A Case of Rickets

Card 1: Case description

Leyla is a 5-year-old girl, born by Caesarean section for fetal macrosomy (birth weight 4520 g), without any perinatal problems. She was exclusively breast fed until 6 months of age, then switched to formula milk.

Since the age of 2 years Leyla has been complaining of recurrent hip pain and the mother reports that the baby does not walk normally. The orthopedist prescribes corrective insoles as he noticed valgism of the knees and foot pronation. Due to the persistence of these signs, the girl undergoes a radiological examination which shows bone deformations and osteopenia. A diagnosis of rickets due to vitamin D deficiency is made and supplementation with vitamin D 400 IU/day is started.

After 2 years a deflection in the growth curve is noted and the child is sent to your specialist outpatient clinic. She is sent without any radiological or laboratory documentation. Upon clinical examination you notice a prominent forehead, valgism of the knees and brevity of the limbs.

Question

1) Which tests would you need to confirm or exclude the diagnosis of rickets?

Free text answer :

Expert answer:

Rickets is a radiological diagnosis. Usually x-ray images of the hands and limbs are obtained.

Card 2: Images

Question:

These are Leyla`s x-rays.

Which abnormalities can be see

Free text answer:

Expert answer:

Hand X-Ray: Marked widening of radial and ulnar metaphyses, swelling of periarticular soft tissue. Marked osteopenia of radial and ulnar diaphysis)

Limb X-Ray: Cup-shaped enlargement of distal femoral and proximal distal metaphases of the tibia. Curved deformity of the femoral, tibial and ulnar diaphyses. Marked osteopenia

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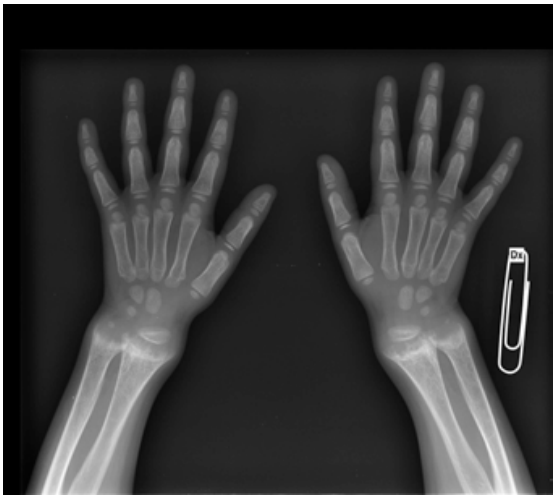
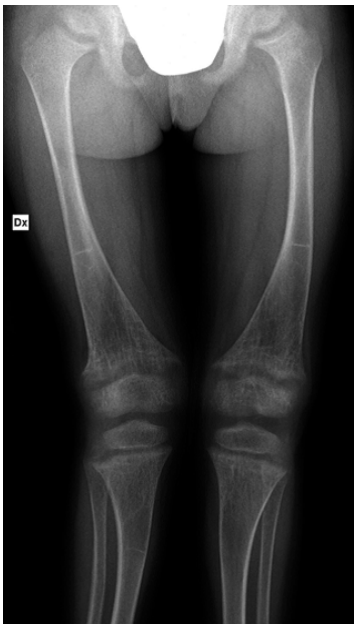




Card 3: Etiology

Question:

Based on the patient history and the X ray findings, what are possible etiologies of the patient's condition?

Multiple Choice question:

Expert answer:

Multiple Choice Answer:
A: X Rickets due to vitamin D deficiency
B: X Renal osteodystrophy
C: X Rickets associated with Fanconi syndrome
D: X Rickets of genetic origin

All answers are correct.

Rickets due to Vitamin D deficiency:
Vitamin D deficiency rickets is the result of insufficient amounts of vitamin D in the body. This deficiency may be caused by poor nutrition, a lack of exposure to the sun, or malabsorption syndromes in which the intestines do not adequately absorb nutrients from food. Vitamin D is needed for the metabolism of calcium and phosphorus in the body and affects how calcium is deposited in the bones.

Renal osteodystrophy:
Renal dysfunction is an important cause of bone disease (renal osteodystrophy), which can include rickets. In children with suspected rickets, renal function should be evaluated by measuring serum creatinine. Bone disease occurs in children with renal insufficiency for many reasons, including reduced formation of 1,25-dihydroxyvitamin D (1,25[OH]2D), secondary hyperparathyroidism, metabolic acidosis, and administration of aluminium containing phosphate binders.

Rickets associated with Fanconi syndrome:
Fanconi syndrome is a disorder of the renal proximal tubules that results in decreased reabsorption of phosphorus, glucose, and amino acids. Patients affected by this disease present hypophosphatemia, hyperphosphaturia, and a low tubular maximum inorganic phosphate concentration. Serum calcium is usually normal, alkaline phosphatase is elevated, PTH and 25(OH)D are normal, but serum 1,25(OH)2D is inappropriately low or low normal. Children with Fanconi syndrome have classic radiographic evidence of rickets.

Rickets of genetic origin:
Hereditary forms of hypophosphatemia or hypophosphatemic rickets include X-linked, autosomal dominant, and autosomal recessive disorders. In recent years several underlying genes have been identified in distinct forms of hypophosphatemic rickets. Phosphate deficiency may result from inappropriate absorption in the gut or reabsorption in the kidney. The latter situation can be further divided between defects of tubular reabsorption and abnormalities of circulating regulators of phosphate reabsorption.

Card 4: Regulation of phosphate homeostasis

Info Text

Regulation of phosphate homeostasis:

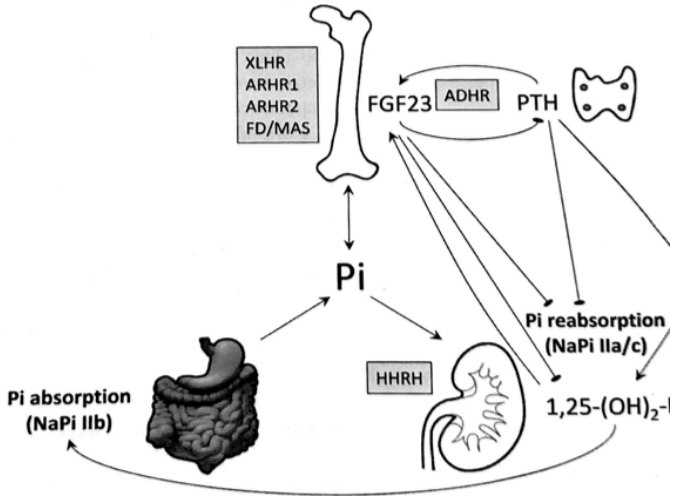
The amount of renal phosphate reabsorption is tightly regulated by dietary Pi intake, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). FGF23 and PTH both increase phosphaturia by reducing renal tubular phosphate reabsorption via inhibiting the sodium-phosphate cotransporters (NaPi IIa/IIc). Moreover, FGF23 inhibits the activation of vitamin D by 1-alpha hydroxylase in the kidney. 1,25(OH)2D increases the intestinal absorption of dietary phosphorus via upregulating NaPi IIb and activates FGF23 production.

In the figure the sites of molecular defects in the different genetic forms of hypophosphatemic disorders are shown:

XLHR: X-linked dominant hypophosphatemic rickets
ARHR1/2: autosomal recessive hypophosphatemic rickets type 1/2
FD/MAS: Fibrous dysplasia / McCune-Albright syndrome
HHRH: Hereditary hypophosphatemic rickets with hypercalciuria
ADHR: X-linked dominant hypophosphatemic rickets

Specific disease-causing mutations in genes involved in the regulation of phosphate homeostasis can be identified in approximately 85% of familial or sporadic cases of hypophosphatemia.

Card Main Multimedia



Card 5: Lab Tests 1

Question

What are the appropriate first-line laboratory tests to narrow down the differential diagnoses?

Freetext answer: (lab value question would also be possible)

Expert answer:

Serum and urine electrolytes
Alkaline phosphatase
PTH
Vitamin D level
Serum creatinine
Urinary glucose
Urinary amino acids

The tests show low serum phosphorus, elevated alkaline phosphatase and PTH, high normal urinary phosphorus concentration, normal vitamin D level, serum calcium and creatinine, and absent glucosuria and aminoaciduria.

Normal vitamin D levels exclude vitamin D deficiency, absent glucosuria and aminoaciduria exclude Fanconi syndrome, and normal serum creatinine rules out CKD-associated osteodystrophy.

Card 6: Lab Tests 2

Question

Urine phosphorus concentration is within the normal range.

Is there a better way to diagnose an inadequately high urinary phosporus excretion?

Multiple Choice Question:

Expert answer:

Multiple Choice Answer:

A: 24-hour phosphorus excretion
B: Urinary phosphorus/creatinine ratio
C: X TMP/GFR
D: Urinary/serum phosphorus ratio

Urine phosphorus concentrations may be normal despite impaired tubular reabsorption in the presence of low serum phosphorus levels.

Renal phosphorus loss can be reliably evaluated by the the tubular transport maximum of phsophorus relative to glomerular filtration rate (Tmp/GFR):

TmP/GFR = Pp - (Up x Pcr/Ucr), where Pp, Up, Pcr and Ucr refer to plasma and urine concentration of phosphate and creatinine, respectively. All values must be expressed in the same units.

The normal range of TmP/GFR is 1.2 to 2.6 mmol/l in infants and young children (0.5-6 years) and 0.6 to 1.7 mmol/l in adults.

The TmP/GFR of our patient is 0.8 mmol/l, i.e. markedly low for her age.

Card 7: Diagnosis

Question

What is the most likely diagnosis at this point?

Multiple Choice Question:

Expert answer:

Multiple Choice Answer:

A: O Rickets due to Vitamin D deficiency
B: O Renal osteodystrophy
C: O Rickets associated with Fanconi syndrome
D: X Rickets of genetic origin

At this point the answer is straightforward: Rickets of genetic origin. We can exclude rickets due to Vitamin D deficiency (Vit D in normal range, disease maniifestation already at 1 year of life), renal osteodystrophy (the patient has normal renal function) and rickets associated with Fanconi syndrome (absence of glycosuria of aminoaciduria).

Card 8: Diagnostics 2

Question

Now that you are suspecting a familial form of rickets, which is your next diagnostic step?

Multiple Choice Question:

Expert answer:

Multiple Choice Answer:

A: O Radiological examination of mother
B: O Radiological examination of father
C: O Laboratory examination of mother
D: O Bone biopsy
E: X Genetic testing in affected child

The clinician should order genetic screening for inherited forms of hypophosphatemic rickets.

The radiological examination of the parents can reveal whether the patient's parents are also affected by the disease (in case the disease is inherited by X-linked or autosomal dominant transmission) but it does not allow us to make a definitive diagnosis.

Bone biopsy will not clarify the etiology of the disease.

Card 9: Genetic result interpretation

Info Text

From the genetic test you learn that Layla carries a heterozygous point mutation in the PHEX gene leading to an amino acid exchange (c.501G>A, p.(Trp167).

Exploring the family history in more detail, you learn that the parents never experienced any bone pain or other bone symptoms and had a completely normal development. The patient's mother is only short in stature.

Question

How is it possible that Leyla is affected by an X-chromosomal disease although none of the parents are clinically affected?

Multiple Choice Question:

Expert answer:

Multiple Choice Answer:

A: O The defect is recessive and was transmitted from both mother and father to Leyla.
B: X She carries a de novo mutation.
C: X The mutation is transmitted as an X-linked dominant trait with complete penetrance, but variable expressivity.
D: X Mother’s short stature suggests that she is mildly affected and transmitted the disease to her daughter.
E: O The genetic test has to be repeated, for sure there is a mistake.

X-linked hypophosphatemic rickets is the most common genetic form of rickets. It is characterized by short stature, bone pain, radiological signs of rickets, increased fractional phosphate excretion, and low levels of 1.25-OH-vitamin D.

X-linked hypophosphatemic rickets, the incidence of which is estimated 1:20.000, is caused by the mutation in the "**P**hosphate regulating gene with **H**omology to **E**ndopeptidases"***(PHEX)*** located on the X chromosome. PHEX encodes an endopeptidase expressed predominantly in bone and teeth that regulates fibroblast growth factor 23 (FGF-23) turnover. PHEX mutations lead to increased circulating levels of FGF-23, a phosphate regulating hormone (phosphatonin) that leads to reduced renal tubular phosphate reabsorption and consequently decreased bone mineralization.

PHEX mutations are transmitted as an X-linked dominant trait with complete penetrance but variable expressivity. This disease seriously affects male subjects (46 xy) and may affect female subjects with variable grade of expressivity (46xx). In Leyla's case her father cannot be the carrier of the mutation as he would be expected to have a severe disease phenotype. The mutation may have been transmitted by her mother or it may have occurred *de novo.*

Card 10: Therapy

Question

What treatment will you initiate for the child?

Expert answer:

Multiple Choice Answer:

A: O Oral phosphorus supplementation
B: O Vitamin D supplementation
C: O Non-steroidal anti-inflammatory drugs
D: X Burosumab (anti-FGF23 antibody)
E: O Infliximab (anti-TNF antibody)

For more than 40 years, treatment for X-linked hypophosphatemia has consisted of multiple daily doses of oral phosphate salts and active vitamin D. The drawbacks of this conventional therapy include poor tolerability and compliance, mineralization of tissues outside bone, especially the kidneys (nephrocalcinosis), and secondary hyperparathyroidism. In addition, conventional therapy does not completely correct bone deformities and impaired growth.

The discovery of the molecular mechanism underlying this disease has permitted to develop a targeted pharmacological therapy, which since 2018 has revolutionized the life of patients affected by genetic forms of rickets.

Burosumab (Crysvita®), a fully human IgG1 monoclonal antibody directed at fibroblast growth factor 23 (FGF23), directly addresses the excessive FGF23 activity present in most genetic forms of rickets by binding to FGF23 and inhibiting its signaling. This leads to mormalized gastrointestinal phosphate absorption and renal phosphate reabsorption, thereby improving serum phosphate levels and consequently bone mineralization.

In clinical trials, two-weekly subcutaneous Burosumab administration increased serum phosphorus levels in pediatric and adult patients with XLH. In children rickets was markedly improved, and adults reported reduced pain and stiffness, improved physical functioning, and markedly accelerated healing of fractures/pseudofractures. Burosumab is well tolerated by children and adults. Currently the drug is approved only for children.

Card 11: Take home messages

Info Text

Summary

- The precise diagnosis of the cause of rickets is fundamental for the correct therapy and prognosis.
- Late rickets is always genetic rickets.
- The most common genetic form of rickets is X-linked hypophosphatemic rickets. This disease is always manifest and severe in males but can express itself with different grades of severity in females.
- Burosumab (Crysvita®), a fully human IgG1 monoclonal antibody directed at fibroblast growth factor 23 (FGF23), is the treatment of choice for X-linked hypophosphatemia (XLH).
