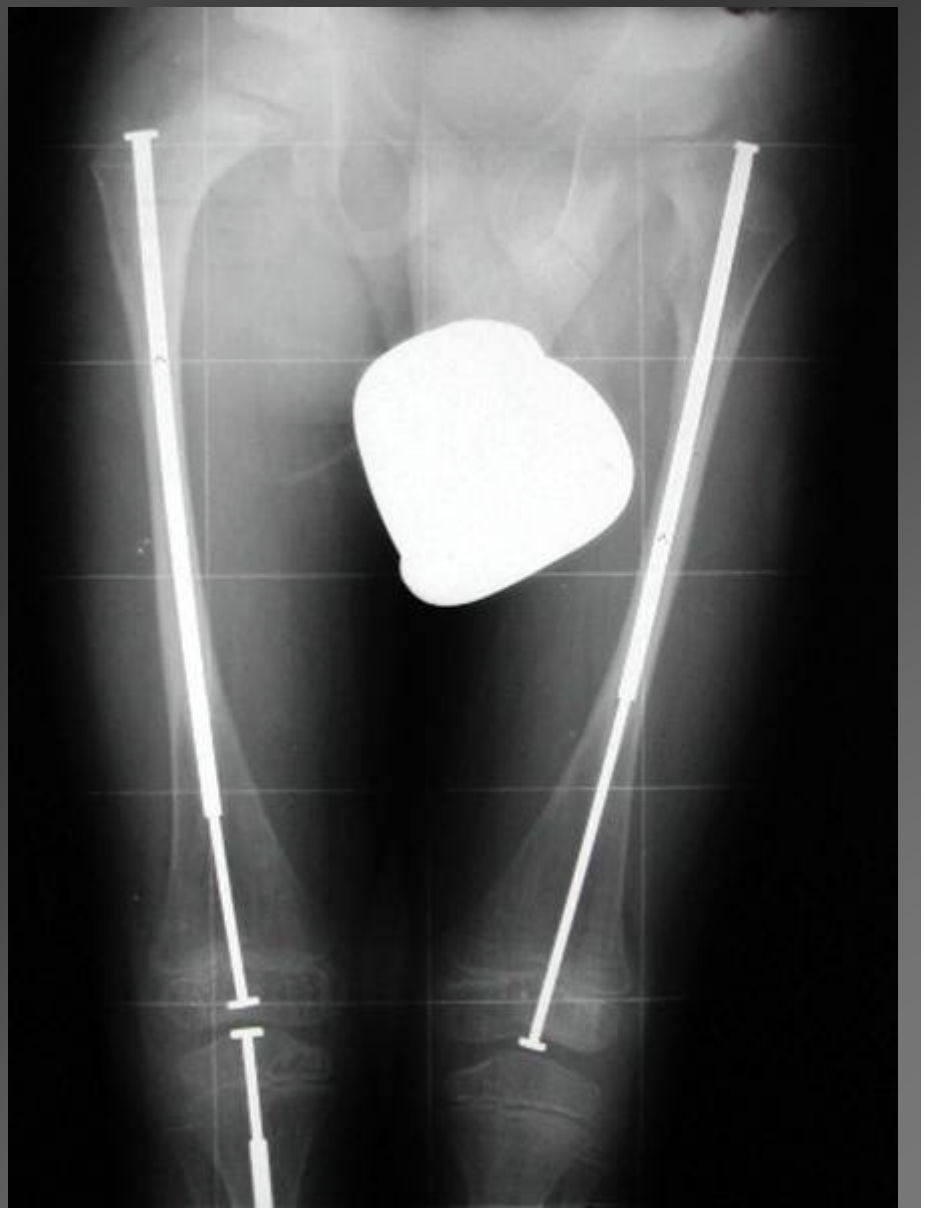
- Correct reduction
- Light material (resin > plaster)
- Short duration of immobilization

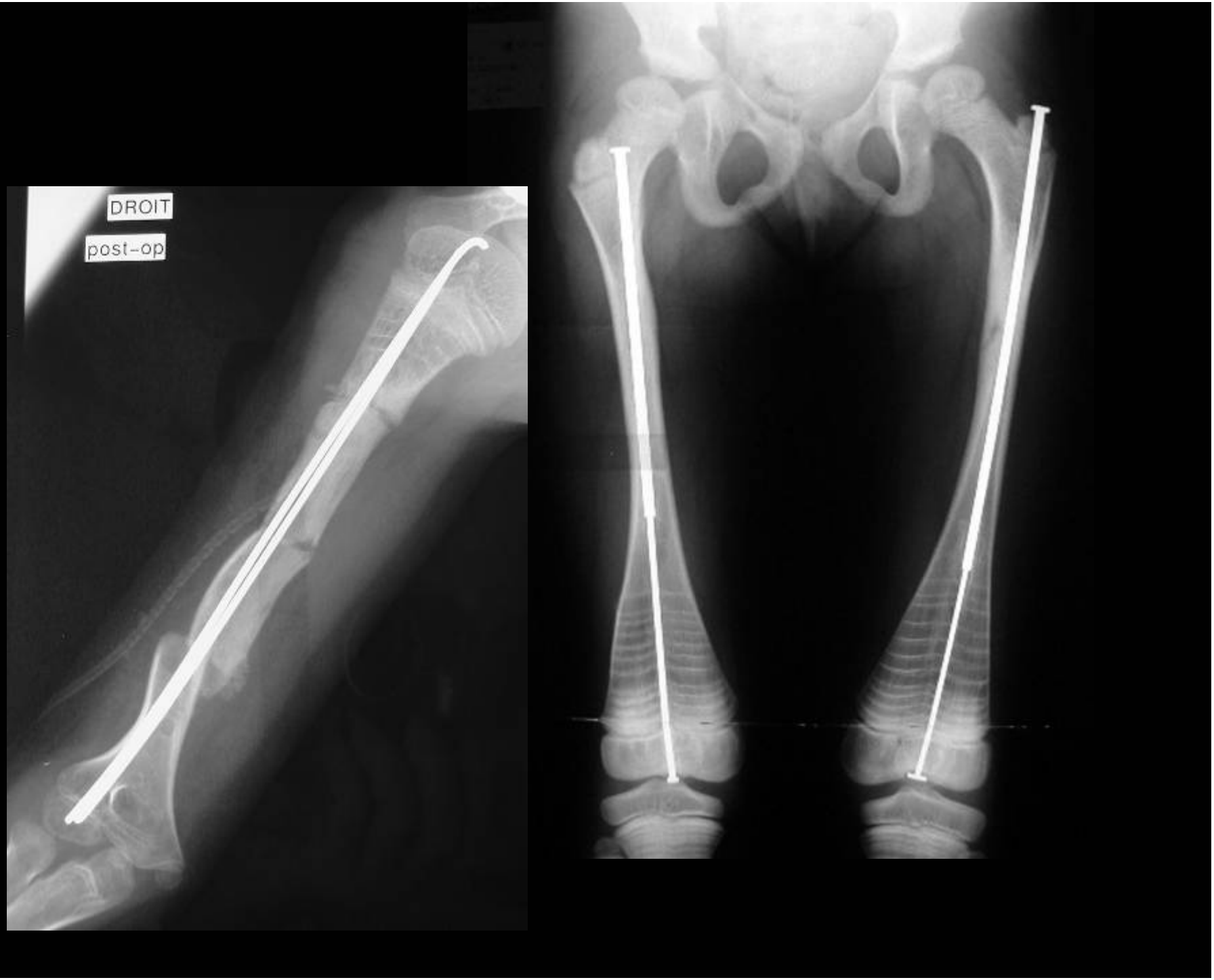
(G. Finidori et al., Necker)

- Centro medullary telescopic nailing is a very effective procedure for the femur.
- It can now be done using a less invasive percutaneous procedure.
- For the tibia, the humerus and the forearm we prefer simpler techniques using telescopic stainless wires.

Intramedullary roding

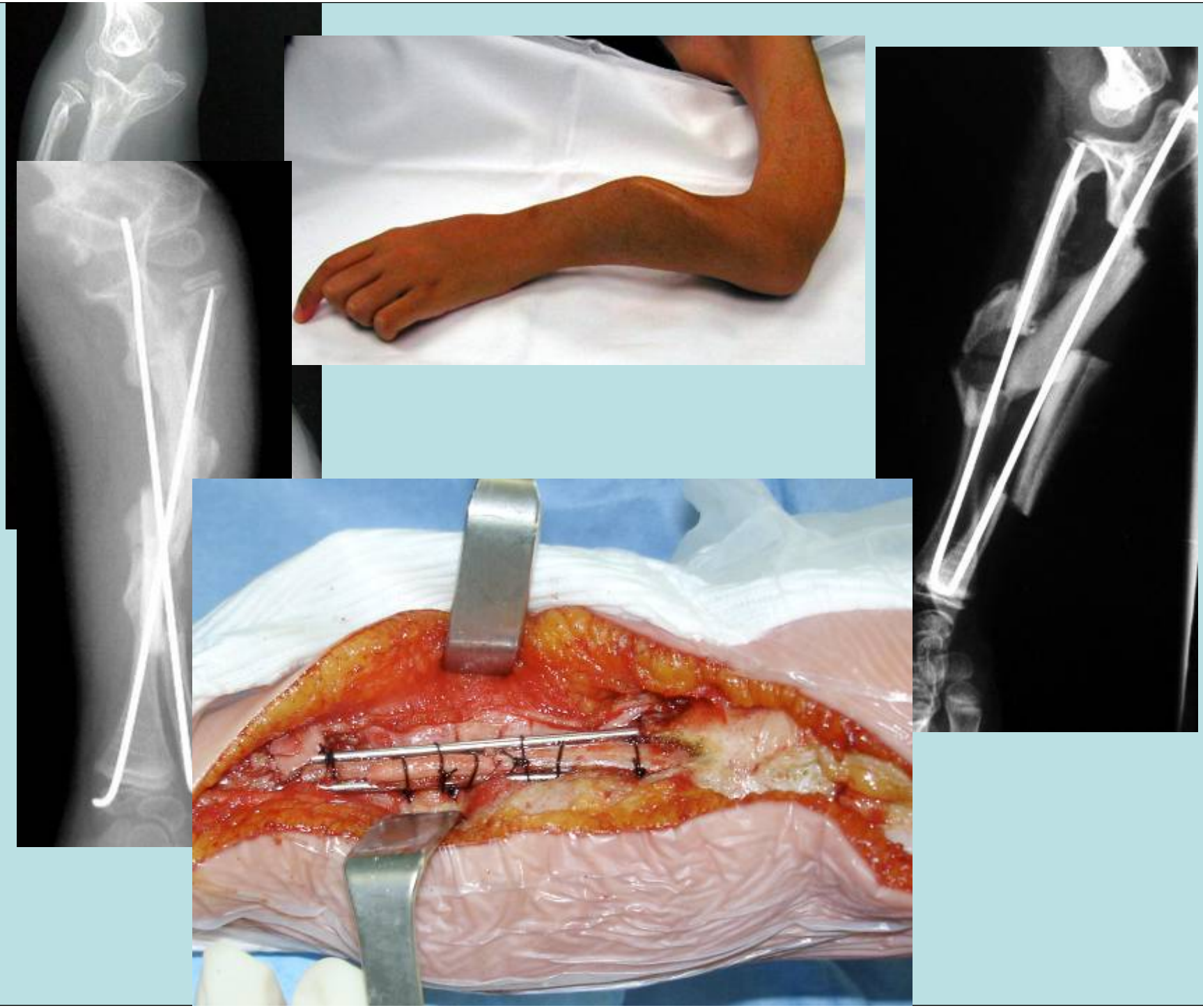


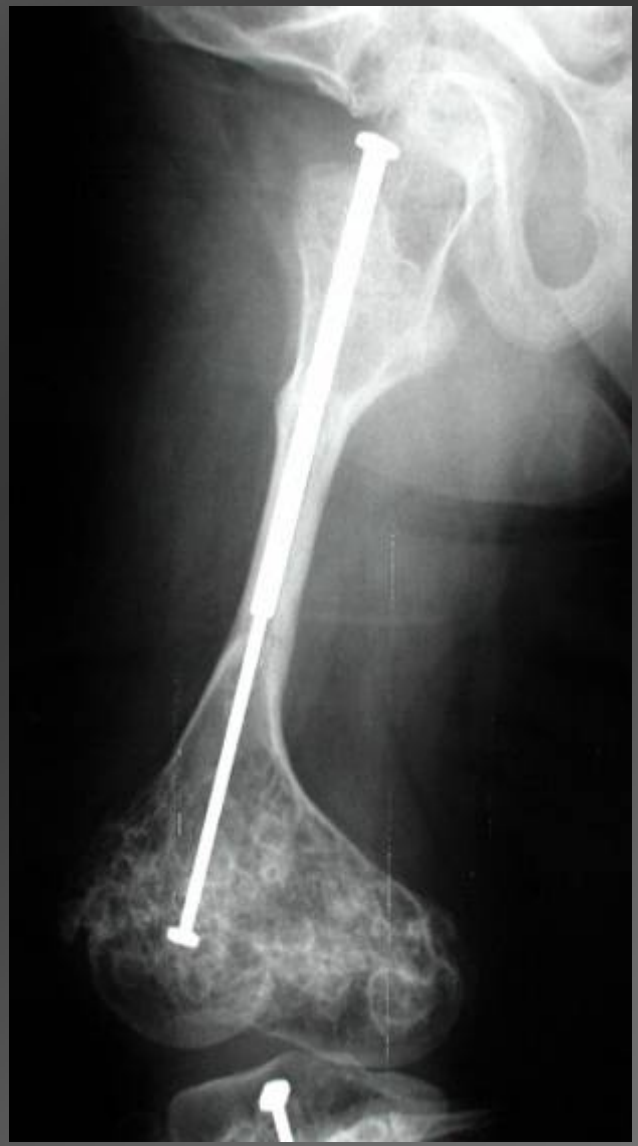



DROIT
post-op

-A central medullar pining is impossible for patients with a severe form of O.I. because the bone has no medullar canal.

-It is then possible to perform an extra diaphyseal wiring.

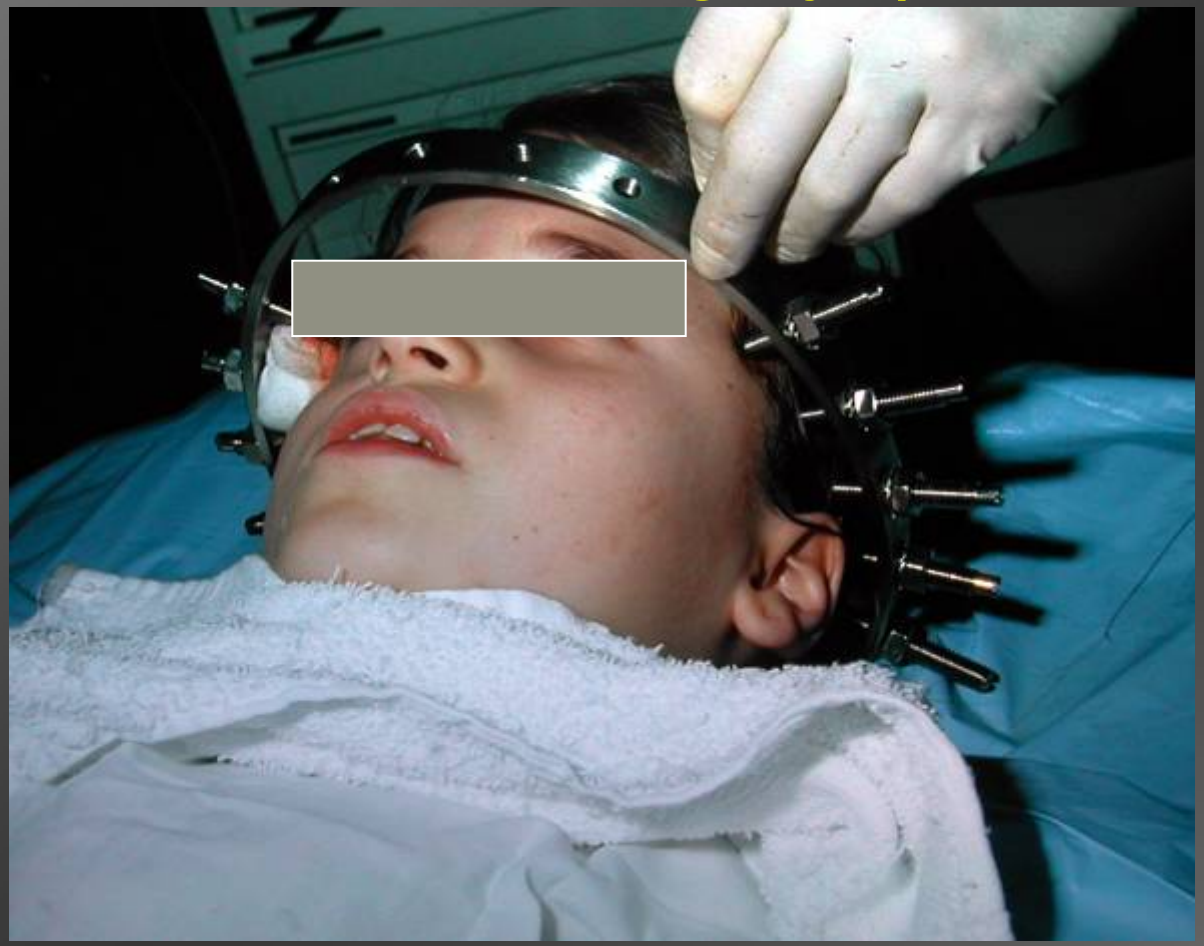




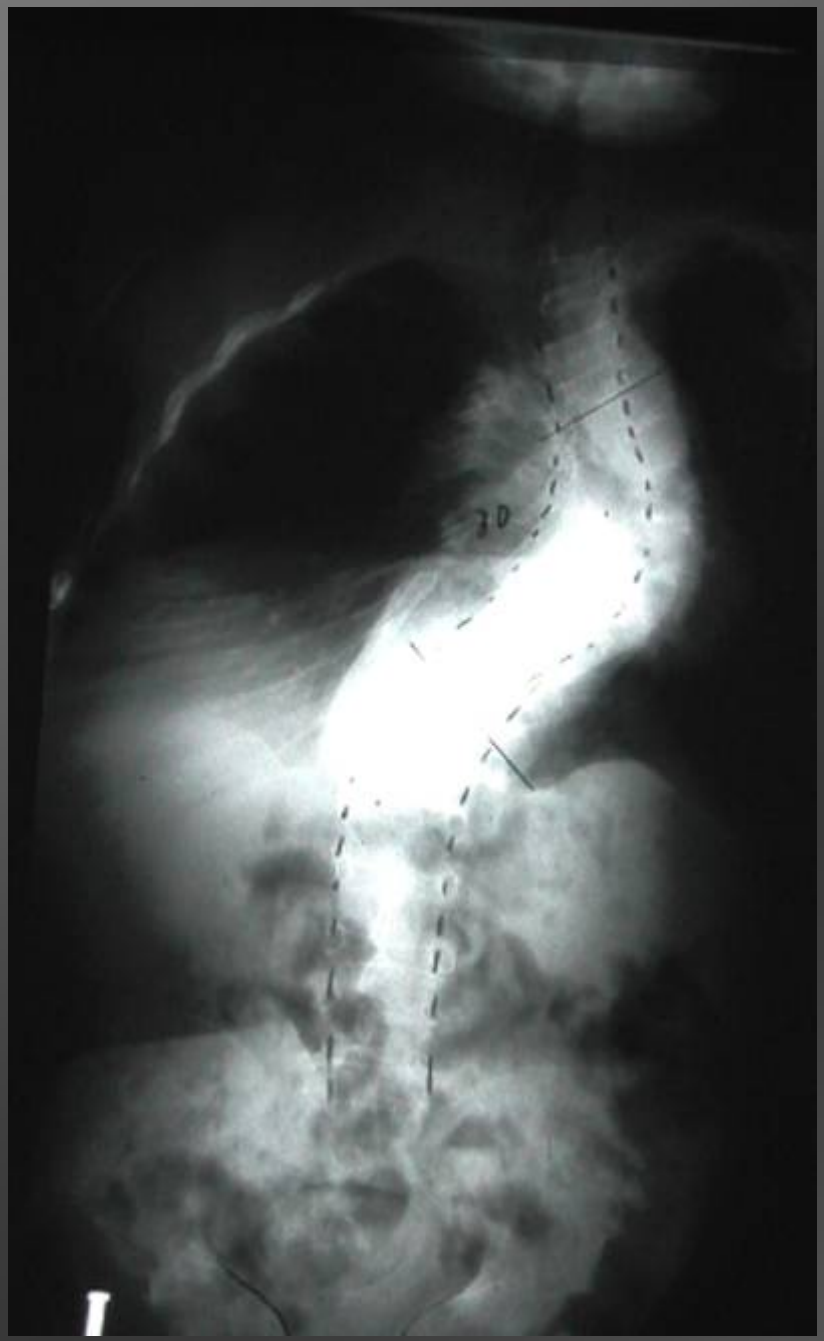
scoliosis

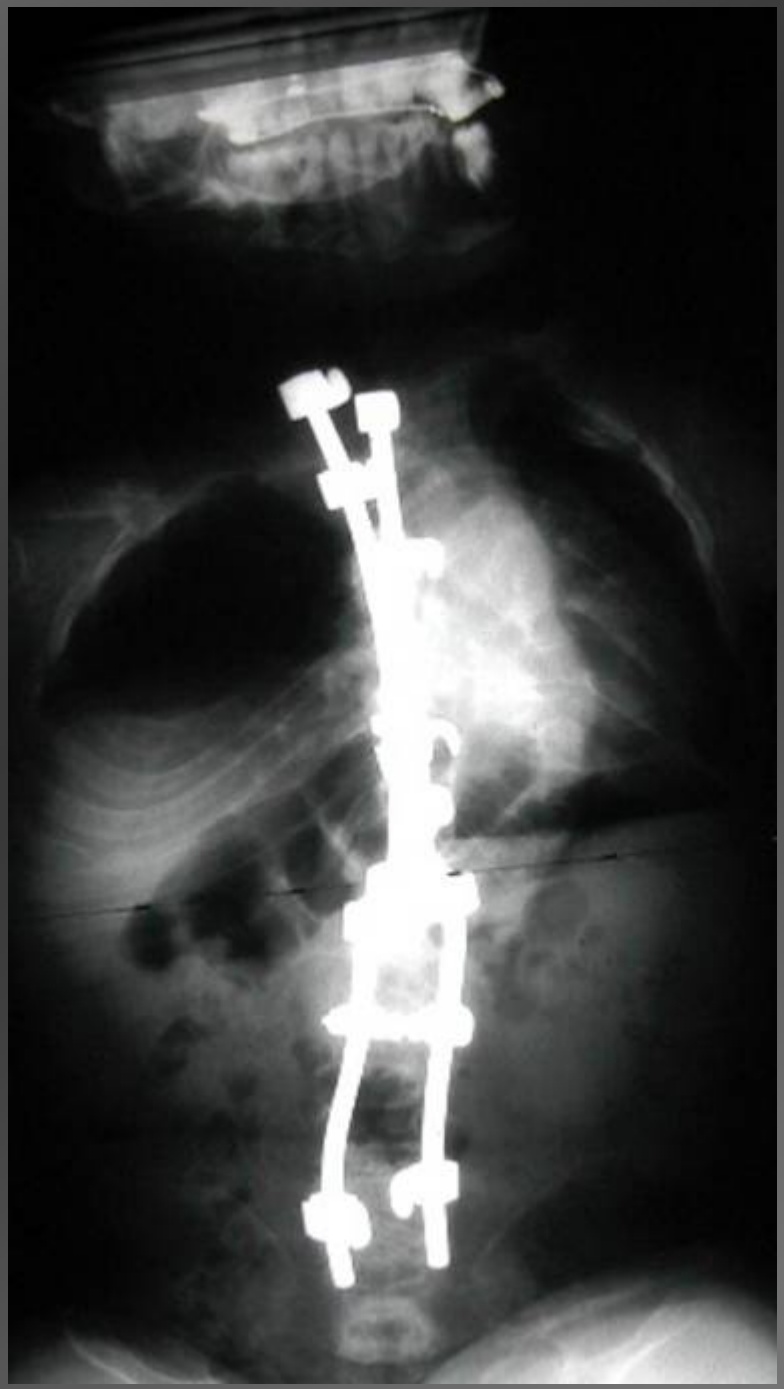
- frequent
- Severe forms
- Classic treatments deletorious

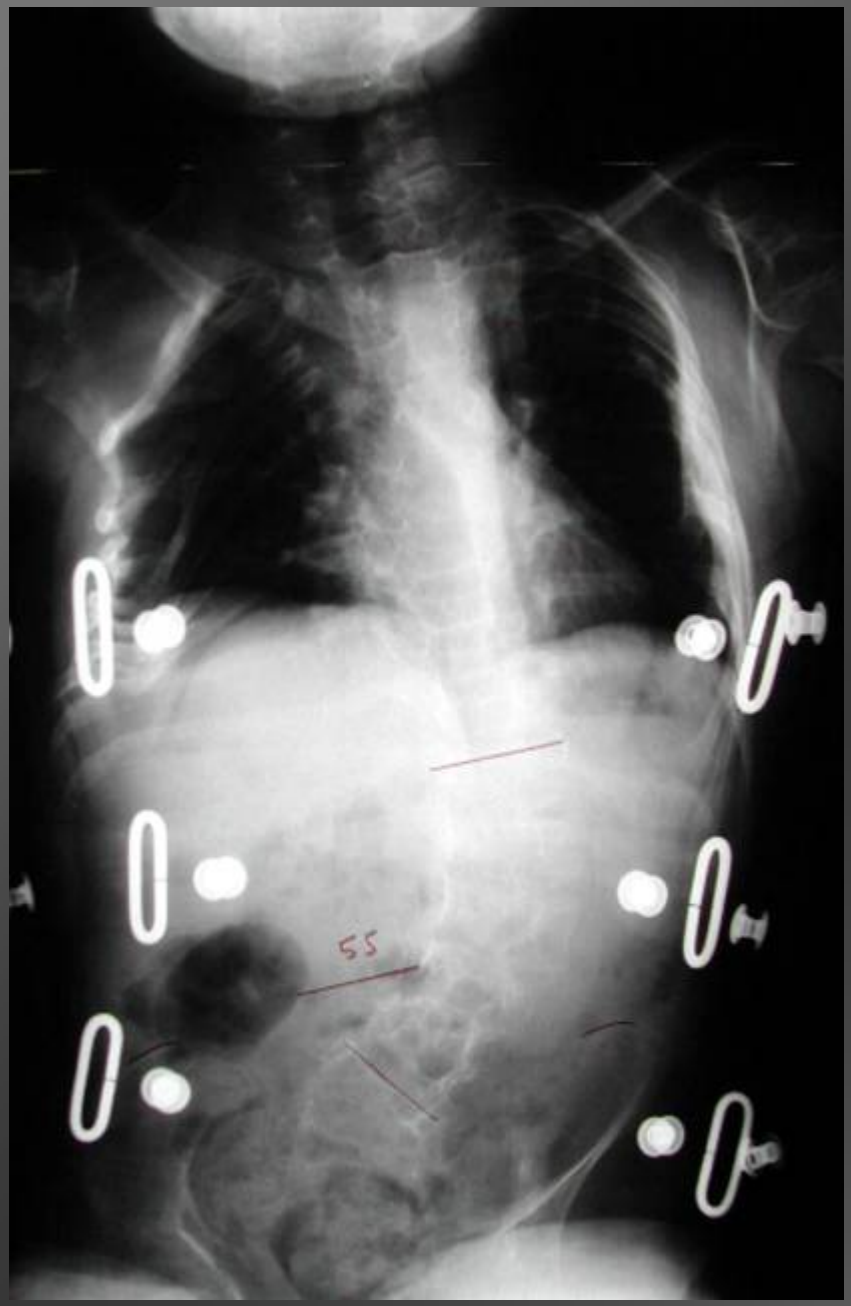
1/ Traction: before surgery, pericranial halo



2/ posterior vertebral fixation



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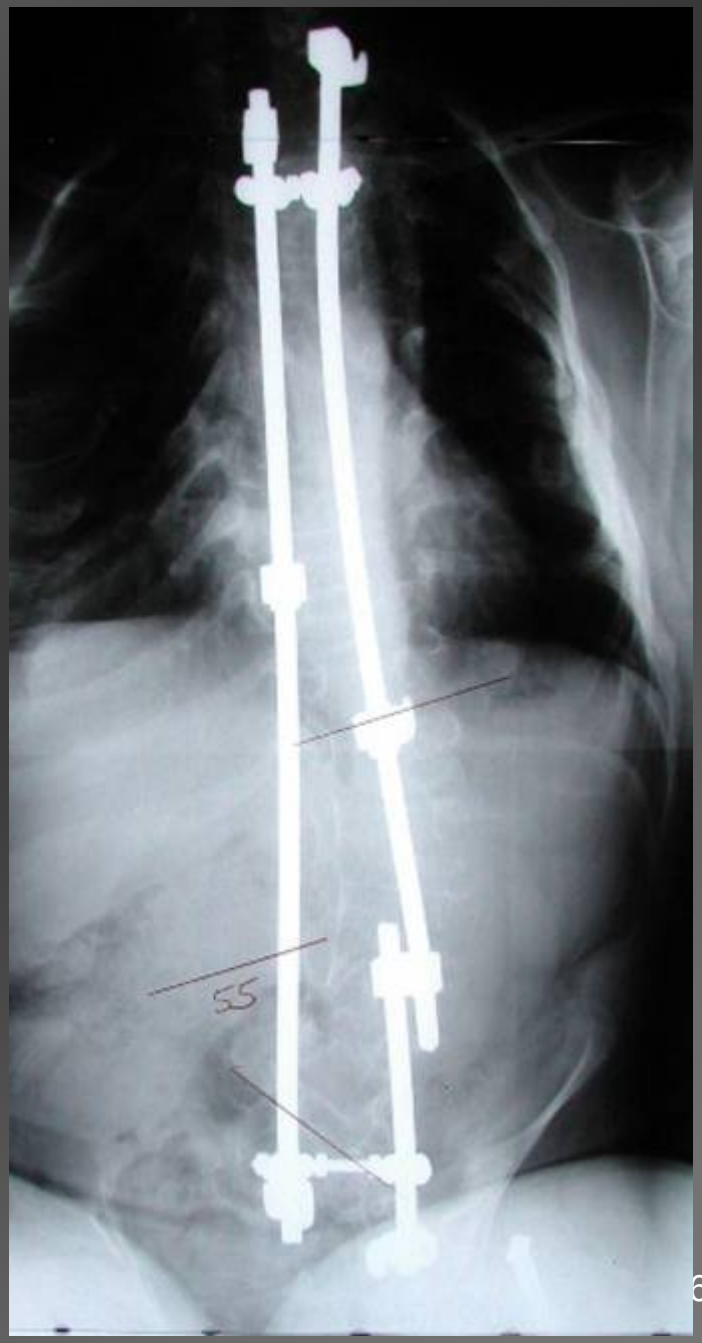
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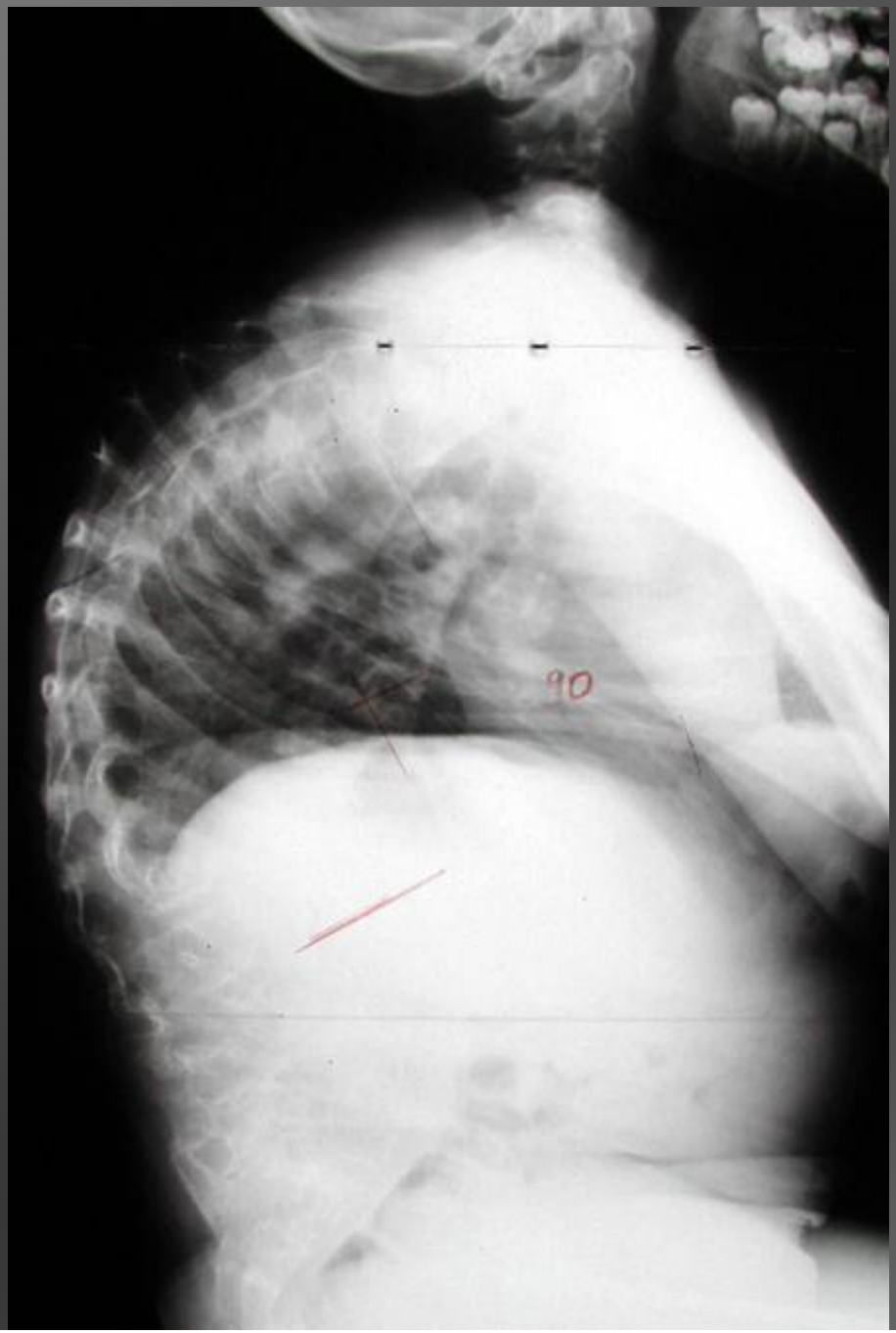
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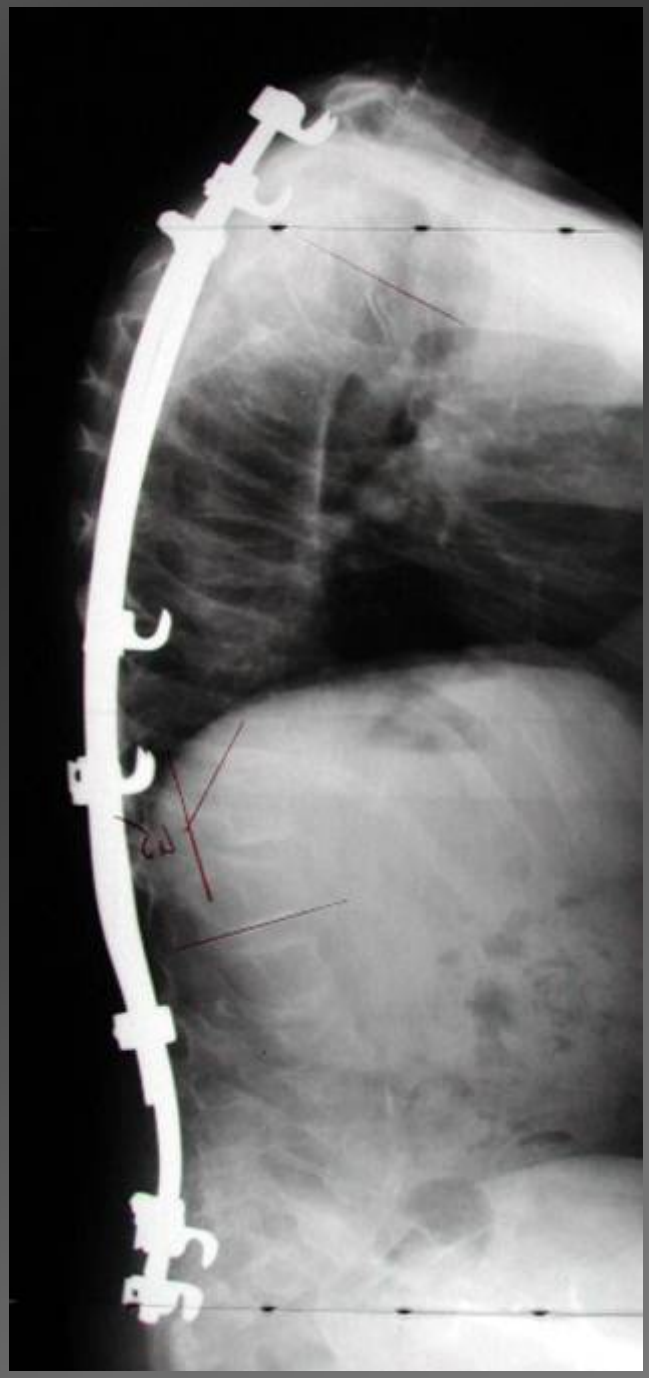
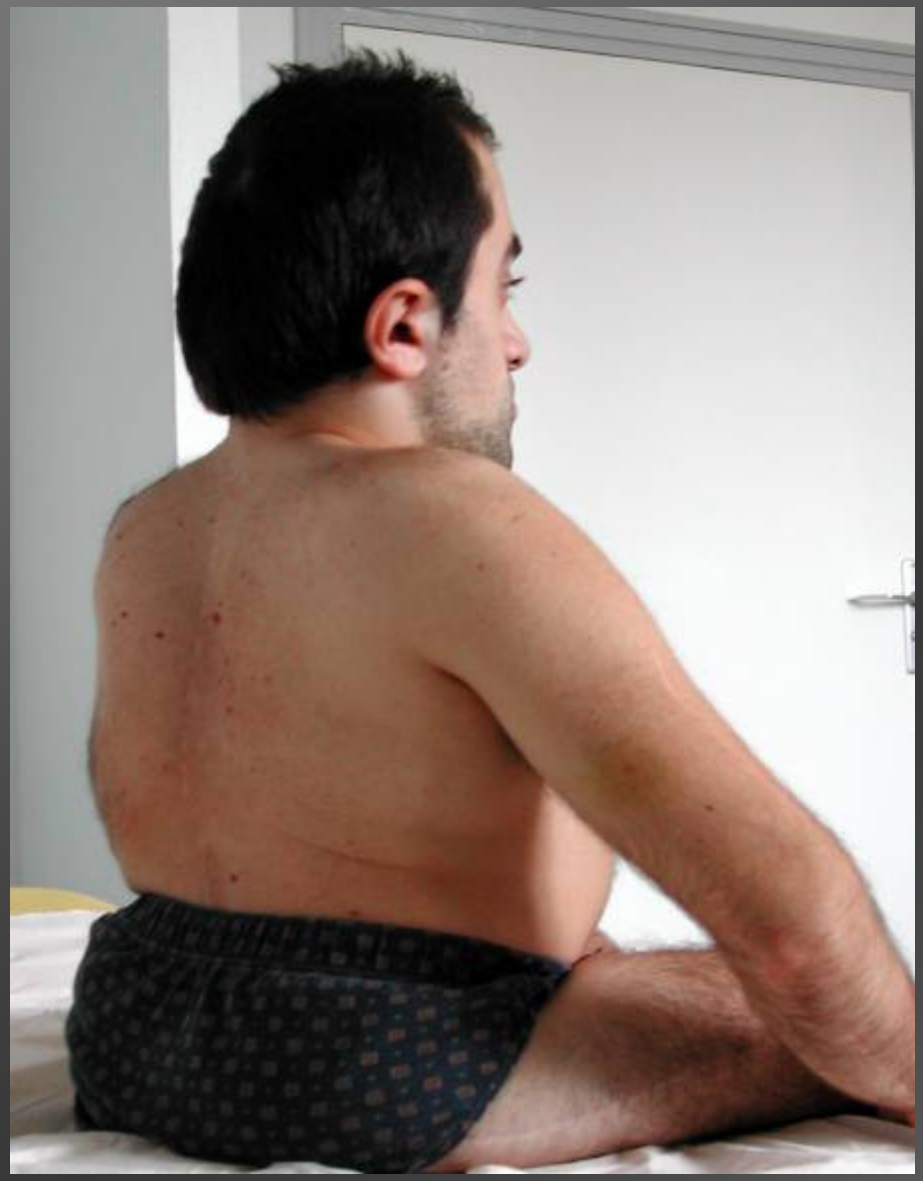
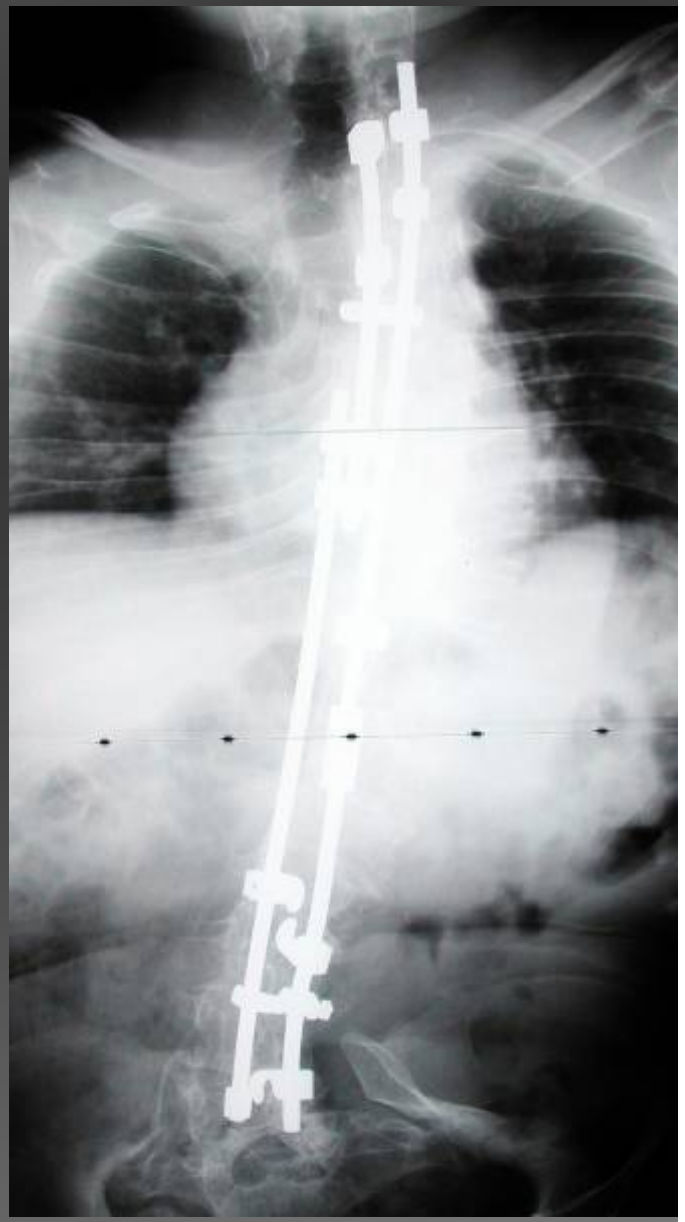
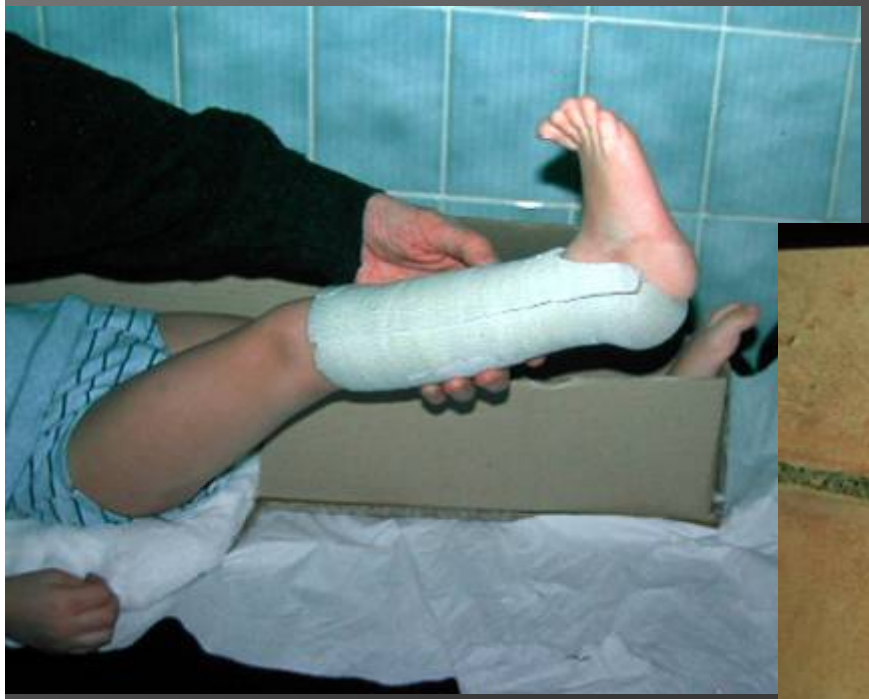
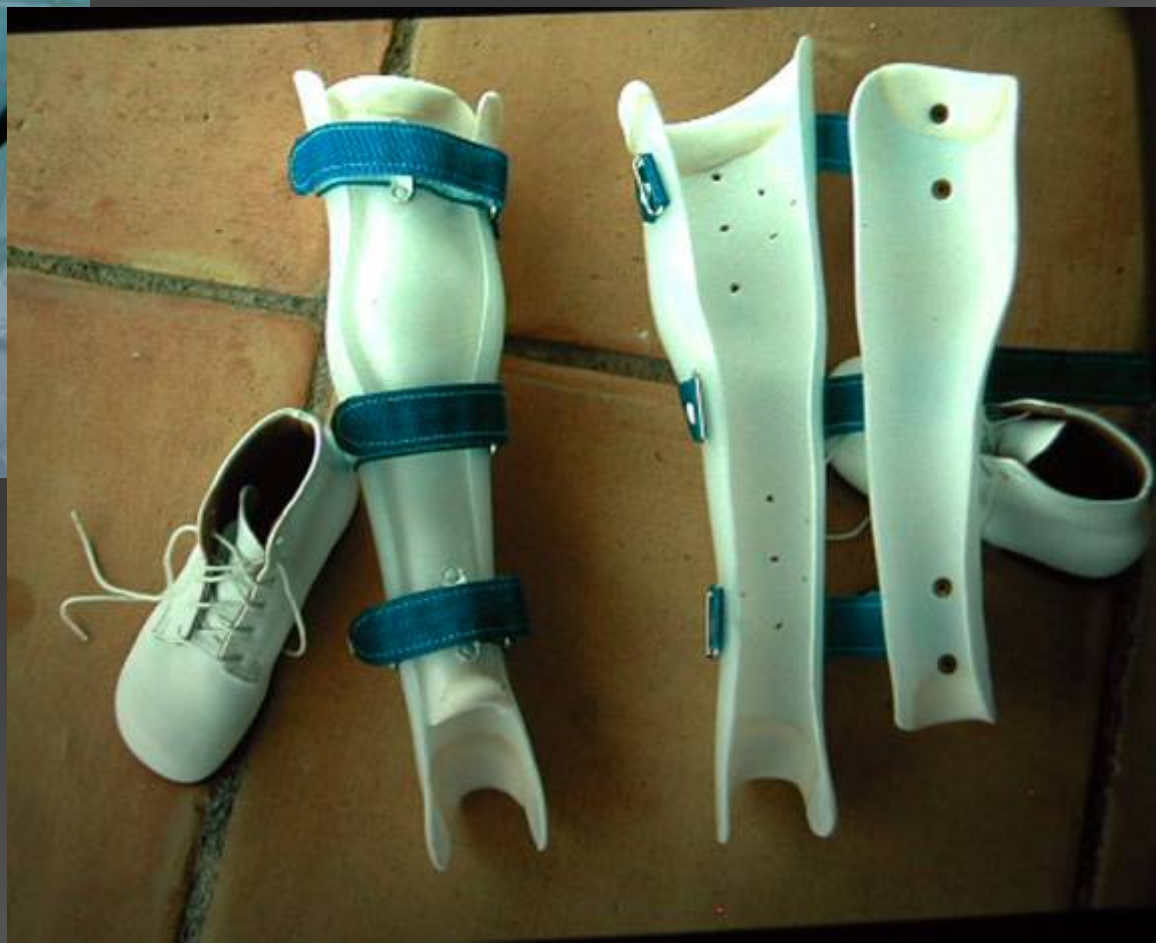


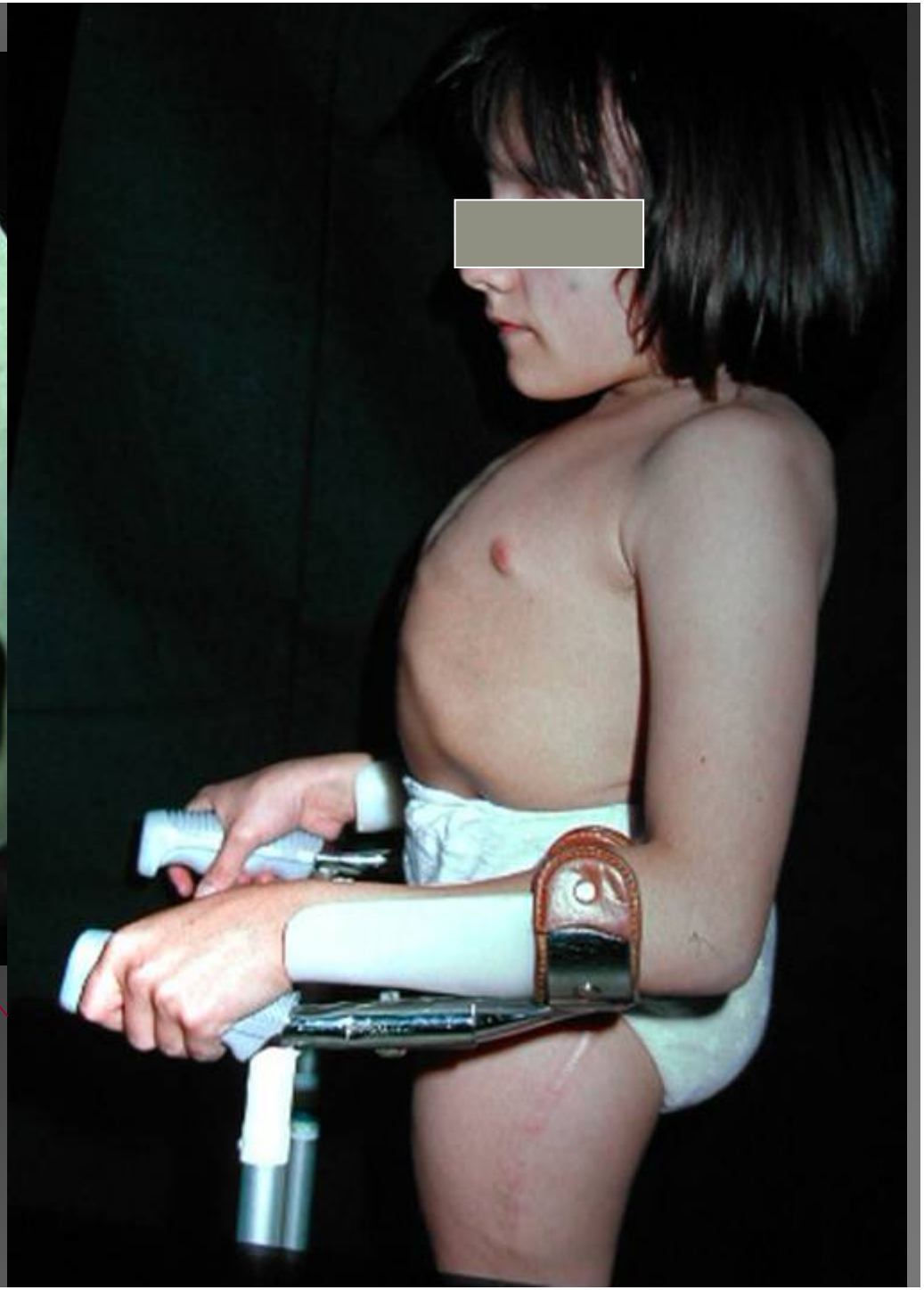




Specific orthopaedic appliance







Other management principes

- Hearing loss
  - Detection after 2 y
  - Conductive and perception
  - 50% of OI adults
  - Delicate surgery (bleeding)
- DI
- Heart defect
  - After 10 years, regular detection
- Pulmonary function
  - Systematic evaluation of respiratory capacities when BP are required (protocol in progress)

OI: a multidisciplinary consortium

- stomatology
- orthopedy
- otorhinolaryngology
- pneumology
- endocrinology
- geneticists
- psychologist
- obstetric

-!!!!Transition between paediactic and adult age

-Génétique

-M. Le Merrer
-V. Cormier Daire
-L. Legeai Mallet
-MC. Nolen
-S. Heuertz
-C. Benoît Lasselin
-E. Mugnery
-L.Schribler
-A.Jonquoy
-A. Munnich
-S. Gauvin

-Orthopédie

- G. Finidori
- V. Topouchian
- S. Pannier
- C. Glorion
- JP Padovani
- P. Anract
- D. Hannouche

Mr Maroteaux

-Rhumatologie-R fonct

- C. Cormier
- C. Job Deslandes
- MC. de Vernejoul
- P. Orcel

-J. Beaudreuil

- C. Roux
- V. Forin

- Anesthésistes
- Neurochirurgiens

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

-Radiologues

-K. Lambot

-Stomatos

-Pr Ginisty
-Dr Michel

-ORL

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

-Psychologues

-MC. Nolen
-A. Blime