Metabolic bone diseases causing tooth formation disturbances

Signe Beck-Nielsen, consultant, Ph.D.
Center for Rare Diseases, Skejby
Aarhus University Hospital
E-mail: sibeck@rm.dk
Tlf.: 51 92 14 60

1

Metabolic bone disease - Definition

- Medical disorders that affect all growing and mineralizing bone
- Caused by lack of minerals for mineralization such as calcium, phosphorous, or vitamin D, in addition to excess of mineralisation inhibitors
- Inborn or acquired hormonal disturbances as
  - Vitamin D deficiency
  - FGF23 excess
  - Hyperparathyroidism
- Tooth formation is affected when disturbances in bone mineralization occur during dental development

2

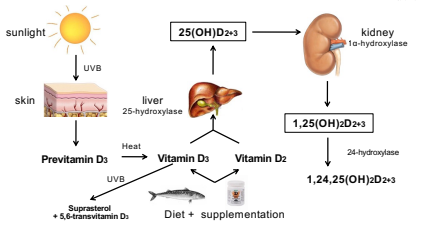
Agenda

- Vitamin D deficiency
  - Acquired: Nutritional VitD deficiency rickets
  - Inborn: VDDR1A
- Disturbances in phosphate homeostasis
  - Acquired: Tumor induced osteomalacia (TIO)
  - Inborn: Hypophosphatemic rickets, Fibrous dysplasia / McCune Albright
- Disturbances in calcium homeostasis
  - Acquired: Nutritional calcipenic rickets
  - Inborn: Hypoparathyroidism, 22q11del
- Increase in mineralization inhibitors
  - Inborn: Hypophosphatasia

→ Disease characteristics
→ Pathogenesis
→ Etiology
→ Dental characteristics
→ Treatment

3

Vitamin D - Synthesis



4

Vitamin D - Function

- Facilitates the intestinal absorption of calcium, magnesium and phosphate to ensure sufficient plasma-levels

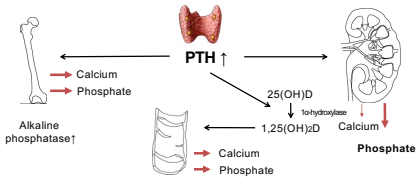
→ Optimal function of the nervous system, muscles and bone

- Extra-skeletal effects:
  Immune system, development of autoimmune diseases and cancer etc.
  But very few RCT, many association studies confounded by:
  - S-25(OH)D being a surrogate marker for a healthy lifestyle

5

Vitamin D Deficiency

When the VitD level is too low for a sufficient uptake of calcium from the diet
→ PTH (parathyroid hormone) increases:



6

Nutritional Rickets - Epidemiology

1985 – 2005

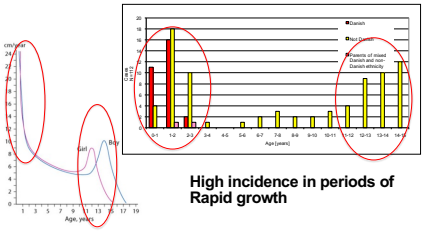
- 112 cases in Region of Southern Denmark
- 74% immigrant children primarily from the Middle East and Africa
  - Incidence 100/100.000/year (age 0-2,9y)
- Danish children aged 5-24 m
  - Incidence 2,0/100.000/year (age 0-2,9y)
  - 73% of all children with hypercalcaemic seizures
  - 53% of all children diagnosed before age 24 m

Ref: Beck-Nielsen SS et al., Eur J Endocr 2009

7

7

Nutritional Rickets - Epidemiology



High incidence in periods of Rapid growth

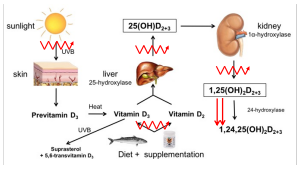
Ref.: Beck-Nielsen SS, et al. Eur J Pediatr 2009

8

8

Nutritional Rickets - Etiology

+ Calcium deficiency rickets



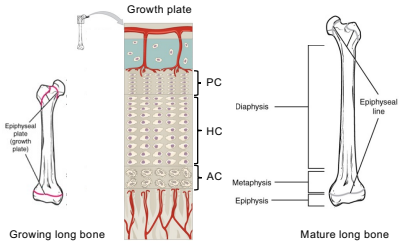
Primary
- Low sun exposure
- Low vitD intake

Secondary
- Malabsorption
- Liver failure
- CKD
- Medically induced

9

9

Growth of Long Bones



PC: Proliferating chondrocytes; HC: Hypertrophic C.; AC: Apoptosis of C.

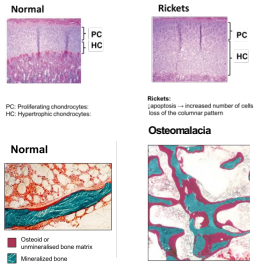
10

10

Rickets vs. osteomalacia

Rickets
- A consequence of long-standing vitamin D deficiency
- Only seen in growing children, characterized by defect mineralization of growth zones

Osteomalacia
- Defect mineralization of newly formed bone matrix, osteoid

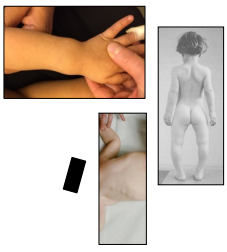


11

11

Rickets – Symptoms / skeletal manifestations

- Epiphyseal swelling
- Genu varus / valgus
- Rachitic rosary
- Hypocalcaemic seizures
- Fractures
- Growth retardation
- Delayed motor milestones



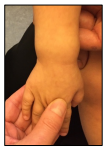
12

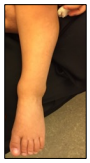
12

Case - Nutritional Rickets

Referral to the outpatient clinic:

- A 2 $^{7}/_{12}$ years old girl from Syria
- Short stature
- Suspicion of rickets

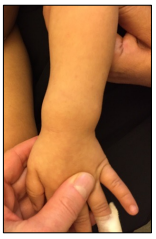


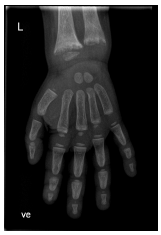


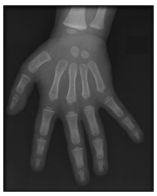
13

13

X-rays - wrist





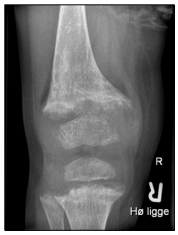


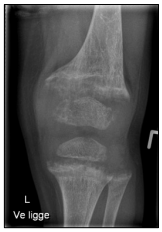
Normal X-ray

14

14

X-rays - knees





15

15

Treatment

- Vitamin D in high doses for 3 months
- Calcium supplementation
- Continued vitamin D prophylaxis

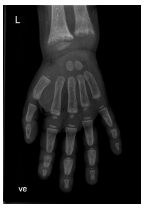
Ref: Beck-Nielsen SS – National behandlingsvejledning VitD mangel og rakitis http://paediatri.dk/

16

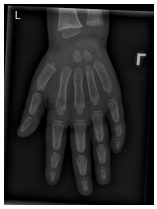
16

X-rays after 3 months of treatment

Debut



After 3 m

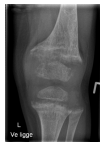


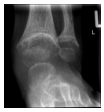
17

17

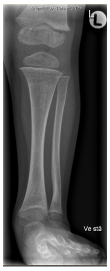
X-rays after 3 months of treatment

Debut





After 3 m



18

18

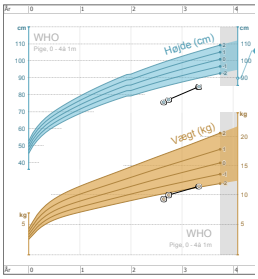
Growth

Debut:

Height: 75,6 cm (-4,5 SD)
Weight: 9,3 kg (-2,8 SD)

After 9 m:

Height 84,8 cm (-3,3 SD)
Weigt 11,5 kg (-1,9 SD)



19

19

Tooth development

Crown Mineralization of Primary Teeth

Tooth	Beginning of Crown Mineralization	End of Crown Mineralization
Central incisor	3–4 intrauterine months	4–5 months
Lateral incisor	3–4 intrauterine months	4–5 months
Canine	5 intrauterine months	9 months
First molar	5 intrauterine months	6 months
Second molar	6 intrauterine months	10–12 months

Crown Mineralization of Permanent Teeth

Tooth	Beginning of Crown Mineralization	End of Crown Mineralization
Central incisor	3–4 months	4–5 years
Lateral incisor	3–4 months	4–5 years
Canine	4–5 months	6–7 years
First premolar	1.5–2 years	5–6 years
Second premolar	2–2.5 years	6–7 years
First molar	Birth	2.5–3 years
Second molar	2.5–3 years	7–8 years
Third molar	7–10 years	12–16 years

ref: Davit-Béal et al, Pediatrics 2014

20

20

Dental manifestations after vitamin D deficiency rickets in an 11y old girl

Enamel hypoplasias of the permanent incisors and canines of the upper and lower dental arch in addition to the the first molars of the upper arch

Symmetric affection within the dental arches

Upper arch; severe affection of the *first molar whereas the **premolars are only slightly affected

Lower arch; severe affection of the *first molar and og ***primary molar, dxt.

Estimated time for disrupted dental formation; before 2,5-3 y

ref: Davit-Béal et al, Pediatrics 2014

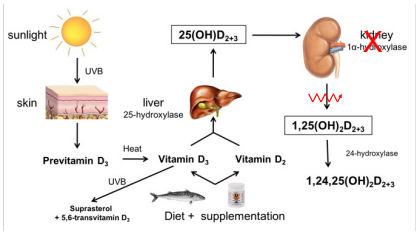
21

21

VDDR-1A, 1α-hydroxylase deficiency

Vitamin D deficiency
VDDR-IA
Disturbances in phosphate homeostasis
Hypophosphatemic rickets
Fibrous dysplasia / McCune-Albright
TIO
Disturbances in calcium homeostasis
Hypoparathyroidism, DiGeorge
Increase in mineralization inhibitors
Hypophosphatasia

Incidence: 0.3/100.000

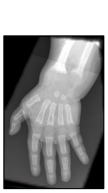


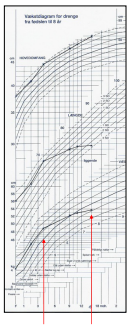
22

22

Case - VDDR-1A

- Referral 15 months of age
- Delayed motor development from 10 months of age and decreased growth velocity
- Height: -2.5 SD
- Weight: -1 SD
- Head circumference: +3 SD
- Clinical signs of rickets
- Laboratory values:
  Hypocalcemia, hyperparathyroidism, low phosphate, elevated ALP, normal 25(OH)D, calcitriol unmeasurable
- Inactivating mutation in *CYP24B1*



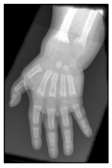


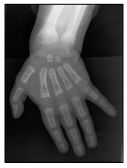
23

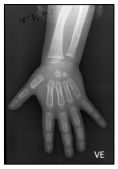
23

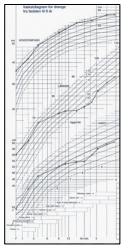
Treatment

- Activated vitamin D (Etalpha®)
- Calcium supplementation









Debut | Treated for 3 mo | Treated for 12 mo

24

24

Dental manifestations at age 8 years

- Enamel hypoplasia and deep cavities in the permanent first molars
- Enamel hypoplasia in the permanent incisors of the lower dental arch

→ Subsequently steel crowns attached to the molars

Gjørup et. al., Clin Oral Invest 2017

25

25

Hypophosphatemic rickets - XLH

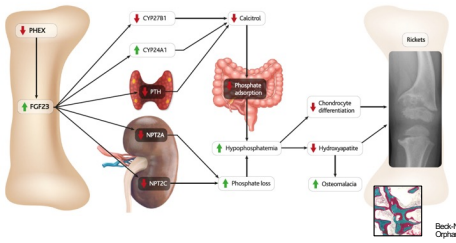
Vitamin D deficiency
Nutritional VitD deficiency rickets
VDDRIA
Disturbances in phosphate homeostasis
Hypophosphatemic rickets
Fibrous dysplasia/ McCune-Albright
TIO
Disturbances in calcium homeostasis
Hypoparathyroidism, 22q11del
Increase in mineralization inhibitors
Hypophosphatasia

- Epidemiology
  - 3.9/100,000/year
- Diagnosis
  - First to second year of life
- Etiology
  - Inactivating mutation in *PHEX*
- Endocrine manifestations
  - Abnormal renal phosphate wasting
  - Inappropriately low $1,25(OH)_2D$, the hypophosphatemia taken into account

26

26

Excess of FGF23 causing hypophosphatemia



Beck-Nielsen SS et.al., Orphanet J Rare Dis. 2019

27

27

XLH - Clinical signs and symptoms

Clinical signs:
- Disproportionate short stature
- Bowing of weight-bearing extremities
- Epiphyseal swelling
- Spontaneous dental abscesses
- Craniosynostosis

Symptoms:
- Pain – refuses weight bearing

History:
- Family history of rickets
- Compliance with vitamin D prophylaxis
- No improvement on vitamin D treatment

With permission from parents
Doyere et al. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2009;107:525

28

28

Chiari type 1 malformation

Chiari I malformation in
~20-50% of XLH[1,2]

Symptoms:
- Headache
- Paraesthesia
- Cerebellar symptoms
- Or asymptomatic

Chiari I malformation
A herniation of the cerebellar tonsils through the foramen magnum of > 5mm

1. Haffner et al. *Nat Rev Nephrol* 2019;15:435
2. Rothenbuhler et al. J Bone Miner Res. 2019;34:490-496. Carranza et al. *Pediatr Radiol* 2007; 37:805-812

29

29

Craniofacial changes

Increased thickening of theca

Flattening of the cranial base

Reduced height of the posterior cranial fossa

Decreased posterior fossa volume

Decreased dimensions
Increased dimensions

Gjorup H et al. Am J Med Genet A. 2011

30

30

Case – XLH

Anamnesis:
Boy 21 months of age

Exhaustion earlier than peers when walking

Bowing of legs worsening after he started ambulating at 13 months
Elongated head shape with narrowing of the occiput since birth

No history of dental problems

No family history, Danish ethnicity

Full compliance to vitD prophylaxis
Low dairy intake – limited to a little breast milk

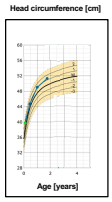
Clinical examination:
Normal dentition
Palpable rachitic rosary and epiphyseal swelling

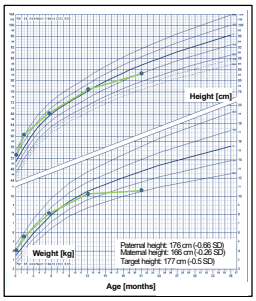
With permission from parents

31

31

Growth charts

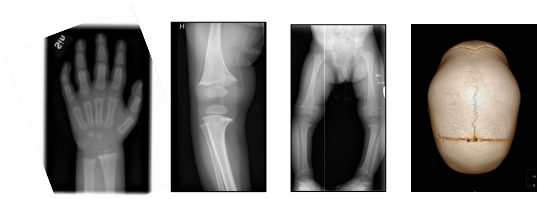




Height: 82.5 cm (-1.1 SD)
Weight: 10.6 kg (-1.9 SD)
Head circumference: 51.3 cm (+1.3 SD)

32

X-rays / CT scan



33

33

Genetic analyses

XLH caused by a *PHEX-mutation*:
= Most common form of hypophosphatemic rickets

***PHEX* c.2248T>C, class 5**

Mother:
Normal phenotype
No dental problems
No history of childhood bowing of legs
Normal height: 166 cm (-0.26 SD)

No *PHEX* mutation

www.xlhlink.com

34

34

Initial treatment

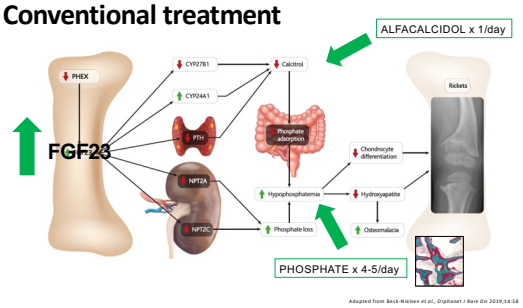
To address calcium insufficiency:
- Increase dairy intake to 0.5+ liters/day

- Treatment for hypophosphatemic rickets is initiated after correction of low calcium intake
  - Up titration of phosphate mixture to 45mg/kg over three weeks
  - One-Alpha 0.5 ug (45 ng/kg)

35

35

Conventional treatment



Adapted from Beck-Nielsen et al., Orphanet J Rare Dis 2019;14:58

36

36

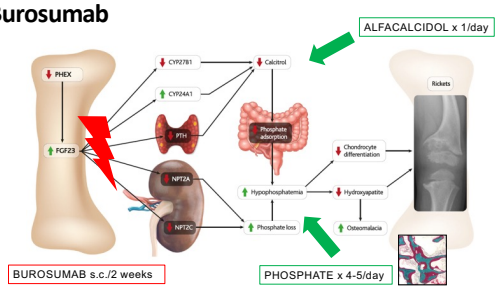
Burosumab treatment

- Treatment initiated when all Danish criteria were fulfilled:
  - Diagnosis of XLH with verified *PHEX* mutation
  - Age > 1 year
  - Hypophosphatemia
  - Thacher Rickets Severity Score (RSS)[1] of 2 or more (= 4.5)
  - Normal eGFR

[1]Thacher TD, et.al.: Radiographic scoring method for the assessment of the severity of nutritional rickets. J Trop Pediatr. 2000;46(3):132-9.

37

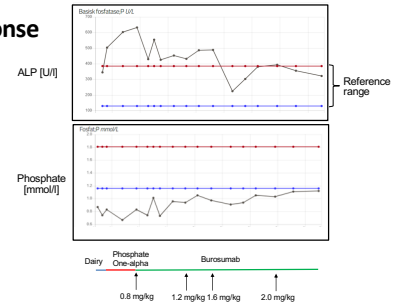
Burosumab



Adapted from Beck-Nielsen et.al., Orphanet J Rare Dis 2019;14:58

38

Treatment response



Treatment:
Increased calcium intake via dairy for 14 days

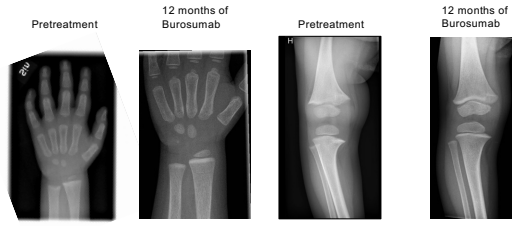
→ Phosphate + One-Alpha: 2.5 months

→ Burosumab: 12 months

ALP: Alkaline phosphatase

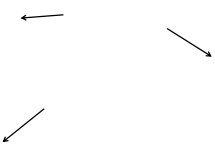
39

Radiolgical treatment response



40

Dental manifestations - XLH



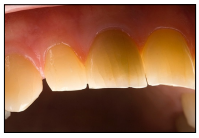
ref: Douyere et al., OOOOE 2009

41

41

Enamel - XLH

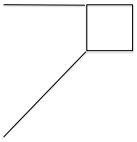
- Infractions – undetermined if greater prevalence compared to the background population
- Normal to thinner enamel (Boukpessi, 2016)
- Normal enamel (Chaussain-Miller 2007)



42

42

Dentin malformation - XLH



Dentin does not undergo remodeling as bone tissue

Large interglobular cavities due to lack of fusion of calcospherites (c) in the dentin

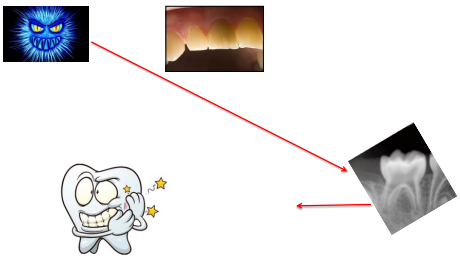
The cavities are filled with umineralized matrix

Ref: Chaussain-Miller et. al., Oal Dis 2007
Douyere et. al., ODODE 2009

43

43

Spontaneous dental abscesses - XLH



44

44

Fibrous Dysplasia (FD)

Vitamin D deficiency
Nutritional rickets/Vitamin D deficiency rickets
VDDRI/II
Disturbances in phosphate homeostasis
Hypophosphatemic rickets
Fibrous dysplasia / McCune Albright
TIO
Disturbances in calcium homeostasis
Hypoparathyroidism 25(OH)d
Increase in mineralization inhibitors
Hypophosphatasia

- Epidemiology
  - Unknown, frequent asymptomatic lesions
- Etiology
  - Post-zygotic activating mutation of the *GNAS* gene
  - Affects only somatic cells → not hereditary
  - → Osteoblastic differentiation defect
  - → Normal bone and marrow is replaced by fibrous tissue
- Diagnosis
  - Radiographic + Bone biopsy
- Endocrine manifestations
  - Excessive FGF23
  - Phosphaturia
  - Hypophosphatemia

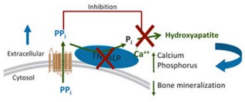
45

45

Hypophosphatasia

Vitamin D deficiency
Nutritional rickets/Vitamin D deficiency rickets
VDDRI/II
Disturbances in phosphate homeostasis
Hypophosphatemic rickets
Fibrous dysplasia / McCune Albright
TIO
Disturbances in calcium homeostasis
Nutritional rickets/Vitamin D deficiency rickets
Hypoparathyroidism 25(OH)d
Increase in mineralization inhibitors
Hypophosphatasia

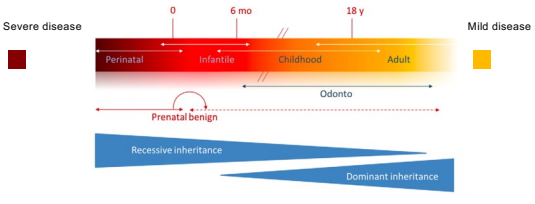
- Epidemiology
  - Estimated 1/100.000
- Etiology
  - Loss of function mutation in *ALPL*
  - Encodes the mineralization-associated enzyme, tissue-non-specific alkaline phosphatase (TNSALP)
  - TNSALP hydrolyses inorganic pyrophosphate (PPi)
  - PP$_i$ is a potent inhibitor of calcium phosphate crystal growth (hydroxyapatite)
  - Hydroxyapatite: inorganic mineral component of bone and teeth
- Diagnosis
  - Premature dental exfoliation
  - Low serum ALP
  - Rickets
  - X-ray: metaphyseal translucent toungue
  - Craniosynostosis / Wormian bones
  - Genetic analysis
- Endocrine manifestations
  - Hypophosphatemia



46

46

Hypophosphatasia - classification



47

47

Hypophosphatasia - Skeletal manifestations

a b c

a) Deformities of lower extremities; joint widening at knees and elbows

b) Hypomineralized bone, metaphyseal radiolucent toungue

c) Craniosynostosis (saggital suture) and Wormian bones

Mannes, I., Pediatric radiology, 2021

48

48

Hypophosphatasia - Dental manifestations

G) Premature loss of primary lower incisors in a 2.5y old child

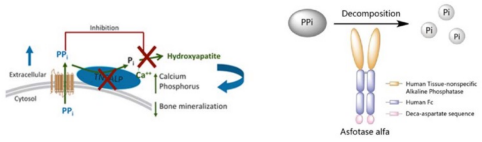
H) Exfoliated primary incisors, no root resorption

49

49

Hypophosphatasia - Medical treatment

- Asfotase Alfa, Strensiq®



50

50

Take home messages

- Dental disorders may be caused by metabolic disturbances in bone diseases
  - Metabolic bone diseases may cause dental disorders
- **TAK for et unikt og meget værdsat samarbejde imellem Center for Sjældne Sygdomme og Odontologisk Videncenter**

51

51

52

52