

RICKETS IN CHILDREN

DEFINITION: Rickets is a disorder of defective chondrocyte differentiation and defective osteoid mineralization of the growth plate, is caused by vitamin D deficiency and/or low calcium intake in children.

- The diagnosis of rickets is made of history, physical examination, biochemical testing and is confirmed by radiographs.
- (Global consensus recommendation..,2016)

Hystory

- Rickets (from Greek word mean spinal column) was known since the first years of the human generation.
- It is described by Galen (134-211 A.D), in detail by a British anatomist and orthopedist Glisson in 1650.
- Incidence:
- Rickets is frequently in premature children and if the children fed only wheat flour.
- In Moldova the incidence of rickets twice less during the last 5 years ().

Maternal risk factors

- High latitude during winter/spring season.
- Dark skin pigmentation.
- Restricted exposure to sunlight (pollution, cloud cover, humid climate).
- Maternal vitamin D or calcium deficiency.

Infant risk factors

- Neonatal vitamin D deficiency secondary to maternal.
- Lack of supplementation with vitamin D.
- Diet low in calcium, phosphorus and vitamin D.
- Exclusive breast-feeding into late infancy, toddlers on unsupervised „dairy-free” diets.
- Prolonged parenteral nutrition in infancy with an inadequate supply of intravenous calcium and phosphate.
- Malnutrition, poverty, strict vegetarian diet.

ETIOLOGY

- Rickets is due to partial deficiency, rarely complete deficiency of vitamin D.
- Vitamin D exist in 2 forms in the human body.
- Vitamin D2, exogenous form (calciferol), from ergosterol in the food
- Vitamin D3, endogenous form (cholecalciferol or provitamin stage 7-dehydrocholecalciferol, naturally present in human skin), activated by UV rays of 296-310nm wave length.
- Natural alimentation does not supply the daily requirement of 400-500IU of vitamin D in a baby.
- Breast milk contains 30-50IU/liter, cow's milk 20-30IU/l, egg yolk contains 20-50IU/10gr.
- 80% of the vitamin D is absorbed in the small intestine in the present of normal biliary secretion.
- Vitamin D reaches the blood through thoracic duct along with chilomicrons.

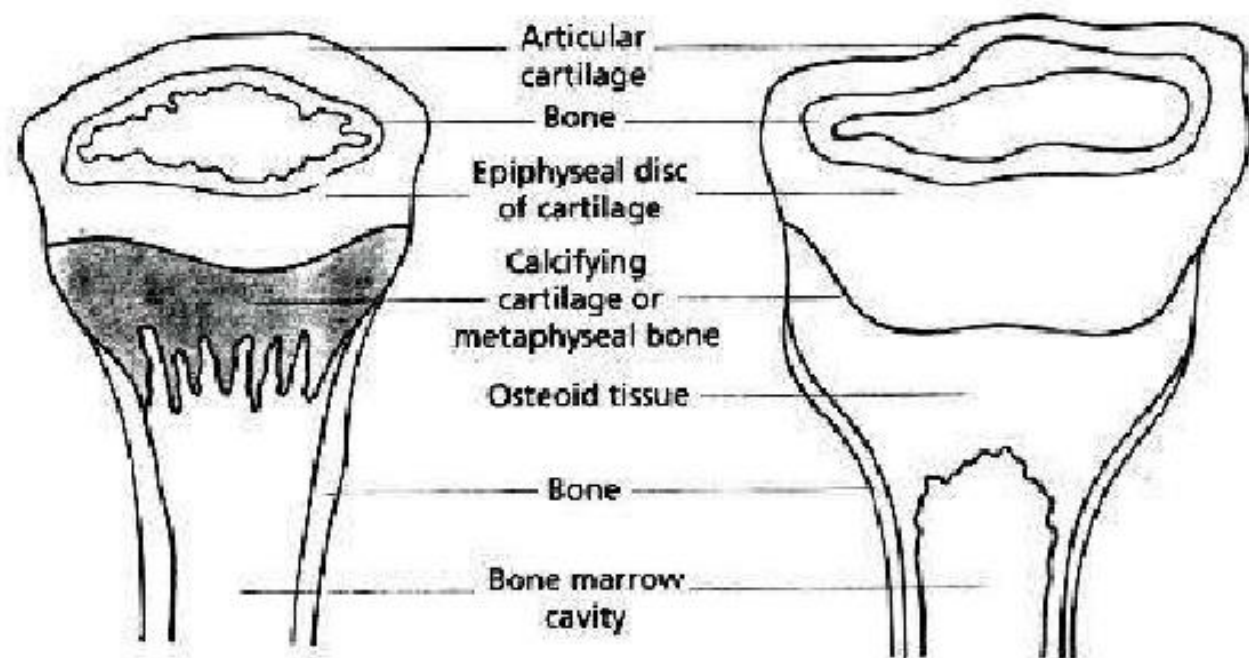
- Intestinal malabsorption: defective production of 25(OH)D3 – liver disease. Increased metabolism of 25(OH)D3 – enzyme induction by anticonvulsants;

Defective production of 1,25(OH)2D3

- Hereditary type I vitamin D-resistant (or dependent) rickets (mutation which abolishes activity of renal hydroxylase);
- Familial (X-linked) hypophosphataemic rickets – renal tubular defect in phosphate transport;
- Chronic renal disease;
- Fanconi syndrome (renal loss of phosphate)
- Target organ resistance to 1,25(OH)2D3- hereditary vitamin D-dependent rickets type II (due to mutations in vitamin D receptor gene).

Pathogenesis

In Ricket cartilage cells fail to complete their normal cycle of proliferation and degeneration; subsequent failure of capillary penetration occurs in a patchy manner(Fig)



(d) Normal tibia

(e) Rachitic tibia

Calcium and phosphorus metabolism

- Calcium is important during child body growth, 90% is localized in the bones, apart Ca ions take part in neuromuscular excitability, blood clotting et al. In blood plasma is bounded with proteins, albumins, anions (lactates, phosphates, bicarbonates, citrates).
- Metabolism of phosphorus interlinked with calcium in bones and cells, both are absorbed in small intestine, and are controlled by vitamin D.
- Parathyroid hormone decreases the level of phosphorus in blood, while calcitonin increases it.

- Calcium regulation in the blood is as follows:
- Vitamin D2 in the food (exogenous) + vitamin D3 (skin, endogenous) \Rightarrow liver microsomal hydroxylase \Rightarrow 25(OH) D3
- In the renal cortical cells \Rightarrow activated from 1 α -hydroxylase in 3 forms:
- 24,25 (OH)₂ D3; 1,24,25 (OH)₂ D3; 1,25 (OH)₂ D3 end product considered a hormone.
- In placental macrophage of pregnancy women are present 1,25(OH)₂ D3

Functions of vitamin D

Intestine- 1,25(OH)₂D₃ promote:

- Increases calcium binding protein
- Active transport in the jejunal cells
- Phosphorus ions absorption through specific phosphate carrier
- Alkaline phosphatase (AP) synthesis
- ATP-ase sensibility to calcium ions

Bones

- Mineralization of the bone and osteoblasts differentiation in presence of adequate calcium and phosphorus
- Deposition and reabsorption of calcium and phosphorus, normal calcification
- Skeletal growth and mineralization involve vitamin D-PTH-endocrine axis, growth hormone via somatomedins, thyroid hormones, insulin, androgens and estrogens in puberty

Kidney

- 1,25(OH)₂D₃ increase tubular reabsorption of calcium and phosphorus
- In rickets PTH blocks phosphorus reabsorption in kidney, elevated serum phosphatase due to increase osteoblastic activity
- Hypophosphatemia blocks PTH secretion and promotes 1,25(OH)₂D₃ synthesis, the most active metabolite of vitamin D

Muscles

- Vitamin D increase the muscular protein and the ATP in myocytes
- Improve tonicity and the normal contraction of the muscles

Parathyroid glands

- $1,25(\text{OH})_2\text{D}$ has direct feedback to PTH synthesis
- Low plasma calcium \Rightarrow PTH secretion restore Ca from bone demineralization
- Secretion of PTH stimulate synthesis of $1,25(\text{OH})_2\text{D}_3$, increase calcium intestinal absorption, renal calcium reabsorption
- Calcitonin (secretion of C cells of thyroid gland) increase bone calcium deposition

Other effects of vitamin D

- Cellular metabolism: citric acid oxidation
- Formation of soluble complex of citrate and Ca in the blood
- Skin differentiations in the local treatment of Psoriasis
- Pulmonary differentiation (increases the surfactant in preterm infants)
- Immunomodulatory action in autoimmune disorders

Biochemical stages of rickets

- Stage 1: Low plasma calcium, normal plasma phosphate level;
- Normal serum PTH, raised serum alkaline phosphatase, Ca and P tubular re-absorption are normal, no amino acid loss in the urine.

Biochemical stages of rickets

Stage 2. Raised PTH in the serum, serum Ca is normalized by bone demineralization.

Change in the ratio of Ca : P (N=2:1), in this stage become 3:1 or 4:1, high serum AP.

Raised Ca tubular re-absorption and decrease phosphate tubular re-absorption.

As a result => hyper-aminoaciduria.
Phosphates are lost in the urine, alkaline Ph.

X-ray findings: Osteoporosis and metaphyseal-epiphyseal changes.

Biochemical stages of rickets

Stage 3. Severe deficiency of vit.D for a long duration. Laboratory reports:

Hypocalcemia, hypophosphatemia, serum elevated of AP, PTH; hyperaminoaciduria, Radiological changes more expressive.

Biochemical disturbances in rickets pathogenesis based on a three-stage classification of vitamin D status (symbolized by the sun) and calcium intake (symbolized by a glass of milk).

Osteoid & Growth Plate Mineralization

Vitamin D - Calcium Intake

Normal		<div>Normal - Normal</div> <div>Normal - Insufficient</div> <div>Insufficient - Normal</div>
<div>Normal</div> <hr style="border-top: 1px dashed red;"/> <div>Early Biochemical Abnormalities</div>		<div>Normal - Deficient</div> <div>Deficient - Normal</div> <div>Insufficient - Insufficient</div>
Rickets Osteomalacia		<div>Insufficient - Deficient</div> <div>Deficient - Insufficient</div> <div>Deficient - Deficient</div>

Classification of vitamin D status

Are based on serum 25-hydroxyvitamin D (25 OHD) concentration in infants with clinical signs of rickets- normal value $>50\text{nmol/L}$. Is not recommended routine 25OHD screening in healthy children.

Depending on the clinical manifestation there are mild, moderate and severe form. Evolution acute, subacute, recurrent.

Depending on vitamin D insufficiency: diet, infections, food diversification, prophylaxis with low dose of vitamin D, drug induced (e.g., phenytoin therapy, phenobarbital).

CLINICAL MANIFESTATIONS

Rickets may develop in any age of an infant, more frequent at 3-6mo, early in premature infants.

- The first signs of hypocalcemia are CNS changes- excitation, restlessness, excessive sweating during sleep and feeding, tremors of the chin and extremities.
- Skin and muscle changes- pallor, occipital alopecia, fragile nails and hair, muscular weakness, motor retardation.
- Complications- apnea, stridor, low calcium level with neuromuscular irritability (tetany).
- CNS changes are sometimes interpreted as CNS trauma and the administration of the Phenobarbital which interfere in metabolism of vitamin D and after 1-2wk of treatment with Phenobarbital the clinical stage worsens.

ACUTE SIGNS

Acute rickets clinical signs:

- Craniotabes— osteomalacia, acute sign of rickets, detected by pressing firmly over the occipital or posterior parietal bones, Ping-Pong ball sensation will be felt. Large anterior fontanel, hyperflexible borders, cranial deformation with asymmetric occipital flattening.

SUBACUTE SIGNS

- Subacute signs are all the following: frontal and temporal bossing
- False closure of sutures (increase protein matrix), in the X-ray craniostenosis is absent.
- Maxilla in the form of trapezium, abnormal dentition.
- Late teeth eruption, enamel defects in the temporary and permanent dentition.
- Enlarged costochondral joints-“rachitic rosary”, felt lateral to the nipple line.
- Chest, sternum deformation, softened lower rib cage at the site of attachment of the diaphragm- Harrison groove.





Poor muscle tone

Relaxation of feet

Bent the limbs into any position



Clinical manifestation of rickets

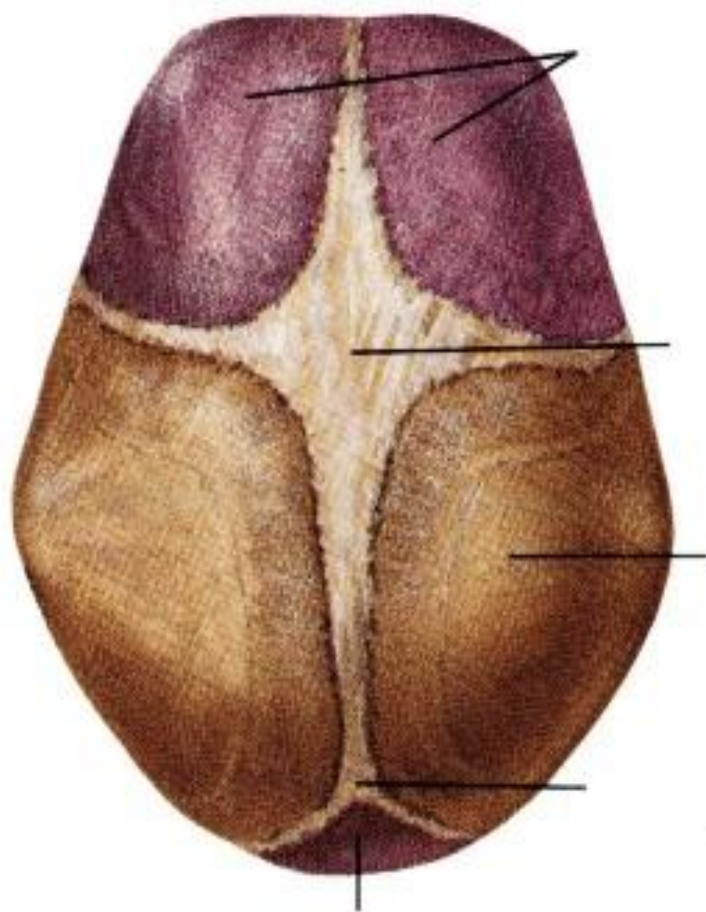
Muscular hypotony



Tibia convexity









boxlike appearance





Subacute rickets signs

- Spinal column- scoliosis, lordosis, kyphosis.
- Pelvis deformity, entrance is narrowed (result in cesarean section in females)
- Extremities- thickening wrist and ankles, tibia anterior convexity, bowlegs or knock knees legs.
- Deformities of the spine, pelvis and legs result in reduced stature, rachitic dwarfism.
- Delayed motor development (head holding, sitting, standing, walking).



Expansion of wrists





Genu varum (bowed legs)



Genu valgum (knock knee)

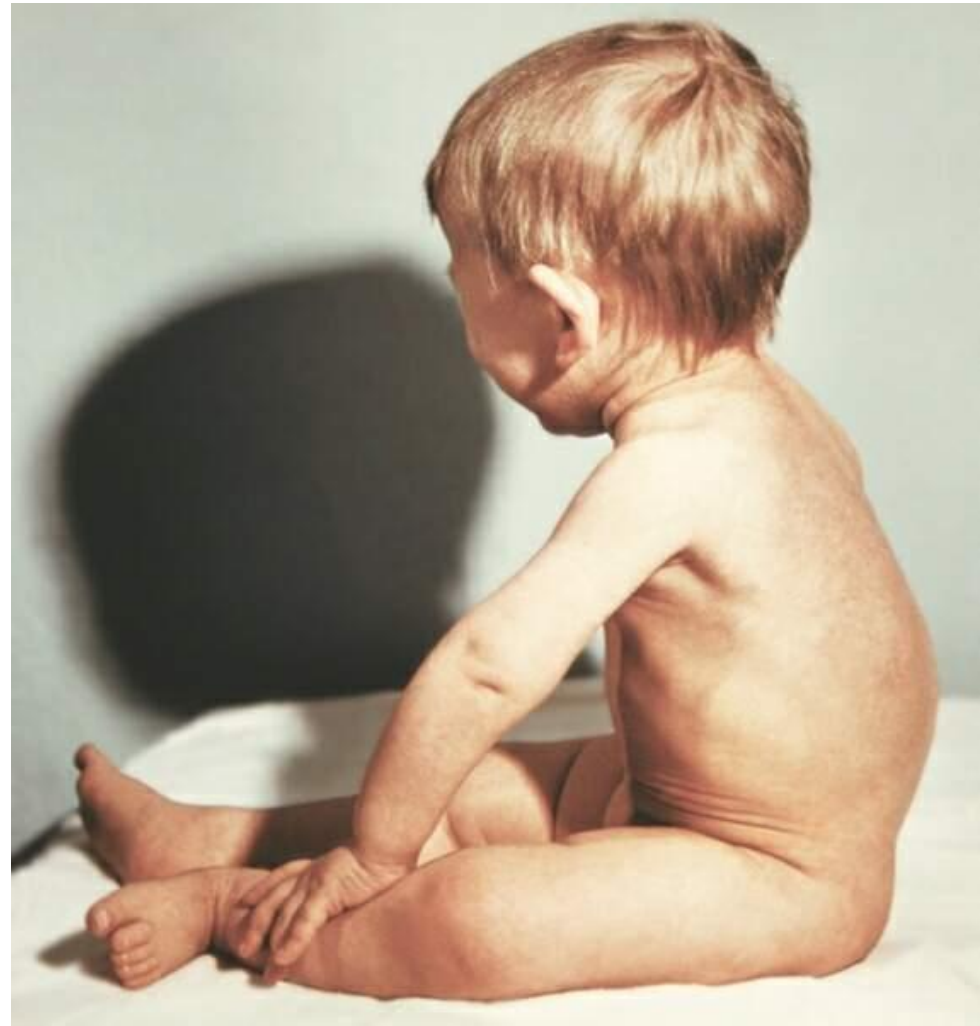


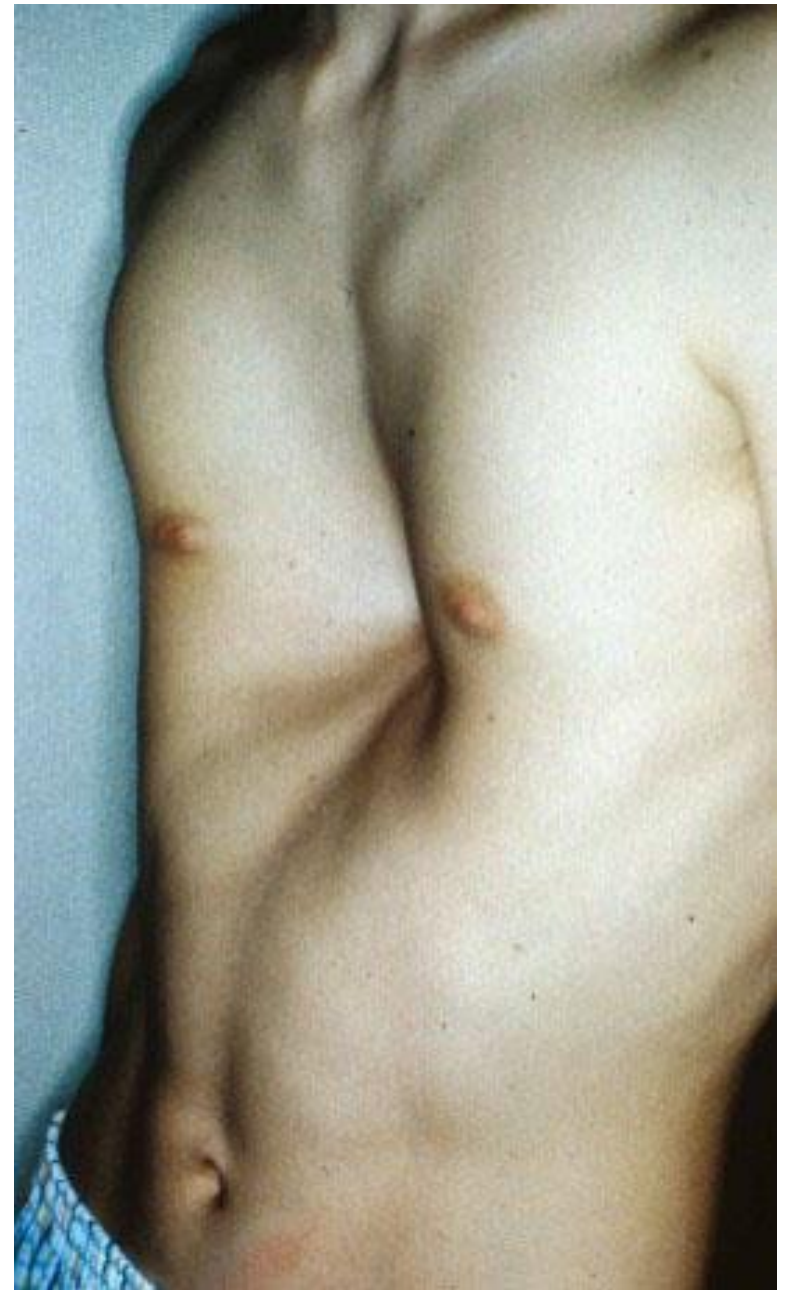
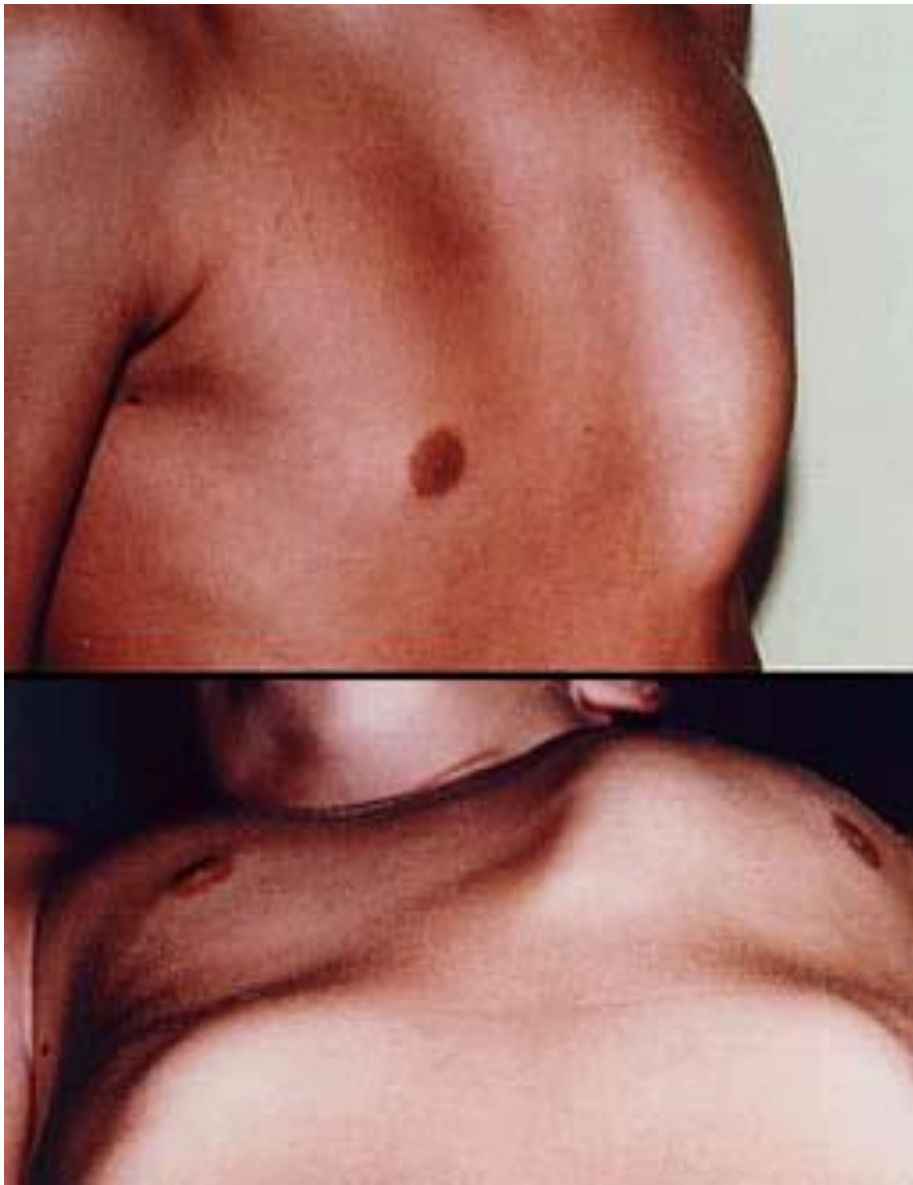
Spine lordosis



Bowed legs

Spine kyphosis





Chest deformities

LABORATORY DATA

1. Serum calcium level (N=2.2-2.6mmol/l). At the level <2.0mmol/l convulsions sets in.
2. Phosphorus normal (1.5-1.8mmol/l). Normal ratio of Ca : P= 2:1; in rickets become 3:1; 4:1.
3. Serum calcitonin 25(OHD) is deficient <30nmol/L-treatment recommended; 30-50nmol/L is inadequate;>50nmol/L is sufficient for whole population.
4. Serum alkaline phosphatase is elevated >500mmol/l.
5. Serum parathyroid hormone (N=598+5.0pM/L)

In urine: Aminoaciduria >1.0mg/kg/day

- Urinary excretion of 3`5`cyclic AMP
- Decrease calcium excretion (N=50-150 mg/24h)

Radiological findings

Only in difficult diagnostic cases.

1. X-ray of the wrist: concave (cupping) ends of ulna and radius in contrast to normally sharply, large rachitic metaphysis and a widened epiphyseal plate.
2. Osteopenia of clavicle, costal bones, shoulder.
3. Greenstick fractures in minimal trauma.
4. Thinning of the cortex, diaphysis and the cranial bones.

EVOLUTION

The evolution is slow with spontaneous healing at the age of 2-3 years.

If vitamin D are administered the normal bony structure is restored in 2-3mo.

Severe chest, spine and pelvis deformities may permanent persist.

DIFFERENTIAL DIAGNOSIS

1. Vitamin D-dependent rickets type I and type II.
2. Malabsorption disorders.
3. Renal tubular disorders: proximal renal tubular acidosis, distal renal tubular acidosis, osteogenesis imperfecta, familial X-linked hypophosphatemia.

VITAMIN D- RESISTANT RICKETS

- Type I called 1-alpha hydroxylase gene deficiency, result in inability to hydroxylate calcidiol in 1,25(OH)D3 (calcitriol)
- Clinical and biochemical evidence of rickets starting in infancy, identified as unique form of vitamin D resistant rickets
- Calcitriol therapy 1-2mcg/day until healed bone, maintain dose varies 0,25-1mcg/day

Vitamin D-resistance rickets

- Type 2 vitamin D-dependent rickets, hereditary autosomal-recessive disorder, with end-organ resistance to calcitriol
- Rickets develop in first 2yr, peculiar syndrome is alopecia, marker of severity
- Additional ectodermal anomalies: multiple milia, epidermal cysts, oligodontia
- Treatment: Calcitriol 2mcg/day, calcium 1g/day, increased gradually to restore normal biochemical parameters

X-linked familial hypophosphatemia

- Autosomal recessive bone disease with tubular phosphorus reabsorption defect and reduced synthesis $1,25(\text{OH})_2\text{D}_3$
- Clinical manifestation of waddling gait, bowing legs, coxa vara, genu varus, genu valgum, short height, enamel defects
- X-ray cupping of distal and proximal metaphysis of arm and legs

Treatment of familial hypophosphatemia

- Infants are treated with sodium phosphates 0.5-1.0 g/24h, preschool children 1-4g/24h+vitamin D2 2000/kg/24h or 1,25(OH)₂ D3 20-50ng/kg/24h
- The recommended treatment are used since patients become complete healing.

Case report: x-linked hypophosphatemia

- 16-year old girl with severe rickets dwarfism.
- Disease started at 18mo with symptoms of rickets resistant to Vitamin D intake, severe hypophosphatemia-0.65mmol/L, high levels of alkaline phosphatase- 800un and excretion of phosphate- 84.2mmol/L.
- PTH and serum calcium were normal.

Case report (cont.)

- An examination: legs deformity, bilateral coxa vara, bone pain, muscle weakness, waddling gait.
- Weight 35kg, height- 127cm(<5percentile).
- Normal develop of teeth
- Laboratory data: hypophosphatemia 1.2mmol/L, urinarany excretion of phosphate 48.6mmol/L, X-ray: carpal bone age match the cronological age



Osteogenesis imperfecta

- Four genetic syndromes account in osteogenesis imperfecta: type I and IV autosomal dominant; type II and III autosomal recessive
- Clinical manifestation are common in all types: bone fragility, fractures, deformity of long bones and spine, short height
- Calcium and calcitonin therapy increase skeletal mass and decrease fractures

Renal tubular acidosis

- Rickets associated with multiple defects of the proximal renal tubule; Fanconi syndrome, genetic disorder of metabolism or primary idiopathic
- Dysfunction in proximal tubule membrane with loss of bicarbonate, aminoaciduria, glycosuria, phosphaturia resulting in metabolic acidosis, hypophosphatemia, impaired conversion of vitamin D=>rickets

Distal renal tubular acidosis

- The type is due to impaired capacity for hydrogen-ion (ammonium) secretion in the collecting tubules, resulting in abnormally high urine $\text{pH} > 5.5$, despite a metabolic acidosis.
- This presents with hyperchloremic hypokalemic acidosis with high urine pH, often associated with hypercalciuria, sometimes resulting in nephrolithiasis and nephrocalcinosis. Distal renal tubular acidosis may be isolated or secondary.

Clinical manifestation of renal tubular acidosis

- The signs and symptoms are related with a mild or moderate metabolic acidosis. At serum $\text{pH} < 7.20$ there is impaired cardiac contractility, increased risk of arrhythmias, decrease cardiovascular response to catecholamine, potentially exacerbating hypotension with volume depletion or shock.
- The normal respiratory response to metabolic acidosis- compensatory hyperventilation, increased respiratory effort with worsening metabolic acidosis..

Diagnosis of renal tubular acidosis

- Other causes of systemic acidosis (e.g., chronic diarrhea, lactic acidosis, diabetic ketoacidosis) should be excluded. Investigations:
- Blood: pH; bicarbonate (low); potassium (low); chloride (high).
- Urine: Early-morning sample
- pH >5.5 suggests distal tubular acidosis
- Variable pH in proximal tubular acidosis

Treatment of renal tubular acidosis

- Correction of acidosis and maintenance of normal bicarbonate and potassium.
- The administration of insulin in diabetic ketoacidosis or restoration of adequate perfusion in lactic acidosis results in normalization of acid-base balance.
- The use of bicarbonate therapy is indicated during the acute illness; in tubular acidosis and chronic renal failure.

Prevention of rickets

In pregnant and lactating women 600IU/day of vitamin D combined with iron, folic acid and 600mg of calcium.

In term infants 500-600IU is adequate dose from birth to 12 months. In preterm 400IU/day.

>12months of age 600IU/day.

SPECIFIC TREATMENT IN RICHETS

The treatment is with vitamin D3 (orally):

Age 10 days-12 months: minimal dose of vitamin D is 2000IU/day for 3 months.

Age 12months- 12 years 3000-6000IU/day for 3 months

> 12 years of age 6000IU/day for 3 months in osteopenia, bone fracture, intestinal malabsorption, chronic liver or kidney disease.

Treatment doses of vitamin D for nutritional rickets

Age	Daily dose for 90 days, IU	Single dose, IU	Maintenance daily dose, IU
<3 months	2,000	NA	400
3–12 months	2,000	50,000	400
>12 months to 12 years	3,000–6,000	150,000	600
>12 years	6,000	300,000	600

Dietary calcium intake

- To prevent rickets for infant 0-6 and 6-12 month of age 200-250mg/day calcium intake.
- Over 12 months of age 500mg/day respectively
- Calcium carbonate, calcium lactate or calcium gluconate are available at low cost.

COMPLICATIONS

- Rickets tetany- result of low serum $\text{Ca} < 2\text{mmol/l}$, failure of PTH compensation
- Hypocalcemic seizures
- Respiratory disorders
- Cardiac disorders-hypocalcemic cardiomyopathy
- Skeletal deformation, bone pain and muscle weakness
- Hypervitaminosis D
- Failure to thrive

Clinical manifestation

1. Manifest tetany:

- Spontaneous spasm: flexion at the elbow, extension of 2-5-th digits, extension and adduction of the thumb.
- Painful extension and adduction in the tibia tarsal joint.
- Rarely contractures in the eyelids and lips muscles.
- Laryngeal or bronchial spasm, manifesting as sudden dyspnea, apnea or cyanosis.

Latent tetany: The symptoms are not evident, but they can be performed.

Chvostek sign- percussion on the facial nerve leading to contraction of the superior lip, nasal wings, hemi or bilateral facial muscle contraction.

Trousseau sign- blood pressure cuff around the mid arm induce carp spasm.

Erb sign- $<5\text{mA}$ galvanic current induced the nerve impulses.

The diagnosis of rickets tetany is based on the clinical manifestation of rickets, low levels of serum calcium, phosphorus, PTH; high serum alkaline phosphatase.

TREATMENT

- 1-2% of calcium lactate in milk- 4-6g/day for the first 2 days; after that 1-3g/day continued for 1-2wk.
- Calcium chloride in more concentrated may cause gastric ulceration. Calcium lactate may be added to milk in 8-10g/day for 10 days.
- Oxygen inhalation is indicated in hypocalcemia and seizures. Started treatment with vitamin D 5000-10000IU/d for 6-8weeks, continued calcium intake. When the rickets is healed, the dose of vitamin D decrease to the usual prophylactic one.

HYPERVITAMINOSIS D

- Symptoms develop in hypersensitivity to vitamin D children or after 1-3mo of high doses intakes of vitamin D; they include apathy, anorexia, vomiting, constipation, polydipsia, dry mouth, polyuria, nocturia, proteinuria, dehydration. High serum level of acetone, nitrogen.
- Serum $\text{Ca} > 2.9 \text{ mmol/l}$ increase calcium concentration in urine may provoke incontinence, renal damage, nephrocalcinosis and renal failure..

Treatment

- Preventing calcium rich food, cheese and cow's milk.
- Stopping all intake of vitamin D and calcium.
- Intake mashed fruits and vegetables, juices, hydrating fluids- Ringer solution, water.
- Vitamin A, B, E according to age. In severe intoxication administration of Phenobarbital for 2-3 weeks or Prednisone 1mg/kg 5-7 days reduces the calcium absorption and increases the calcium excretion.

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