

RICKETS IN CHILDREN

DEFINITION: Rickets is consequence of the vitamin D deficit and may occur due to calcium and phosphorus metabolic disorders.

- Blood analysis shows hypocalcemia and hypophosphatemia.
- Histology- Failure in mineralisation of the bone and cartilaginous tissues .
- Clinical- manifests as skeletal growth disorder.

Hystory

- Rickets (from Greek word meaning spinal column) was known since the first years of the human generation. It is described by Soran Efess (A.D) and by Galen (134-211 A.D).
- It is described in detail by a British anatomist and orthopedician, Glisson in 1650.
- Incidence:
- Rickets is frequently in premature children and if the children fed only wheat floor.
- In Moldova diagnosis was confirm in 35.5%, X-Ray -21.5% (A.Voloc, M.Garabedian, 1996)

Risk factors

- Living in northern latitudes ($>30^\circ$);
- Black children- inadequate skin penetration of sunlight;
- Decreased exposure to sunlight (polluted geographical areas, humid climate);
- Maternal vitamin D deficiency;
- Diets low in calcium, phosphorus and vitamin D, e.g. exclusive breast-feeding into late infancy, toddlers on unsupervised “dairy-free” diets;
- Macrobiotic, strict vegan diets;
- Phytates of cereals, stearic and palmitic acids decrease calcium absorption;
- Prolonged parenteral nutrition in infancy with an inadequate supply of intravenous calcium and phosphate;

- Intestinal malabsorption: defective production of $25(\text{OH})\text{D}_3$ – liver disease. Increased metabolism of $25(\text{OH})\text{D}_3$ – enzyme induction by anticonvulsants;

Defective production of $1,25(\text{OH})_2\text{D}_3$

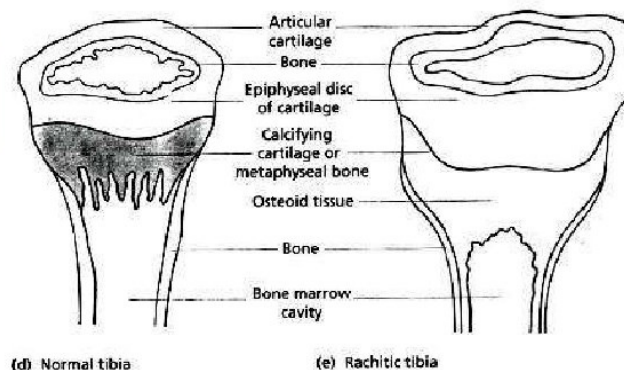
- Hereditary type I vitamin D-resistant (or dependent) rickets (mutation which abolishes activity of renal hydroxylase);
- Familial (X-linked) hypophosphataemic rickets – renal tubular defect in phosphate transport;
- Chronic renal disease;
- Fanconi syndrome (renal loss of phosphate)
- Target organ resistance to $1,25(\text{OH})_2\text{D}_3$ - hereditary vitamin D-dependent rickets type II (due to mutations in vitamin D receptor gene).

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 chylomicrons.

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)



- Calcium regulation in the blood is as follows:
- Vitamin D2 in the food (exogenous) + vitamin D3 (skin, endogenous) => liver microsomal hydroxylase => 25(OH) D3
- In the renal cortical cells => 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

- $1,25(\text{OH})_2\text{D}_3$ 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 $1,25(\text{OH})_2\text{D}_3$ 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 serum Ca level, normal serum P; normal serum PTH, little raise AP, 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.

CLASSIFICATION

Calcium deficiency rickets can be classified in to 3 grades-
I, II, III,

Depending on the duration, evolution and the complication:

1. Grade I, II, III; evolution acute, subacute, recurrent.
2. Depending on vitamin D insufficiency:
 - A) Diet
 - B) Infections
 - C) Food diversification
 - D) Habitual
 - E) No prophylaxis
 - F) Prophylaxis with low dose
 - G) Phenobarbital induced

COMPLICATIONS

- Rickets tetany
- Convulsions
- Respiratory disorders
- Cardiac disorders
- Skeletal deformation
- Frequent illness

Poor muscle tone

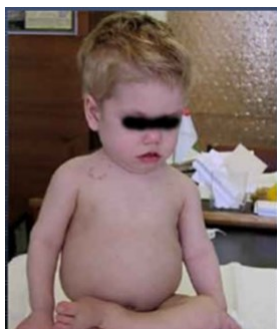
Relaxation of feet

Bent the limbs into any position



Clinical manifestation of rickets

Muscular hypotony



Tibia convexity



CLINICAL MANIFESTATIONS

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

- The first signs of hypocalcaemia 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

Florid (acute) rickets clinical signs:

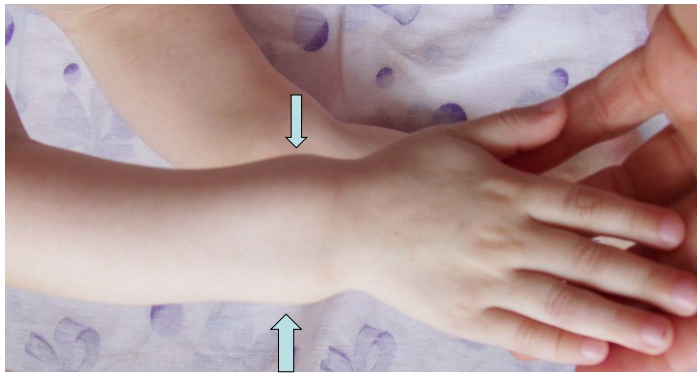
- Craniotabes– osteomalacia, acute sign of rickets, detected by pressing firmly over the occipital or posterior parietal bones, ping-pong ball sensation will be felt. Large anterior fontanella, with hyperflexible borders, cranial deformation with asymmetric occipital flattening.

SUBACUTE SIGNS

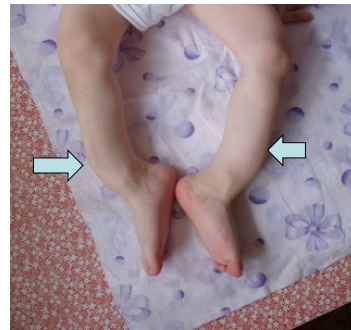
- Subacute signs are all the following: frontal and temporal bossing
- False closure of sutures (increase protein matrix), in the X-ray craniostenosis is absent.
- Maxilla in the form of trapezium, abnormal dentition.
- Late teeth eruption, enamel defects in the temporary and permanent dentition.
- Enlargement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

Subacute rickets signs

- Spinal column- scoliosis, lordosis, kyphosis.
- Pelvis deformity, entrance is narrowed (add to 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)



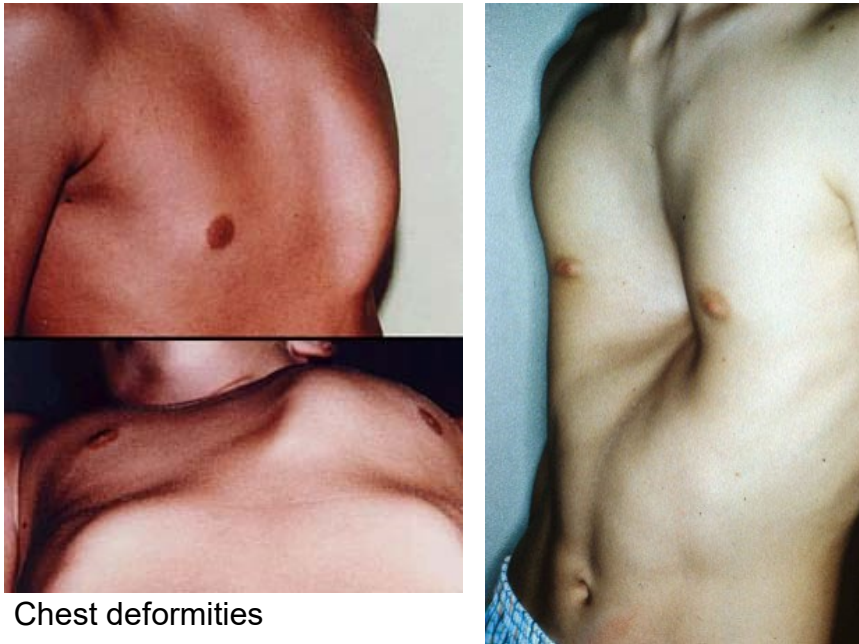
Spine lordosis



Bowed legs

Spine kyphosis





Chest deformities

LABORATORY DATA

1. Serum calcium level ($N=2.2-2.6\text{mmol/l}$). At the level $<2.0\text{mmol/l}$ convulsions sets in.
 2. Phosphorus normal ($1.5-1.8\text{mmol/l}$). Normal ratio of Ca : P = 2:1; in rickets become 3:1; 4:1.
 3. Serum $25(\text{OH})\text{D}_3$ ($N=28+2.1\text{ng/ml}$); and $1,25(\text{OH})_2\text{D}_3$ ($N=0.035+0.003\text{ng/ml}$)
 4. Serum alkaline phosphatase is elevated $>500\text{mmol/l}$.
 5. Thyrocalcitonin can be appreciated ($N=23.6+3.3\text{pM/l}$)
- Serum parathyroid hormone ($N=598+5.0\text{pM/l}$)
- In urine: Aminoaciduria $>1.0\text{mg/kg/day}$
- Urinary excretion of 3'5' cyclic AMP
 - Decreased calcium excretion ($N=50-150\text{mg/24h}$)

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. Osteoporosis of clavicle, costal bones, humerus.
3. Greenstick fractures.
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. Hereditary Fanconi syndrome- multiple defects of proximal renal tubules, familial X-linked hypophosphatemia, renal tubular acidosis, osteogenesis imperfecta

Vitamin D-resistance 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 stature, enamel defects
- X-ray cupping of distal and proximal metaphysis of arm and legs

Treatment of familial hypophosphatemia

- Infants intake of sodium phosphate 0.5-1.0 g/24h, older children 1-4g/24h+vitamin D2 2000/kg/24h or 1,25(OH)₂ D3 20-50ng/kg/24h
- Treatment 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, urinary excretion of phosphate 48.6mmol/L, X-ray: carpal bone age match the chronological 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 stature
- Calcium and calcitonin therapy increase skeletal mass and decrease fractures

Fanconi syndrome

- Rickets associated with multiple defects of the proximal renal tubule; de Toni-Debre-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

PROPHYLAXIS IN RICKETS

Specific antenatal prophylactic dose administration : 500-1000IU/day of vitamin D3 solution at the 28-th week of pregnancy. The total dose administered is 135000-180000IU. In term infants prophylactic intake of vitamin D2 700IU/d started at 10 days of age during the first 2 years of life; in premature the dose may increase to 1000IU/day.

PROPHILAXIS IN RICKETS

WHO recommendation for rickets prophylaxis in a children coming from unfavorable conditions and who have difficult access to hospitals is 200000IU vitamin D2 i/muscular,

On the 7day, 2, 4, 6 month- total dose 800000IU. In case of the necessary prolongation 700IU/day till 24mo are given.

SPECIFIC TREATMENT IN RICHETS

The treatment is with vitamin D3 depending on the grade.

In grade I- 2000-4000IU/day for 4-6weeks, totally 120000-180000IU.

In grade II- 4000-6000IU/day for 4-6 weeks, totally 180000-230000IU.

In grade III- 8000-12000IU/day for 6-8 weeks, totally 400000-700000IU.

SPECIFIC TREATMENT IN RICHETS

- Along with vitamin D, calcium is also administered (40 mg/kg/day for a term baby, 80 mg/kg/day for a premature baby); also indicate vitamin B&C preparations.
- From the 7-th day of the treatment massage can be started.
- Intramuscular administration of 1% ATP solution in case of myopathy 1ml/day is preferred.

RICKETS COMPLICATIONS

1. Rickets tetany in result of low concentration of serum calcium ($<2\text{mmol/l}$), failure of the PTH compensation and muscular irritability occur.
2. Hypervitaminosis D occur after high oral dosing, extensive skin exposure to sunlight.

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- <5mA 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 chloride 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 10-12g/d for 10 days.
- Oxygen inhalation is indicated in convulsive 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 hypotonia, anorexia, vomiting, irritability, constipation, polydipsia, polyuria, sleep disorder, dehydration. High serum level of acetone, nitrogen
- $\text{Ca} > 2.9 \text{ mmol/l}$ are found. Increase calcium concentration in urine may provoke incontinence, renal damage and calcification.

Treatment

- Preventing calcium rich food, cheese and cow's milk
- 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. In the case of acidosis 4% sodium hydrocarbonate 5ml/kg is given.

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