Pediatrics 4 year

Module 1: Deficiency states

By Olena Debretseni

TOPIC: Rickets
Title of the seminar: Rickets etiopathogenesis, symptoms, diagnosis, differential diagnosis, treatment and prevention. Hypovitaminosis D.

Name of the tutor: Olena Debretseni
Duration: 90 min
Audience: 4rd course students
Goals:
General: Rickets diagnosis based on the learning of the clinical and laboratory data, treatment and prevention activities on different stages of child's development.
Special goals:
• Knowledge: to learn the main symptoms in rickets patients and history-taking.
• Practical skills: physical examination, analyze clinical and laboratory data, be able to evaluate information on the preliminary diagnosis, using a standard procedure based on the results of laboratory and instrumental studies.

Methodology of the seminar:
5 minutes Short introduction
5 minutes Ice breaker
20 minutes Theory presentation (Power Point presentation)
35 minutes Interactive
Use of “OPEN” QUESTIONS and ROLE-PLAY TEACHING METHODS in the “history-taking” part of the class.
Practical training of collect data on patient complaints, medical history, life history, conduct and evaluate the results of physical examination (on patients, on each other)
15 minutes Control – verbal interview
10 minutes Feedback from each participant: take home notes: “What was new for me today? What did I learn/practice? What will I introduce into my future practice?”
Results: we expect each participant:
• Master the basics of history-taking collecting data on patient complaints, medical history, life history, conduct and evaluate the results of physical examination patients with rickets
• Practice to perform physical examination, analyze clinical and laboratory data, evaluating information on the preliminary diagnosis, using a standard procedure based on the results of laboratory and instrumental studies.

Theoretical questions for the class

1. The functions of vitamin D, parathormone and calcitonin.
2. A normal electrolytes calcium and phosphorus level of the blood plasma.
3. Daily child's needs of vitamin D.
4. Classification of rickets.
5. The dynamics of calcium and phosphorus level in different periods of rickets.
7. Therapeutic and preventive doses of vitamin D.
8. The levels of the vitamin D in blood serum according to hypervitaminosis.
9. Changes of the phosphorus level in blood serum according to hypervitaminosis.
10. Rickets and hypervitaminosis D changes visualized on radiographs.
11. Classification of the hypervitaminosis D.
12. Treatment of the hypervitaminosis D.

Rickets is a disease of children of first two years. Rickets in itself is not a fatal disease, but complications and intercurrent infections such as pneumonia, tuberculosis, and enteritis are more likely to cause death in rachitic children than in normal children. Rickets is a condition that weakens and softens bones in children. It usually happens in children who don't get enough vitamin D. They may not get enough sun exposure, the primary source of vitamin D, or are not getting enough vitamin D in their diet.

The origins of the term “rickets” remains somewhat unclear. However, it likely originates from the German word “wricken” which translates to “twisted” (16). The first clear descriptions of rickets occurred in the seventeenth century, by the English physicians Daniel Whistler (1645), and Francis Glisson (1650) (17) (see Figure 1). However, early descriptions were recognized well before this time. In hindsight, not only was presumed rickets described in early Roman and Greek and medical writings of the first and second century AD (18), but the essential need for vitamin D is considered to be a leading theory to explain the evolution from dark to light of skin color in humans, in regions of seasonal variation in UVB availability (19). Rickets is also increasingly documented in archaeological evidence from pre-industrial Europe. Skeletal changes indicative of childhood rickets and/or adult osteomalacia have been found in the archaeological records of fourth century France (20), sixteenth century Italy (21), Roman Dorset, UK (22), and Medieval North Yorkshire, UK (23).

Etiology.

There are the following predisposal factors for appearance of rickets:

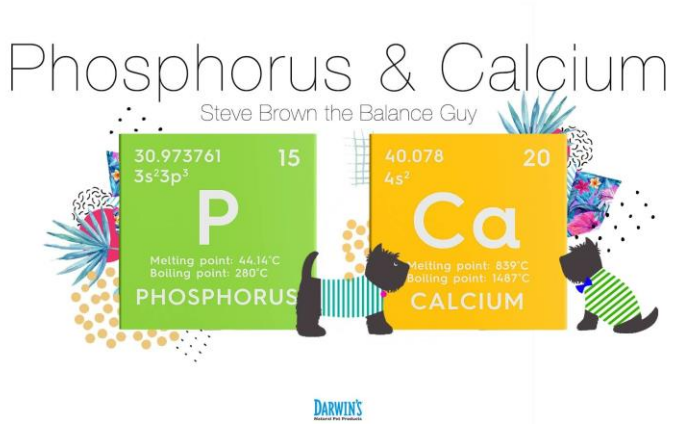
1.Deficiency of UV irradiation and staying out-doors, because 90% of endogenously created vit D3 in organism is synthesized in skin under influence of sun beams. It is necessary to take into account that because of pollution of atmosphere of big cities, only minimal quantity of sun beams having antirachitic activity reaches the earth.

2.Food factors. Increase of frequency and severity of rickets was confirmed in groups of children receiving:
non-adapted mixtures (to which vit D is not added);
milk feeding only for a long time (1L of woman's milk contains 40-70 IU of vit D, cow's milk - 5-40 IU), late prescription of additional food (1 g of egg's yolk contains 140-390 IU of vit D);
vegetarian additional food predominantly (vegetables, porridges) without sufficient quantity of animal proteins and fats.

It is necessary to pay attention that not deficiency of vit D in food is a cause of rickets, but feeding not providing optimal conditions for entering of P and Ca from food and for proteins, lipids, microelements, other vitamins metabolism.

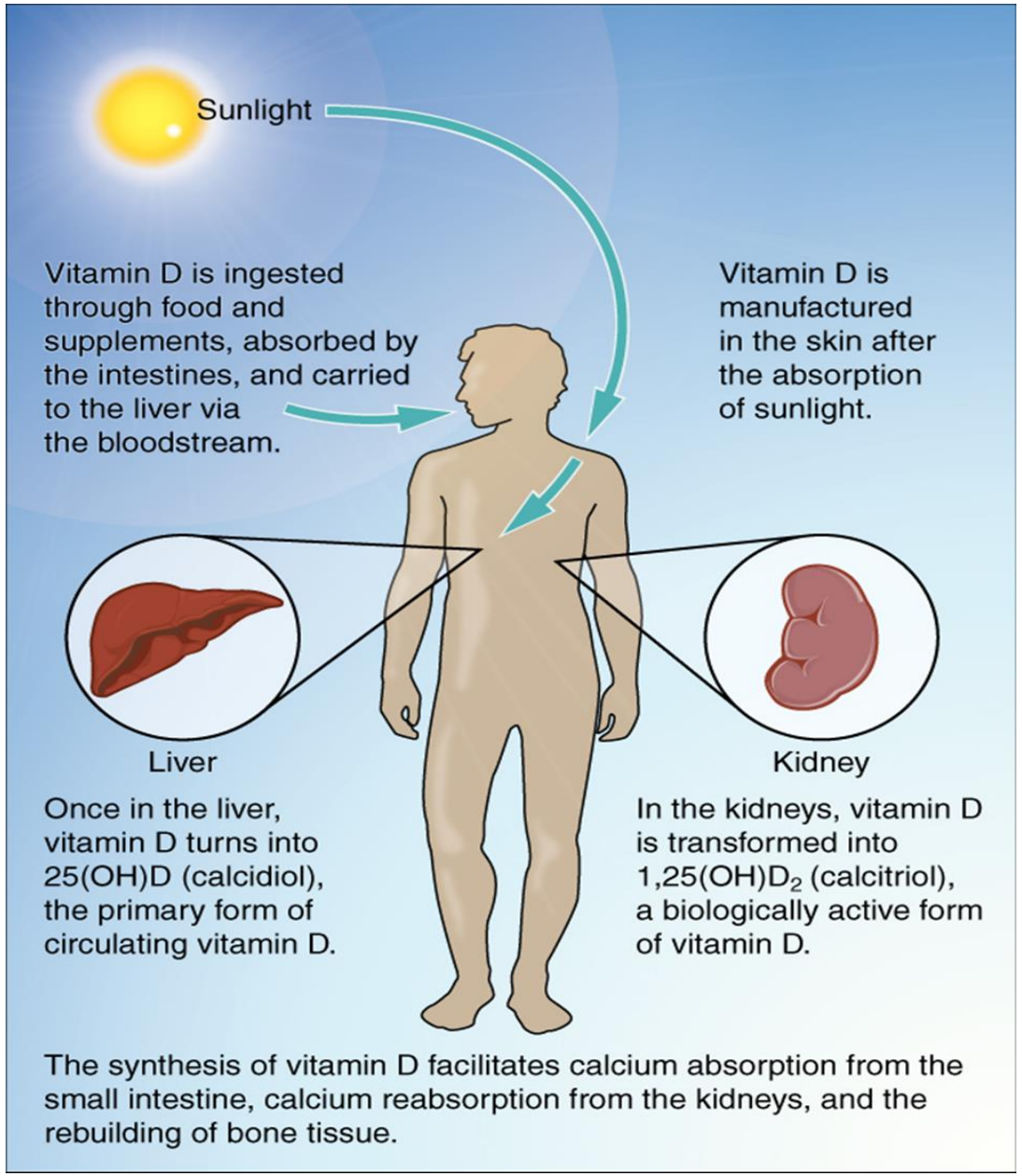
In particular, there is a lot of phytin acid in cereals which binds Ca in intestine, and lignin as well which provides the same effect upon vit D and its metabolites. A great quantity of vegetables and cow milk nowdays contain plenty of phosphates (because of wide use of phosphate fertilizers), that inhibits absorption of Ca.

3. Perinatal factors. Prematurity predispose to rickets because the most intensive income of Ca and P from mother to fetus takes place during last months of pregnancy, so a baby born earlier than 30 weeks of gestation very often has osteopenia- more low content of mineral substances in bone. At the same time they are need in greater quantity of Ca and P in food because of greater rate of postnatal growth comparatively with mature children. Besides, prematurity, as well as placental insufficiency, is combined with much more low reserve in organism and more low level of vit D and its metabolites in cord blood.

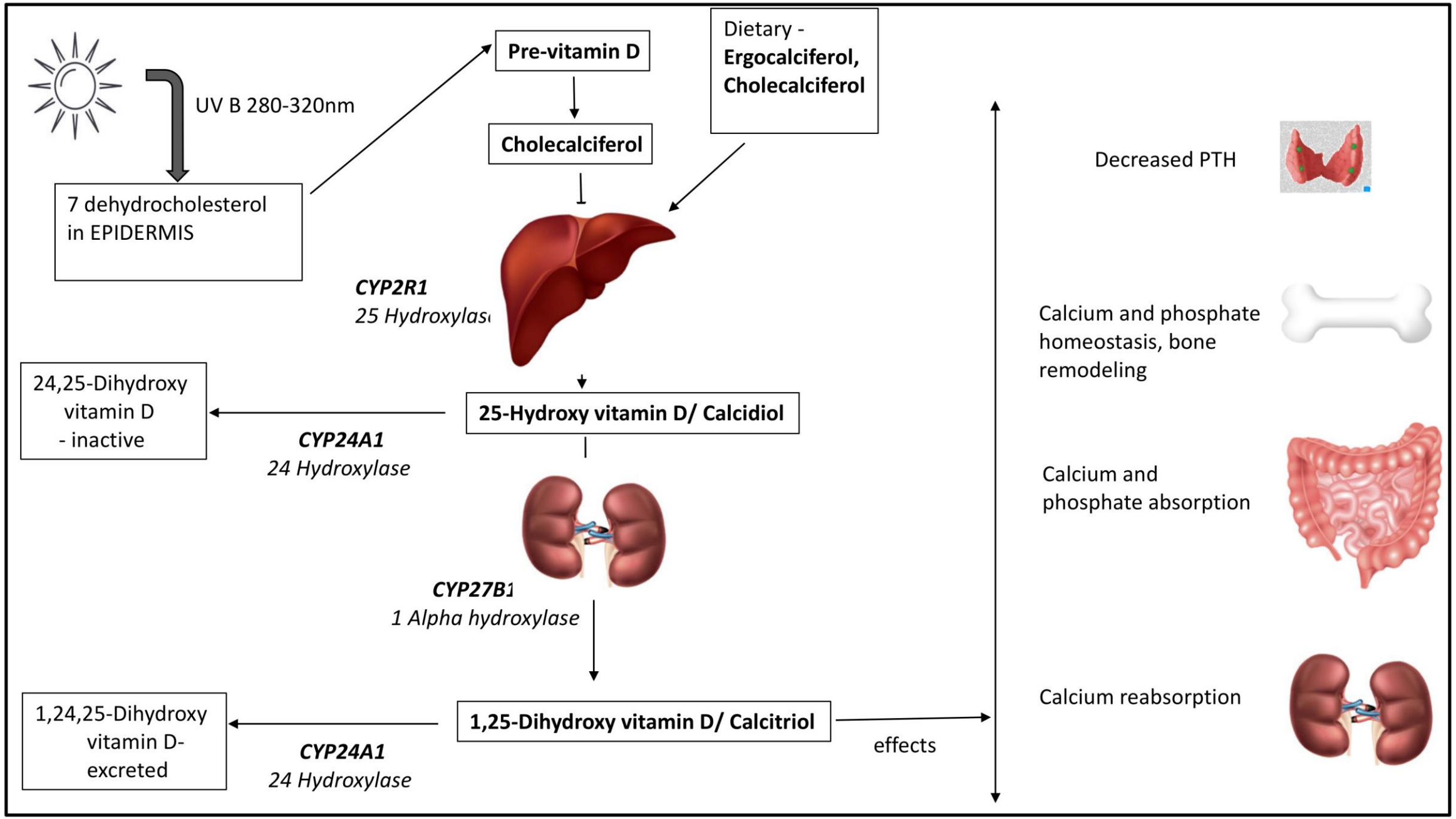


4. Insufficient motor activity because of not only perinatal encephalopathies, but absence of physical culture also: as blood flow of long bones is increased during muscular activity.
5. Dysbacteriosis with diarrhea.

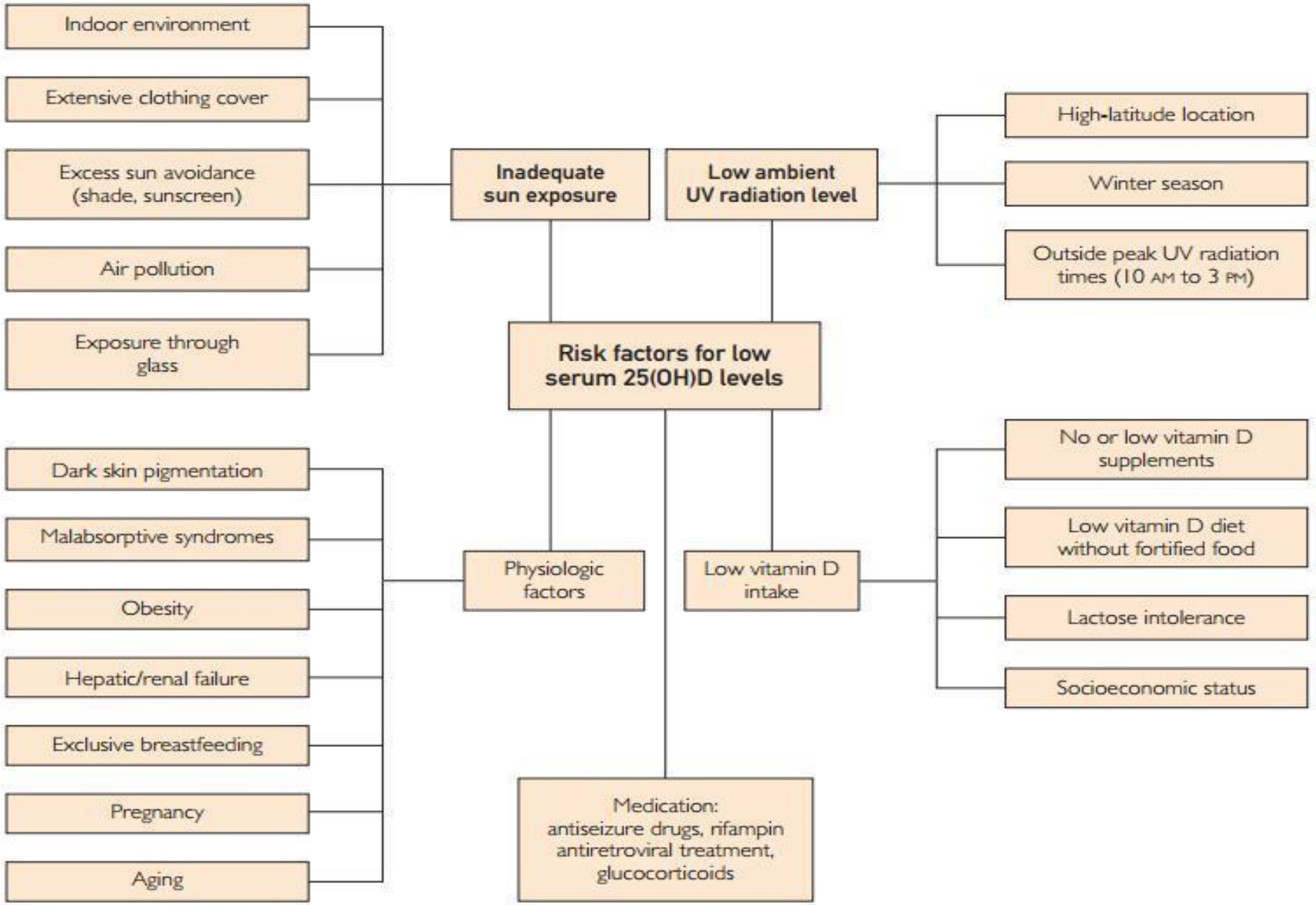
6. Anticonvulsive prolonged therapy, which leads to speeding up metabolism of active forms of vit D.
7. Syndromes of malabsorption, chronic diseases of liver and kidney, which lead to disorders of formation of active forms of vit D.
8. Hereditary anomalies of metabolism of vit D, Ca and P.
9. Ecological factors. Excess of strontium, zinc and other metals in soil, water, food leads to partial substitution of Ca by these substances.
10. Pigmentation of skin decreases intensity of creation of chotecalciferol in skin.



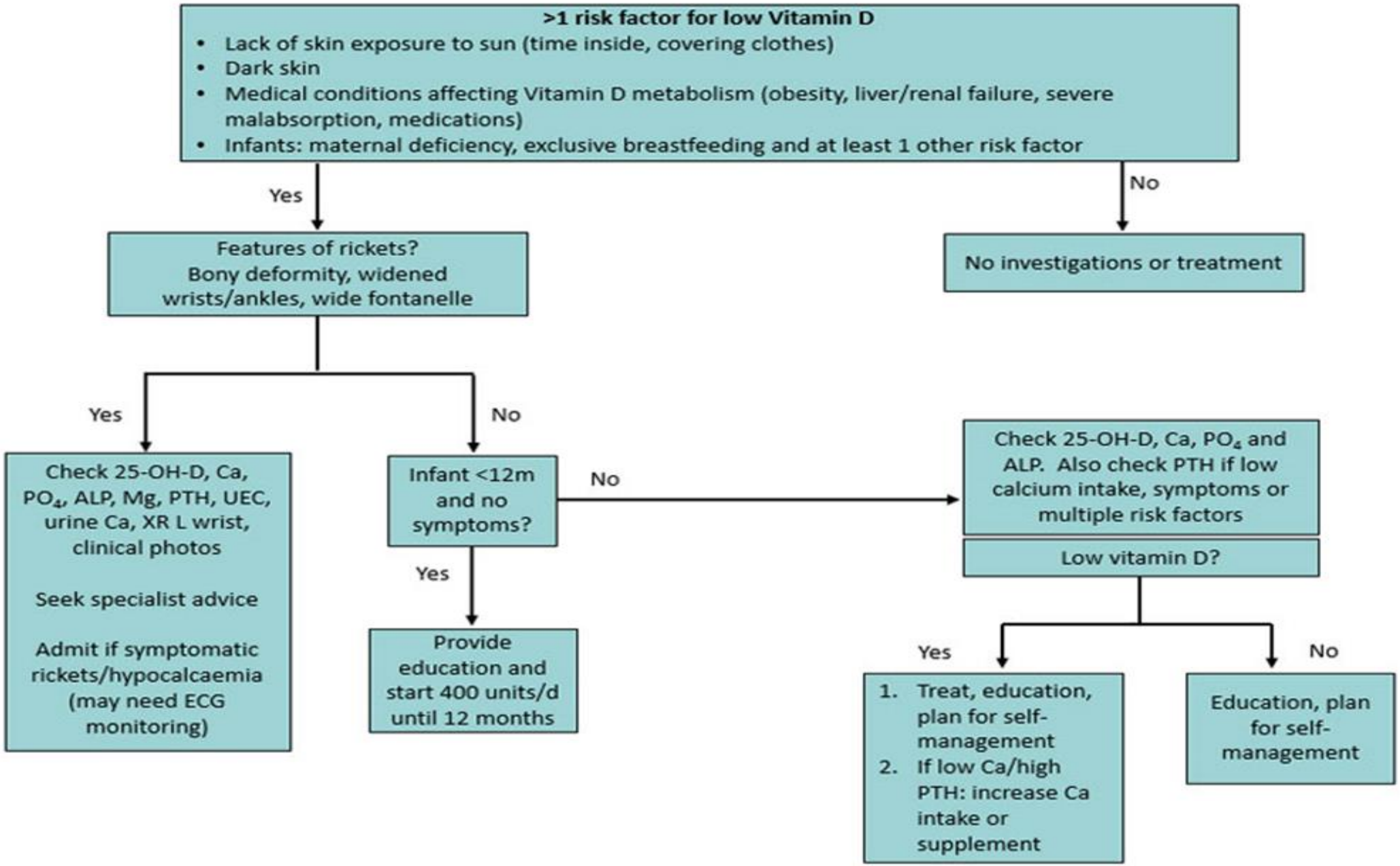
Endogenous vit D3 (cholecalciferol) is synthesized in skin from 7-dihydrocholesterin under influence of ultraviolet rays. More than 60 its metabolites are created in organism later, but nowadays only 2 of them are considered to influence actively upon metabolism of Ca and P - 1,25-dihydrocholecalciferol and 24,25-dihydrocholecalciferol. Both of them are created in kidneys, and intermediate metabolit (25-hydrocholecalciferol) - in liver. The main effects of active metabolites of vit D3 are stimulation of absorption of Ca and P in intestine and stimulation of bone's mineralization. They activate synthesis of Ca-bounding proteins and increase activity of adenilatcyclase; that's why we consider vit D3 to be hormone.


UV B 280-320nm
7 dehydrocholesterol in EPIDERMIS
Pre-vitamin D
Cholecalciferol
Dietary - Ergocalciferol, Cholecalciferol
CYP2R1
25 Hydroxylas
25-Hydroxy vitamin D/ Calcidiol
CYP24A1
24 Hydroxylase
24,25-Dihydroxy vitamin D - inactive
CYP27B1
1 Alpha hydroxylase
1,25-Dihydroxy vitamin D/ Calcitriol
CYP24A1
24 Hydroxylase
1,24,25-Dihydroxy vitamin D- excreted
effects
Decreased PTH
Calcium and phosphate homeostasis, bone remodeling
Calcium and phosphate absorption
Calcium reabsorption

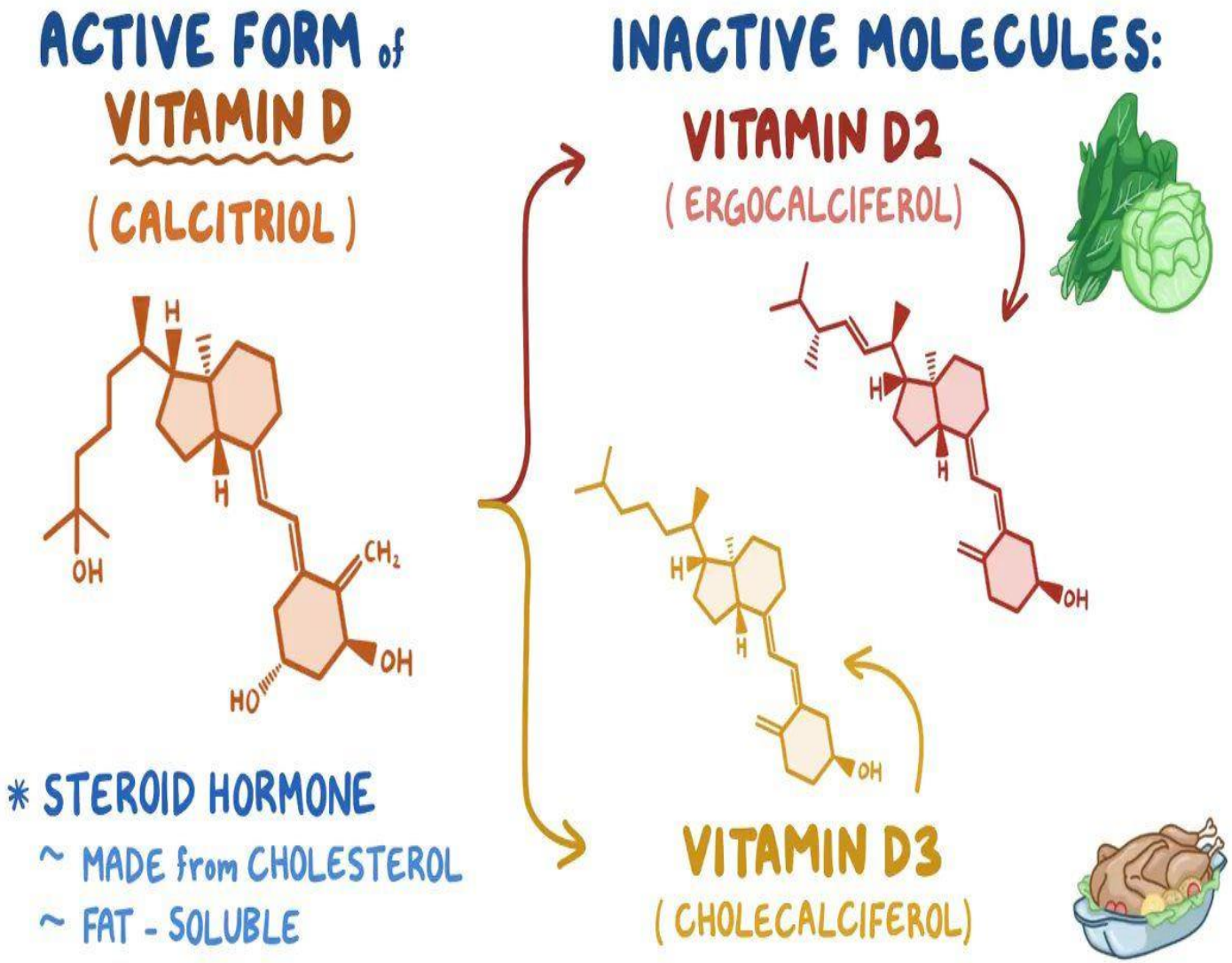
Risk factors:
- Lack of skin exposure to sun (time inside, covering clothes)
- Dark skin
- Medical conditions affecting Vitamin D metabolism (obesity, liver/renal failure, severe malabsorption, medications)
- Infants: exclusive breastfeeding AND any of: the above risk factors, maternal deficiency or prematurity



Managment


>1 risk factor for low Vitamin D
• Lack of skin exposure to sun (time inside, covering clothes)
• Dark skin
• Medical conditions affecting Vitamin D metabolism (obesity, liver/renal failure, severe malabsorption, medications)
• Infants: maternal deficiency, exclusive breastfeeding and at least 1 other risk factor
Yes
No
Features of rickets? Bony deformity, widened wrists/ankles, wide fontanelle
No investigations or treatment
Yes
No
Check 25-OH-D, Ca, PO4, ALP, Mg, PTH, UEC, urine Ca, XR L wrist, clinical photos
Seek specialist advice
Admit if symptomatic rickets/hypocalcaemia (may need ECG monitoring)
Infant <12m and no symptoms?
No
Yes
Provide education and start 400 units/d until 12 months
Check 25-OH-D, Ca, PO4 and ALP. Also check PTH if low calcium intake, symptoms or multiple risk factors
Low vitamin D?
Yes
No
1. Treat, education, plan for self-management
2. If low Ca/high PTH: increase Ca intake or supplement
Education, plan for self-management

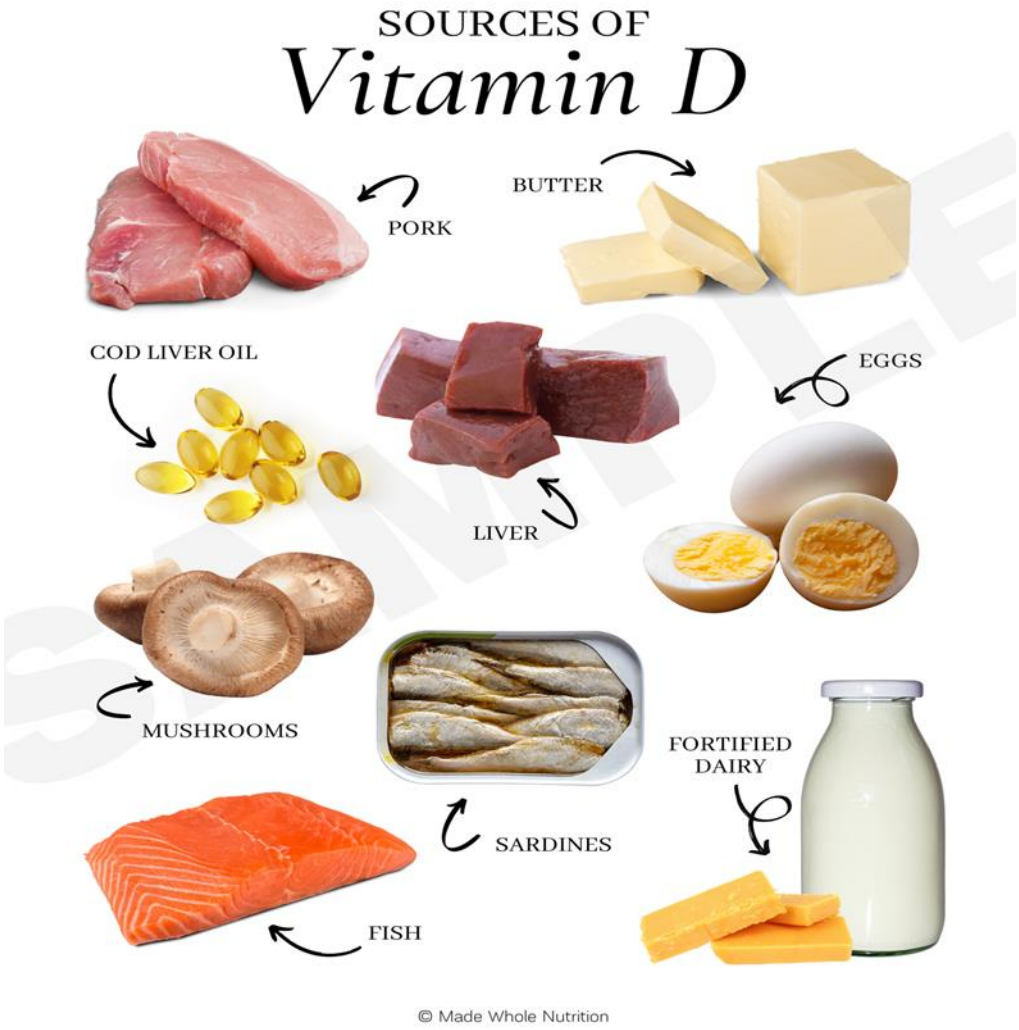
Vitamin D (also referred to as “calciferol”) is a fat-soluble vitamin that is naturally present in a few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet (UV) rays from sunlight strike the skin and trigger vitamin D synthesis. Vitamin D obtained from sun exposure, foods, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first hydroxylation, which occurs in the liver, converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as “calcidiol.” The second hydroxylation occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as “calcitriol” [1].



Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal bone mineralization and to prevent hypocalcemic tetany (involuntary contraction of muscles, leading to cramps and spasms). It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts [1-3]. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis.

Vitamin D has other roles in the body, including reduction of inflammation as well as modulation of such processes as cell growth, neuromuscular and immune function, and glucose metabolism [1-3]. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many tissues have vitamin D receptors, and some convert 25(OH)D to 1,25(OH)2D.

In foods and dietary supplements, vitamin D has two main forms, D2 (ergocalciferol) and D3 (cholecalciferol), that differ chemically only in their side-chain structures. Both forms are well absorbed in the small intestine. Absorption occurs by simple passive diffusion and by a mechanism that involves intestinal membrane carrier proteins [4]. The concurrent presence of fat in the gut enhances vitamin D absorption, but some vitamin D is absorbed even without dietary fat. Neither aging nor obesity alters vitamin D absorption from the gut [4].



In children, vitamin D deficiency is manifested as rickets, a disease characterized by a failure of bone tissue to become properly mineralized, resulting in soft bones and skeletal deformities [5]. In addition to bone deformities and pain, severe rickets can cause failure to thrive, developmental delay, hypocalcemic seizures, tetanic spasms, cardiomyopathy, and dental abnormalities [6,7].

SYMPTOMS OF VITAMIN D DEFICIENCY

- Frequent Muscle Cramps
- Increased Bone Fractures
- Shorter than Average Height
- Dental Cavities
- Fatigue
- Bone or Joint Pain
- Anxiety
- Hair Loss
- Frequent Illness
- Weight Gain

Rickets can be classified into 2 major groups: phosphopenic and calcipenic[5,6] Rickets, a common disease worldwide,[8,9]substantially affects the health, growth, and development of children and adolescents. It results from abnormalities of the growth plate cartilage predominantly affecting longer bones and leads to poor bone growth, defective mineralization, and bony deformities, such as bow-legs and knock-knees.[10] This is usually secondary to deficiencies of calcium or phosphorus because they are essential for normal bone growth and mineralization.[11,12]

Types of rickets

Calcipenic rickets

- **Vitamin D deficiency or resistance**
  - Dietary deficiency
  - Malabsorption
  - Lack of sunlight exposure
  - Defect in 25 hydroxylation of vitamin D (e.g., liver disease, medications such as phenytoin)
  - Failure of 1 hydroxylation of vitamin D due to inherent deficiency of 1 alpha hydroxylase secondary to defects in the 1 alpha hydroxylase gene (VDDR I)
  - End-organ resistance to vitamin D (VDDR II)
- **Calcium deficiency**
- **Renal rickets secondary to CKD**

Phosphopenic rickets

Renal tubular phosphate loss

- Isolated phosphate loss secondary to genetic mutations:
  - XLHR
  - ARHR
  - ADHR
  - Hypophosphatemic rickets with hypercalciuria
- Renal Fanconi syndrome
- Dietary phosphate deficiency
- Phosphate malabsorption

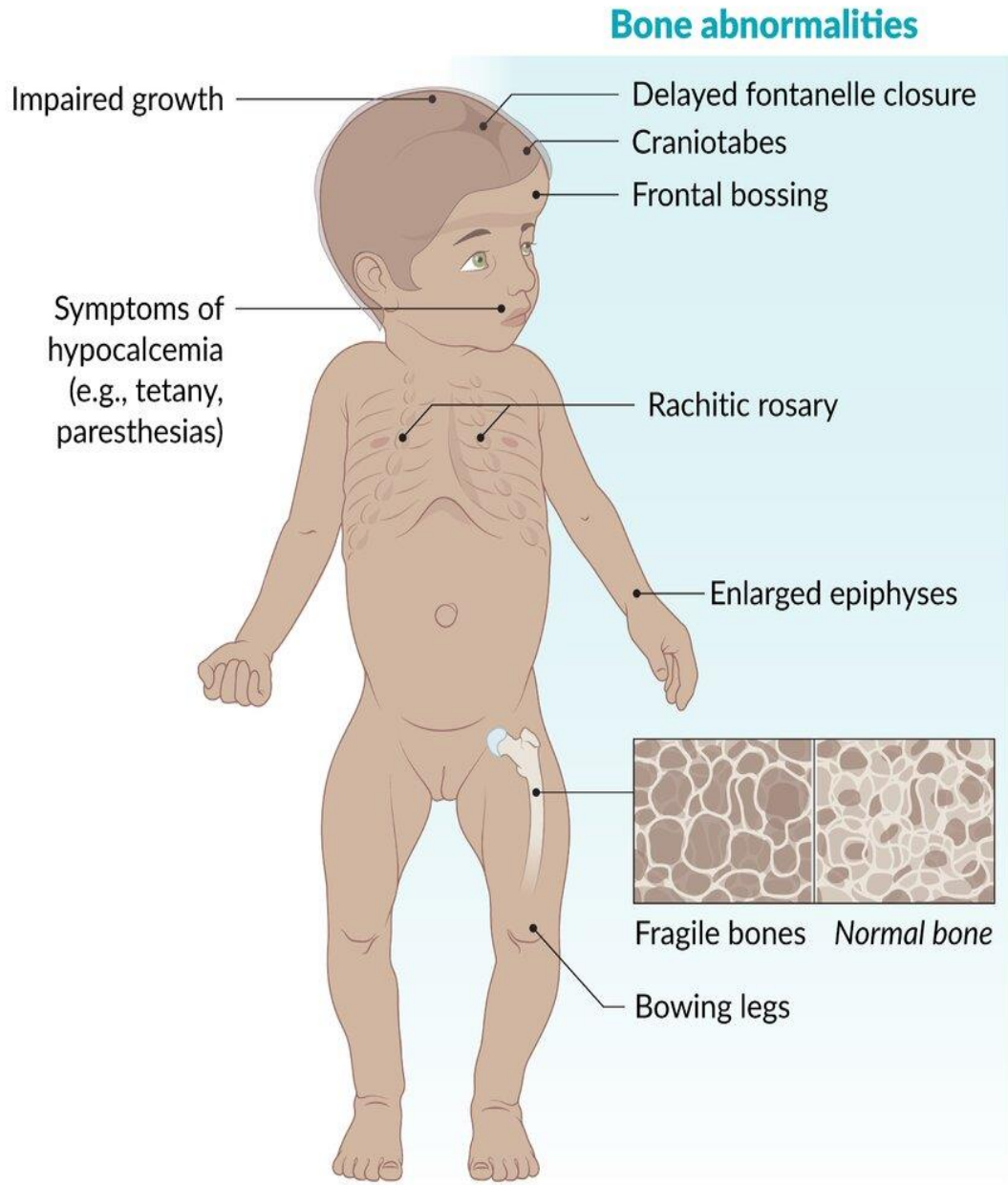
Rickets secondary to vitamin D deficiency

Etiology
- Vitamin D deficiency due to:
  - Insufficient synthesis due to low UV radiation exposure (e.g., northern climates) and/or dark skin
  - Insufficient oral intake (e.g., in infants who are exclusively breastfed)
  - Malabsorption
  - Defective vitamin D metabolism

Pathophysiology
Vitamin D deficiency → defective mineralization of osteoid and growth plates

Diagnostics
↓ Vitamin D, ↓ serum Ca^{2+}, ↑ PTH, ↓ PO_4^{3-}, ↑ ALP

Treatment
- Dietary supplementation (vitamin D, calcium)
- Treatment of underlying cause



Severity of 25 (OH) vitamin D deficiency

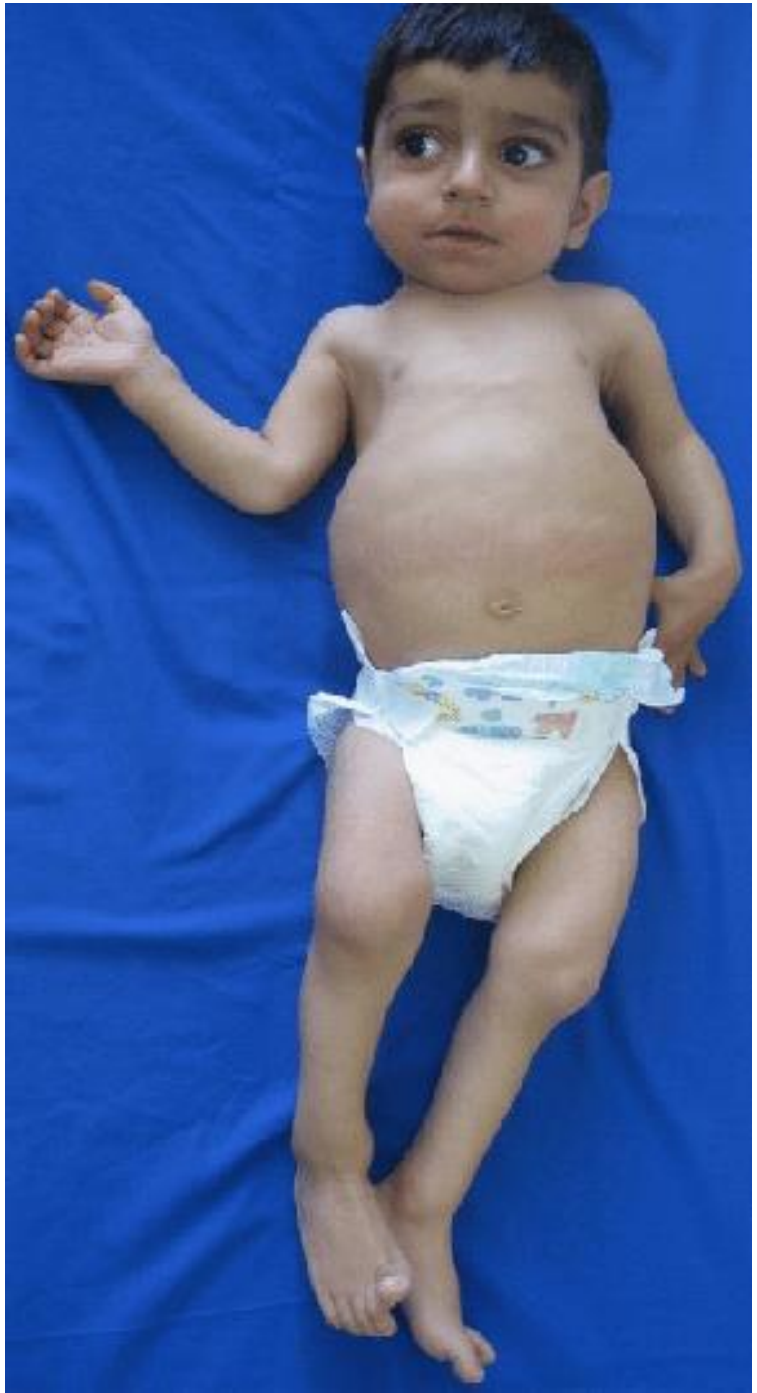
Vitamin D status	ng/ml
Deficiency	<30
Insufficiency	30–50
Adequate	>50
Toxicity	>250

Nutritional Rickets/Vitamin D Deficiency Rickets is the most common form of bone disease, primarily affecting infants and young children. Although primarily caused by vitamin D deficiency, calcium and phosphate deficiencies also play a significant role. Vitamin D regulates calcium and phosphorus in the blood and deficiency of vitamin D does result in inadequate mineralization of osteoid produced by osteoblasts.[13]

Classification of Rickets

Degree of severity	Period of disease	Course
Mild	Initial	Acute
Moderate	Height of disease	Subacute
Severe	Convalescence	Recurring
	Residual symptoms	

Clinical manifestations. Osseous changes of rickets can be recognized after several months of vitamin D deficiency. In breast-fed infants whose mothers have osteomalacia rickets may develop within 2 mo. Florid rickets appears toward the end of the 1st and during the 2-nd year of life. Later in childhood, manifest vitamin D deficient rickets is rare.

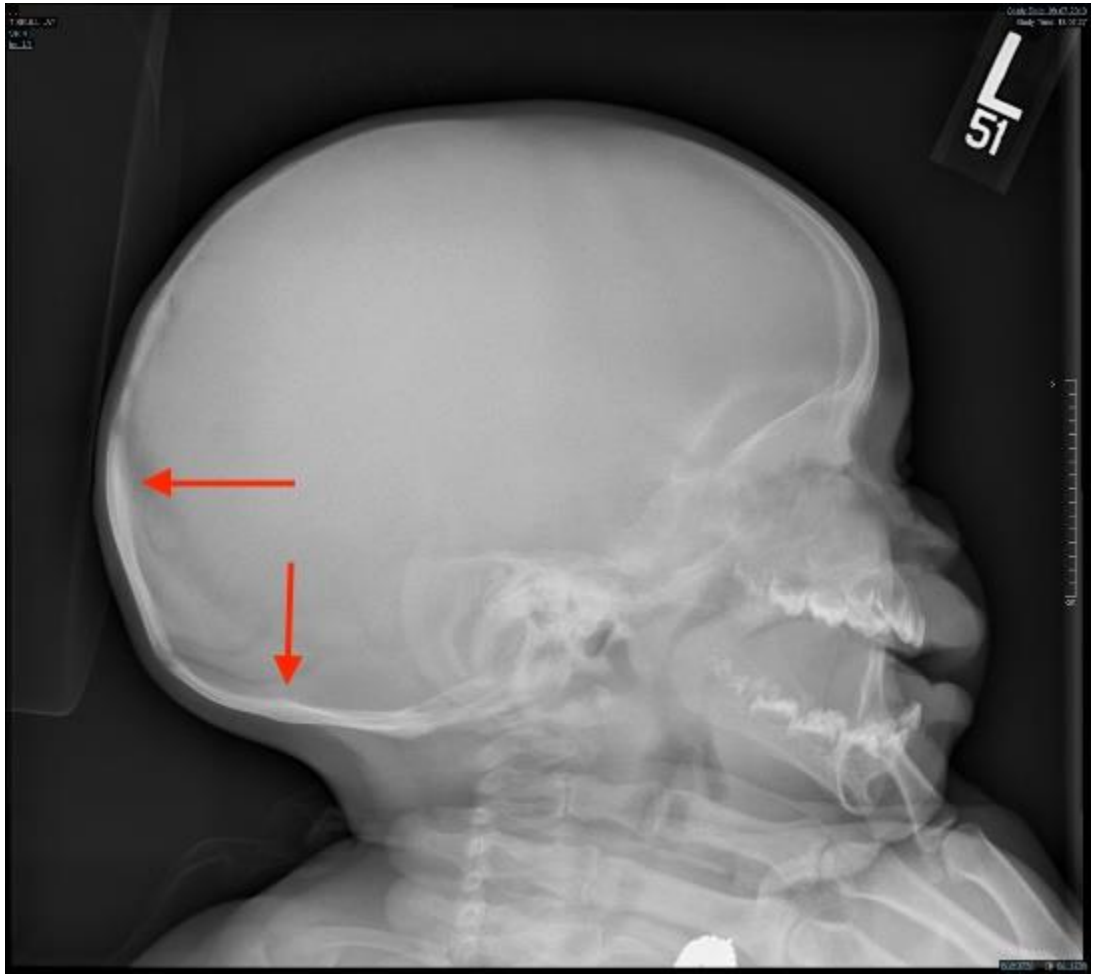


One of the early signs of rickets, craniotabes, is due to thinning of the outer table of the skull and detected by pressing firmly over the occiput or posterior parietal bones. A ping-pong-ball sensation will be felt. Craniotabes near the suture lines is a normal variant. Low-birthweight infants are particularly susceptible to the early development of rickets and to craniotabes.

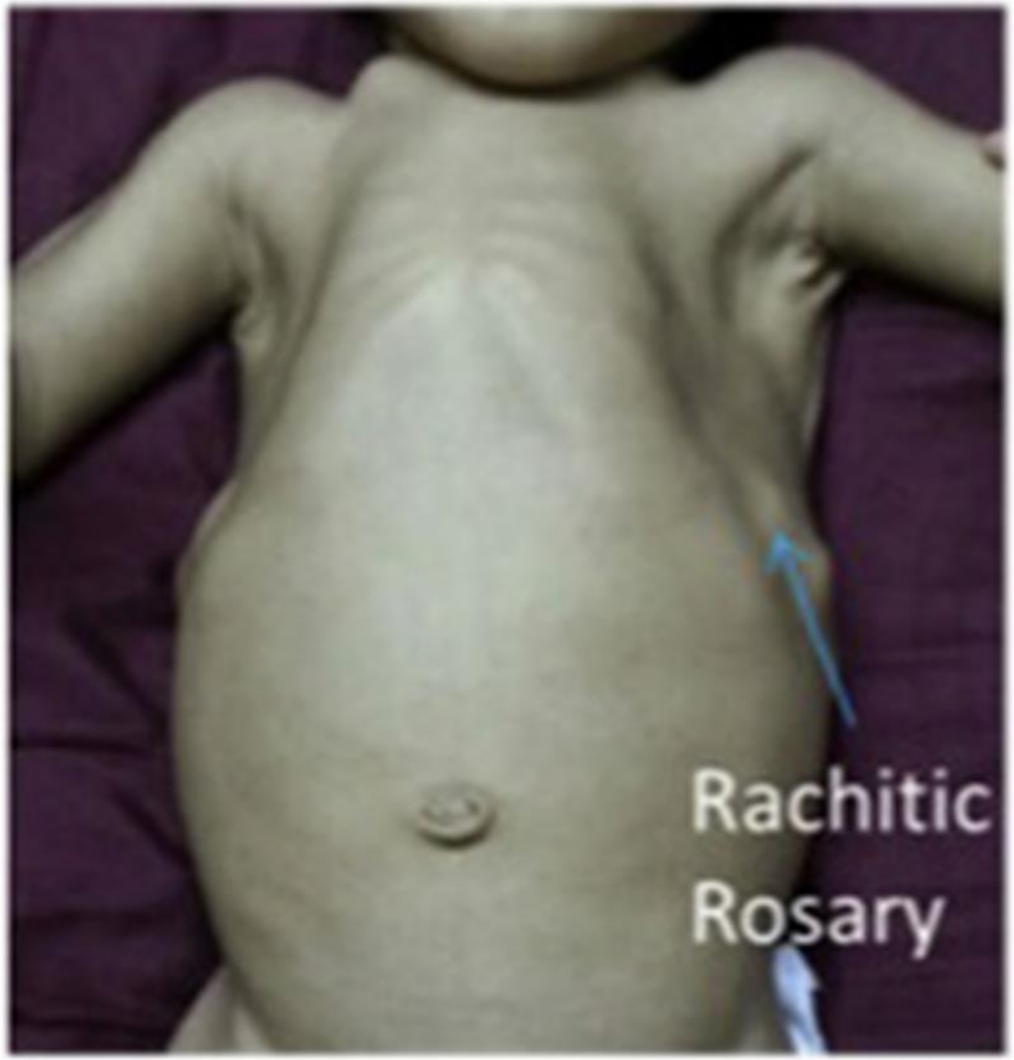
Rickets: Craniotabes

Head. Craniotabes may disappear before the end of the 1st year, although the rachitic process continues. The softness of the skull may result in flattening and, at times, permanent asymmetry of the head. The anterior fontanel is larger than normal; its closure may be delayed until after the 2nd year of life. The central pans of the parietal and frontal bones are often thickened, forming prominences or bosses, which give the head a boxlike appearance (caput quadratum).

The head may be larger than normal and may remain so throughout life. Eruption of the temporary teeth may be delayed, and there may be defects of the enamel and extensive caries. The permanent teeth that are calcifying may also be affected; the permanent incisors, canines, and first molars usually show enamel defects.



Palpable enlargement of the costochondral junctions (the "rachitic rosary") and thickening of the wrists and ankles are other early evidences of osseous changes. Increased sweating, particularly around the head, may also be present.



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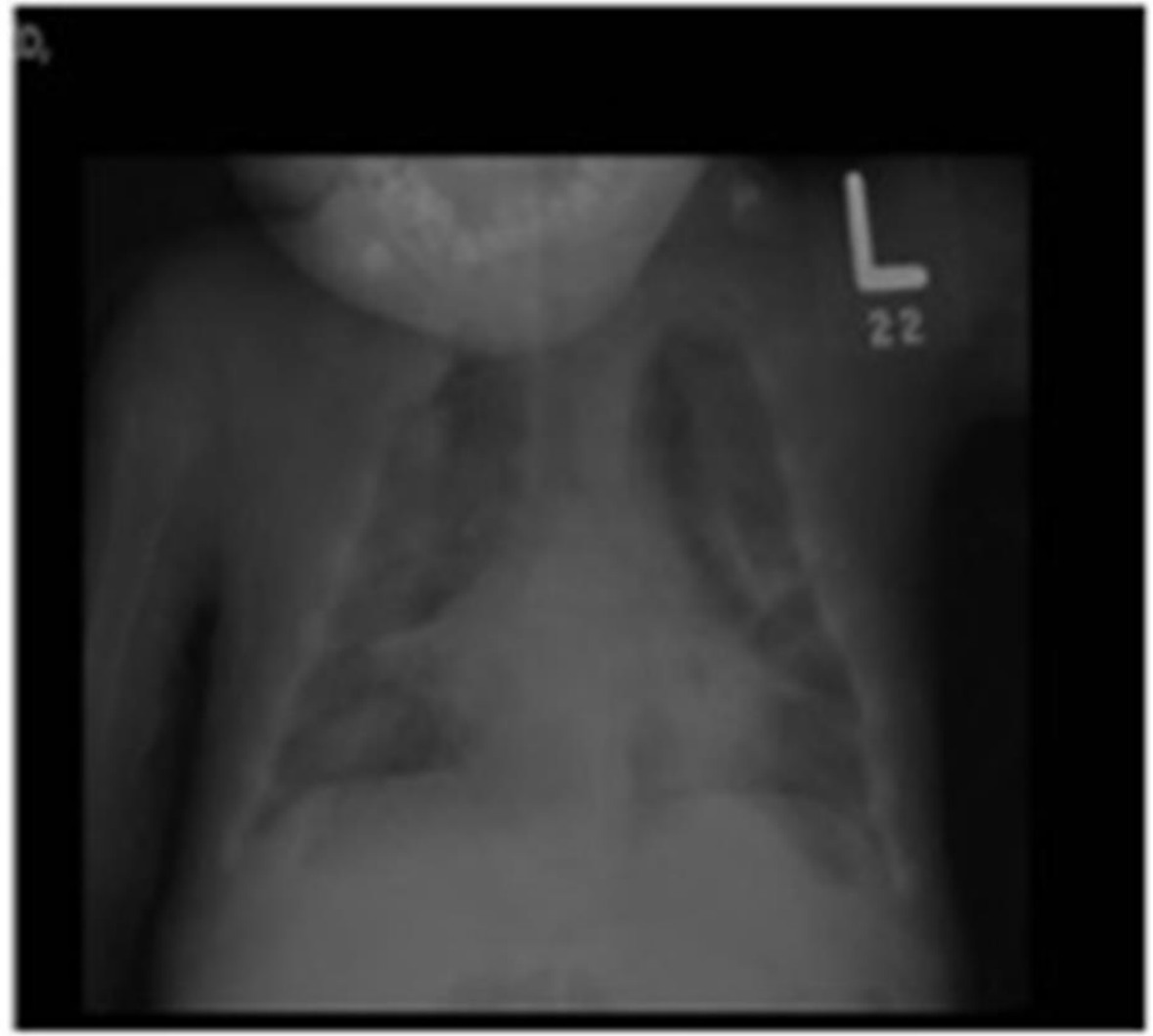
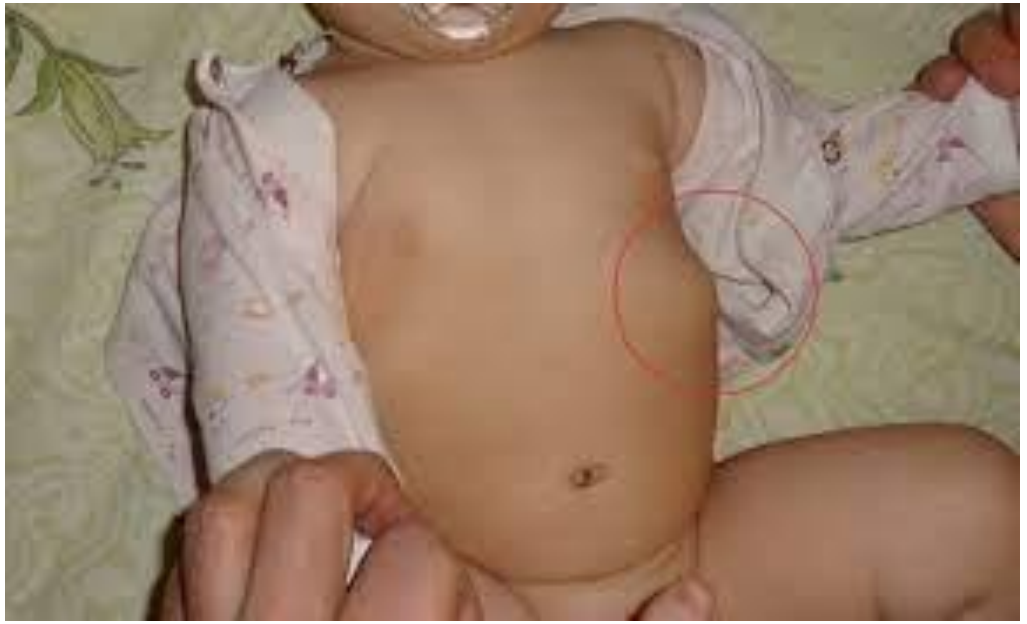


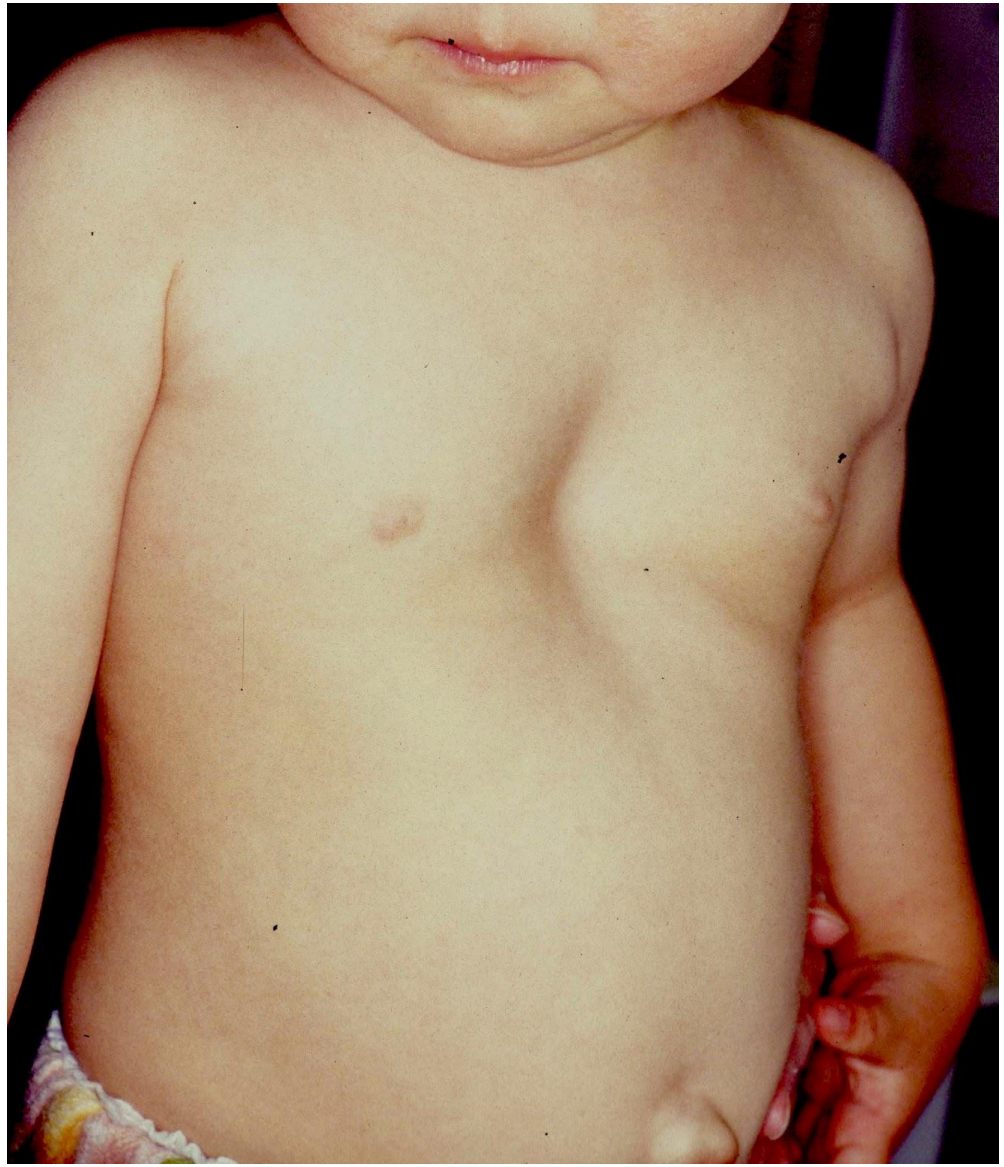
b

Thorax. Enlargement of the costochondral junctions may become prominent; the beading of the ribs is not only palpable but also visible. The sides of the thorax become flattened, and the longitudinal grooves develop posterior to the rosary. The sternum with its adjacent cartilage appears to be projected forward producing the so-called pigeon breast deformity.

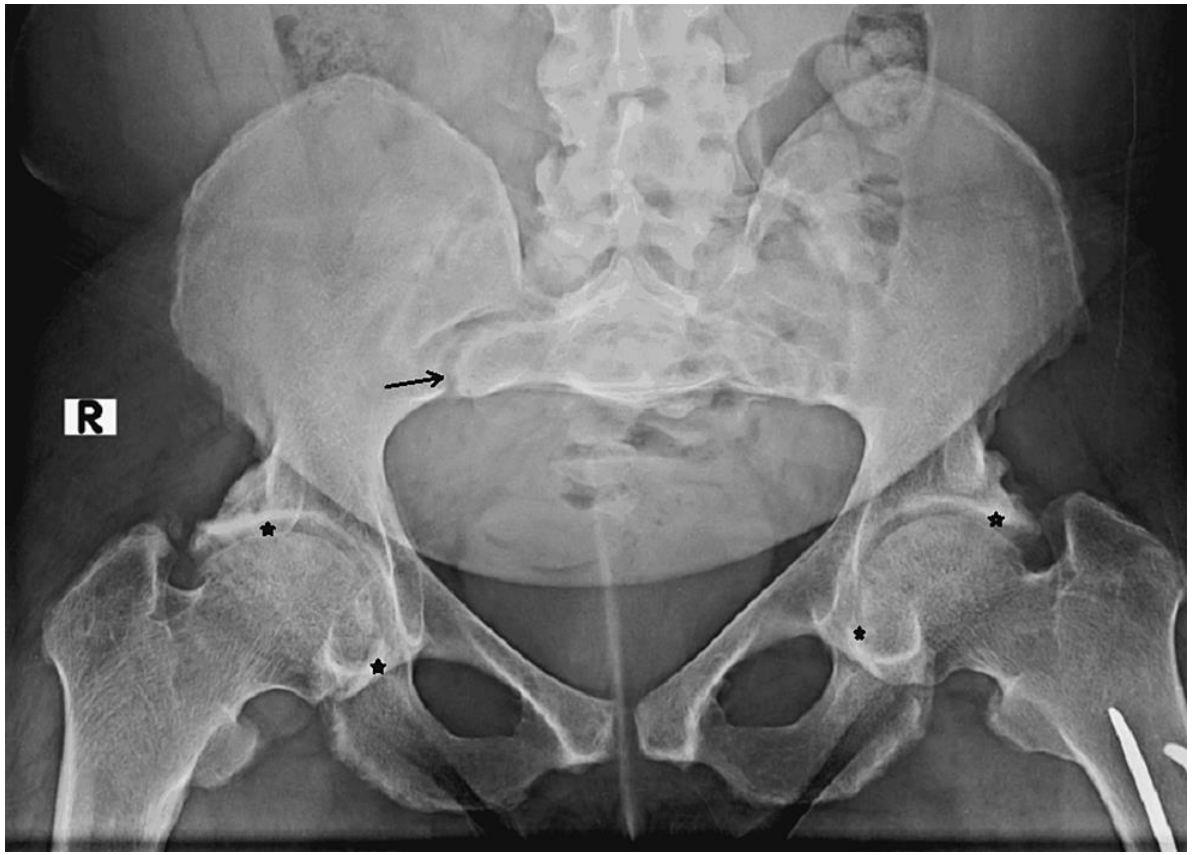
Along the lower border of the chest develops a horizontal depression, Harrison's groove which corresponds with the costal insertions of the diaphragm. There may be a variety of other thoracic deformities, including those of the shoulder girdle.



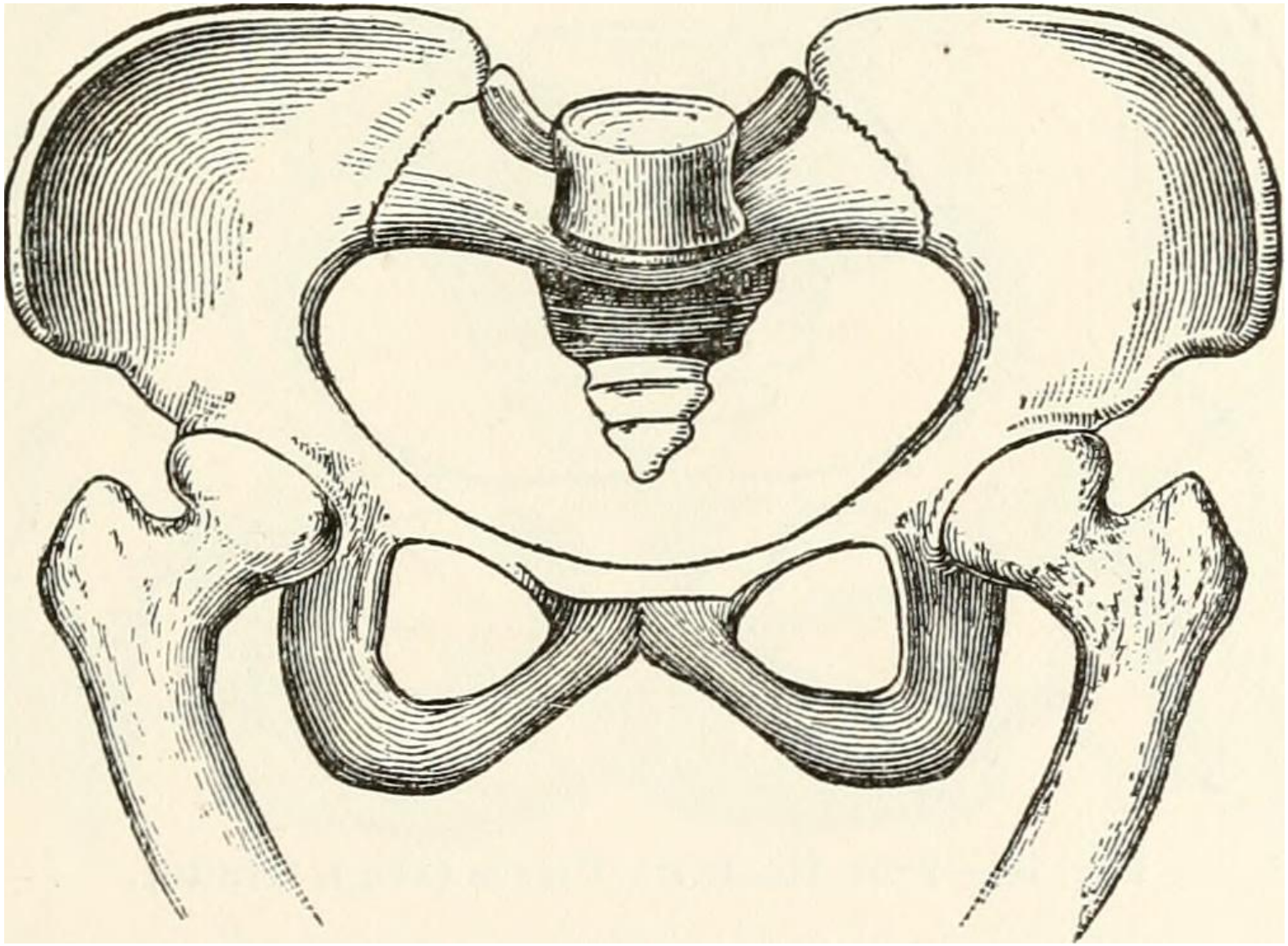
Spinal Column. Slight to moderate degrees of lateral curvature (scoliosis) are common, and a kyphosis may appear in the dorsolumbar region of rachitic children when sitting. Lordosis of the lumbar region may be seen in the erect position.



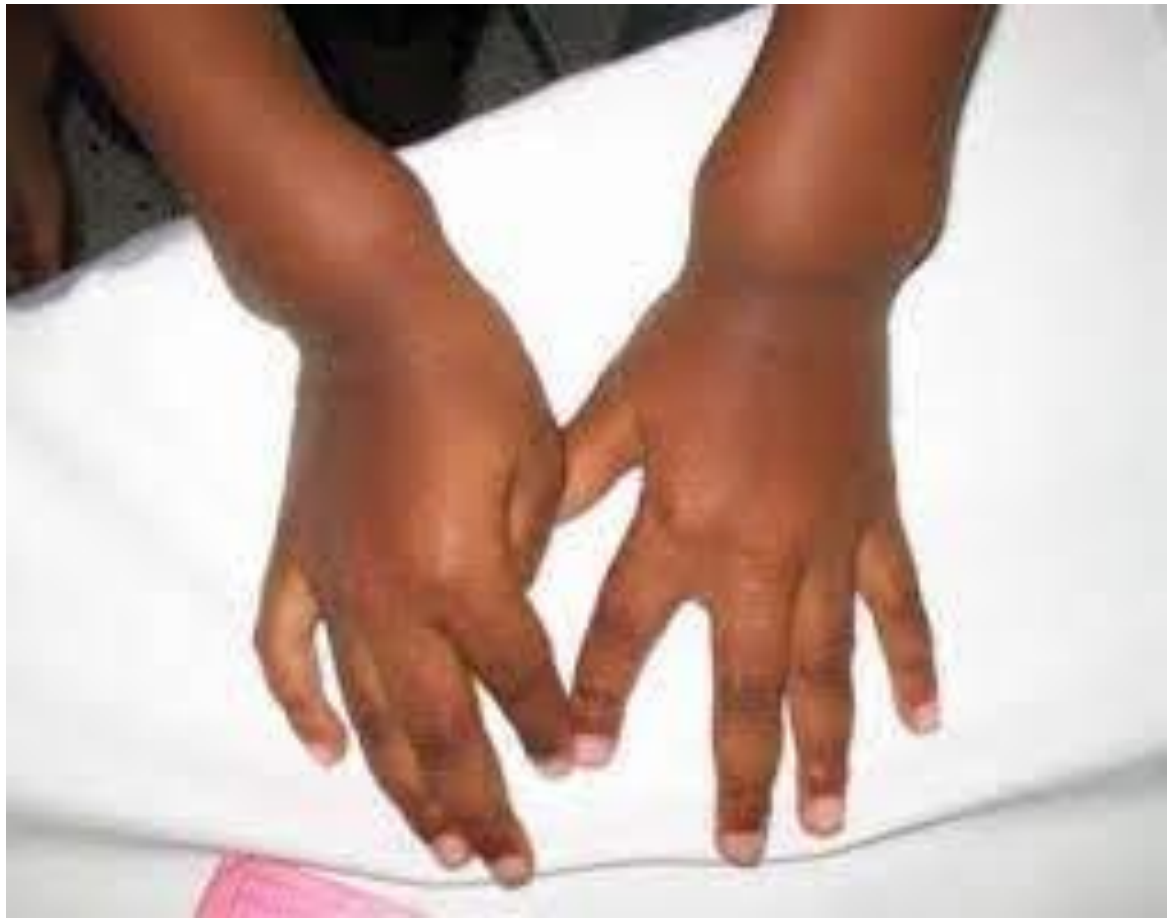
Pelvis. In children with lordosis there is frequently a concomitant deformity of the pelvis, which is also retarded in growth. The pelvic entrance is narrowed by a forward projection of the promontory the exit, by a forward displacement of the caudal part of the sacrum and the coccyx.



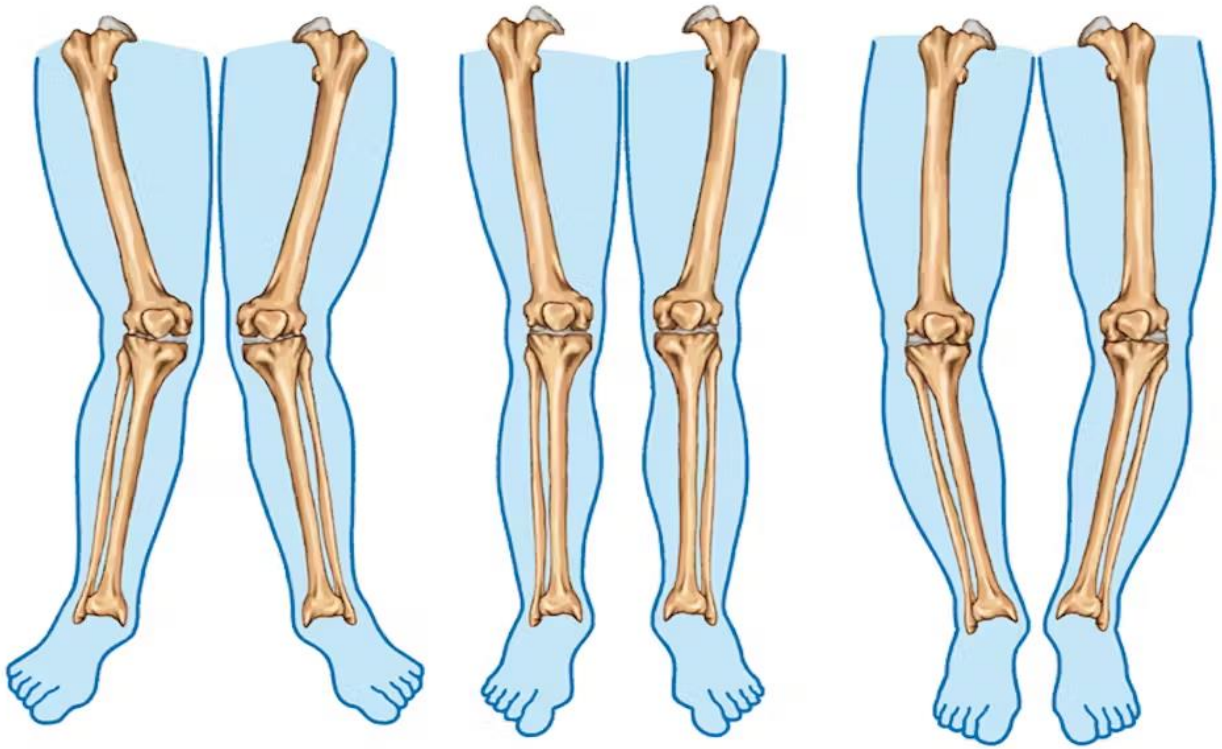
In the female, these changes, if they become permanent, add to the hazards of childbirth and may necessitate cesarean section.

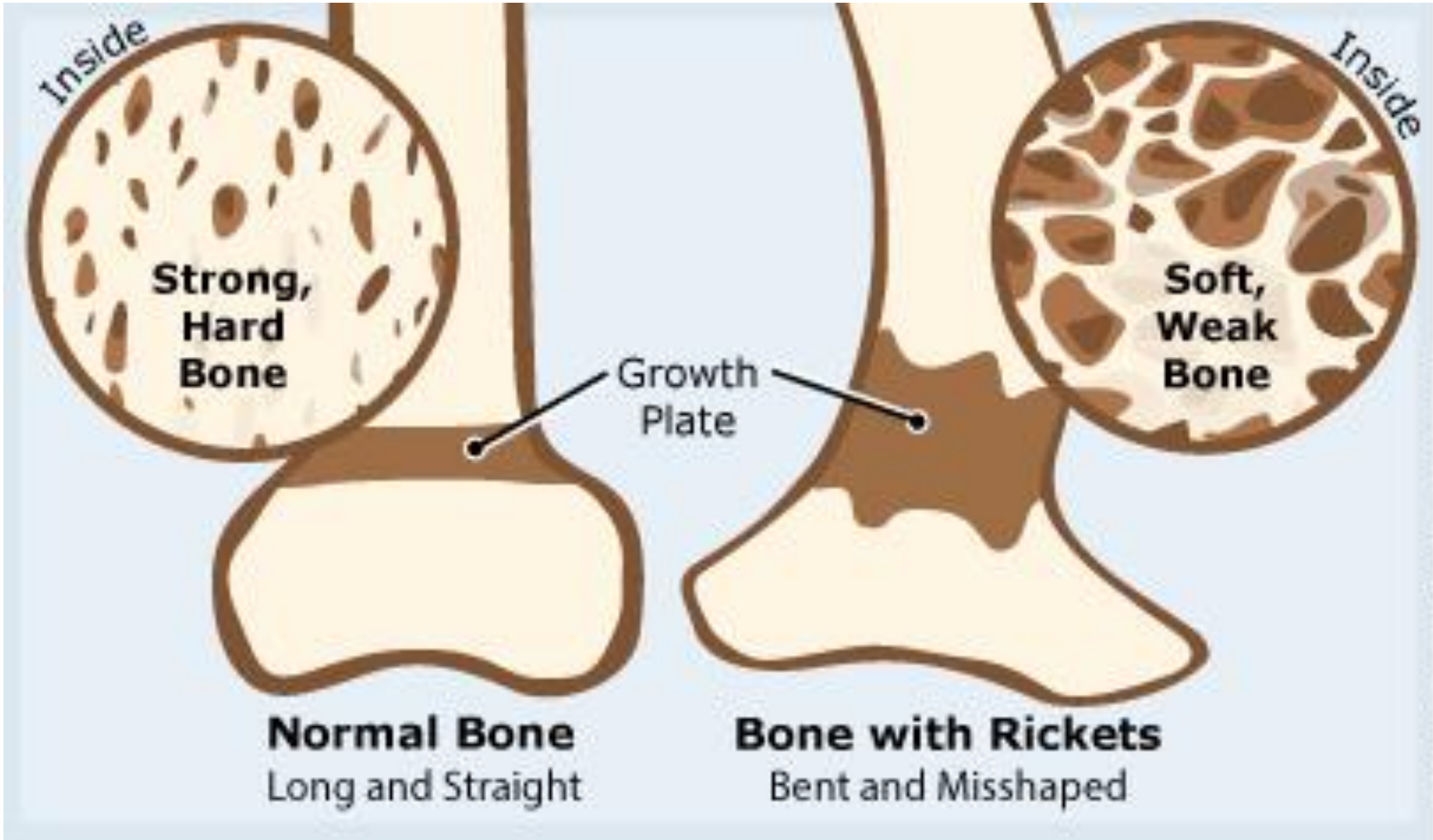


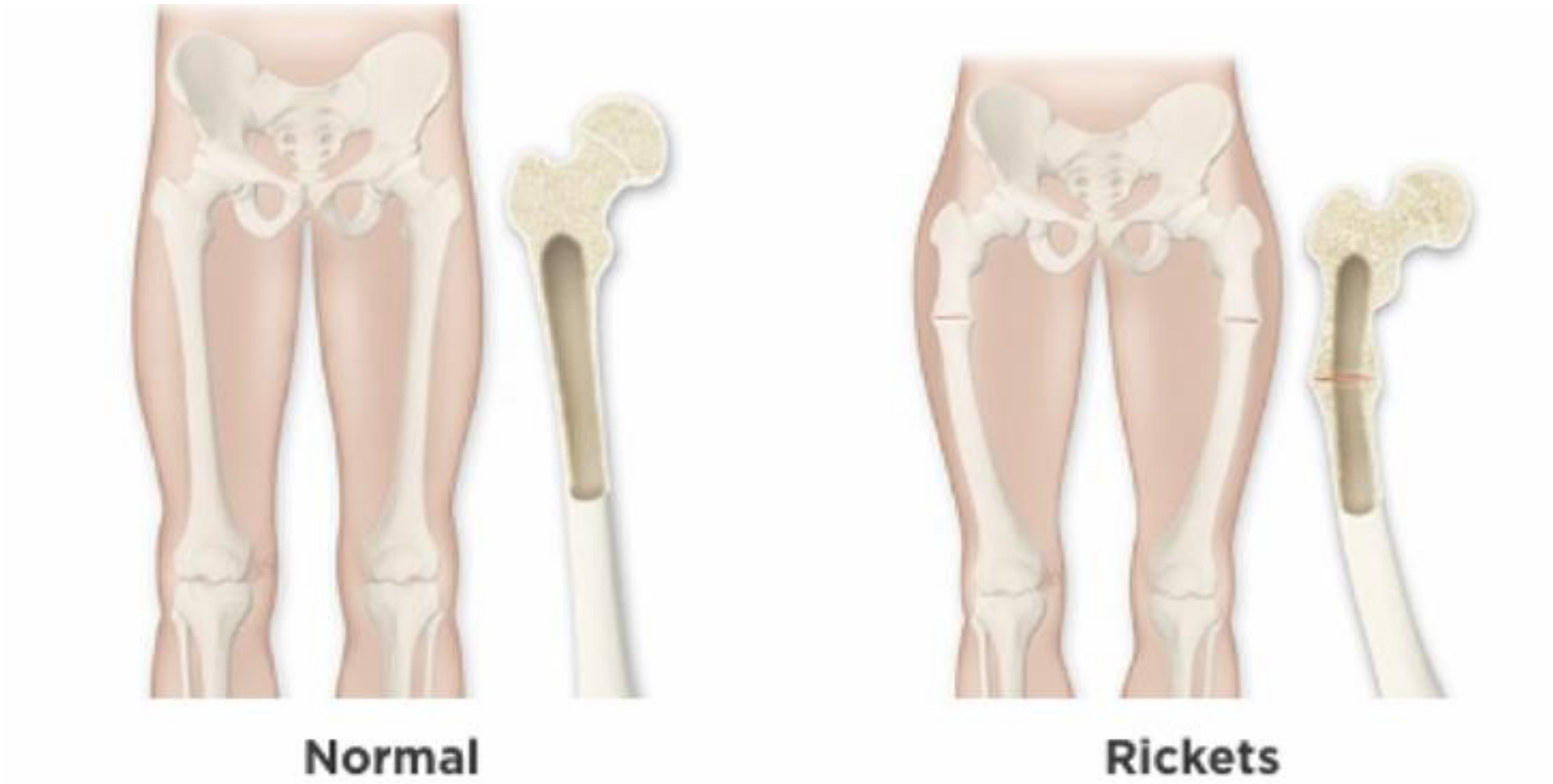
Extremities. As the rachitic process continues, the epiphyseal enlargement at the wrists and ankles becomes more noticeable. The enlarged epiphyses can be seen or palpated but are not distinct in roentgenograms because they consist of cartilage and uncalcified osteoid tissue.

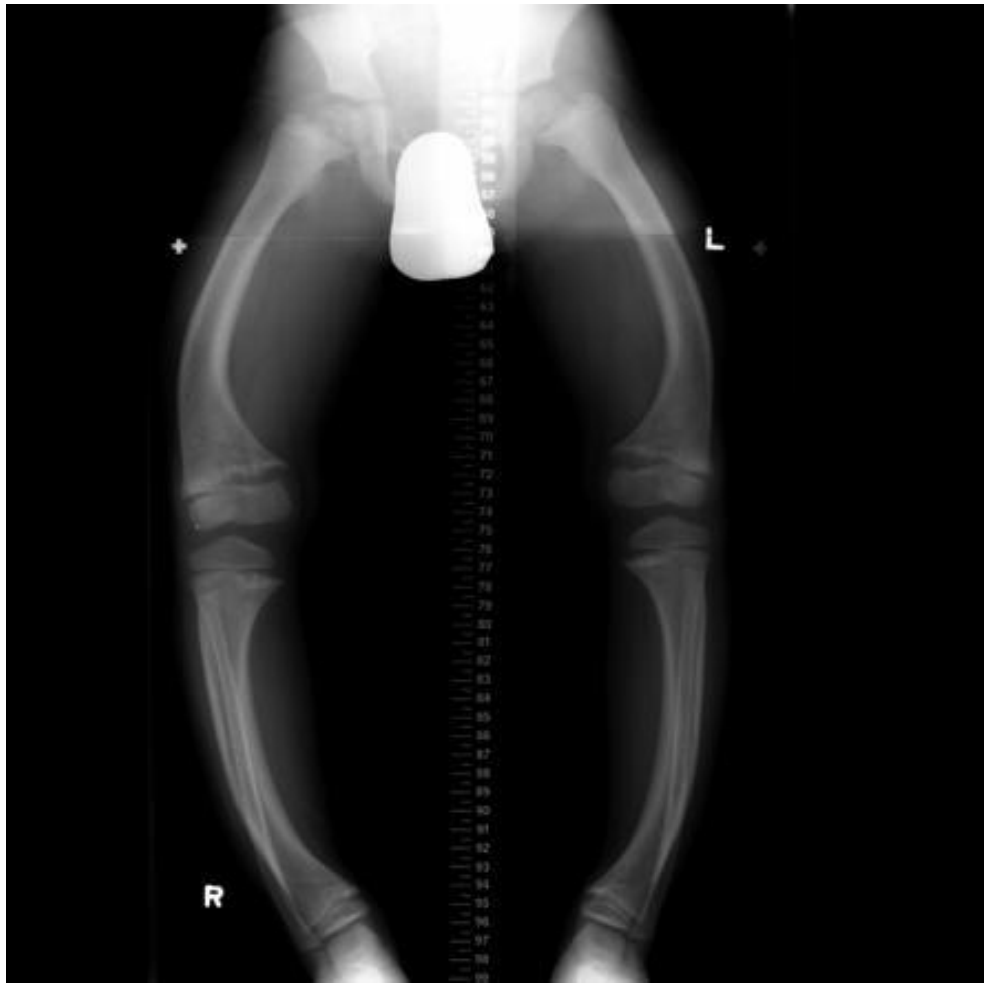


Bending of the softened shafts of the femur, tibia, and fibula results in bow-legs or knock-knees; the femur and the tibia may also acquire an anterior convexity. Coxa vara is sometimes the result of rickets. Greenstick fractures occur in the long bones; often there are no clinical symptoms.






Normal
Rickets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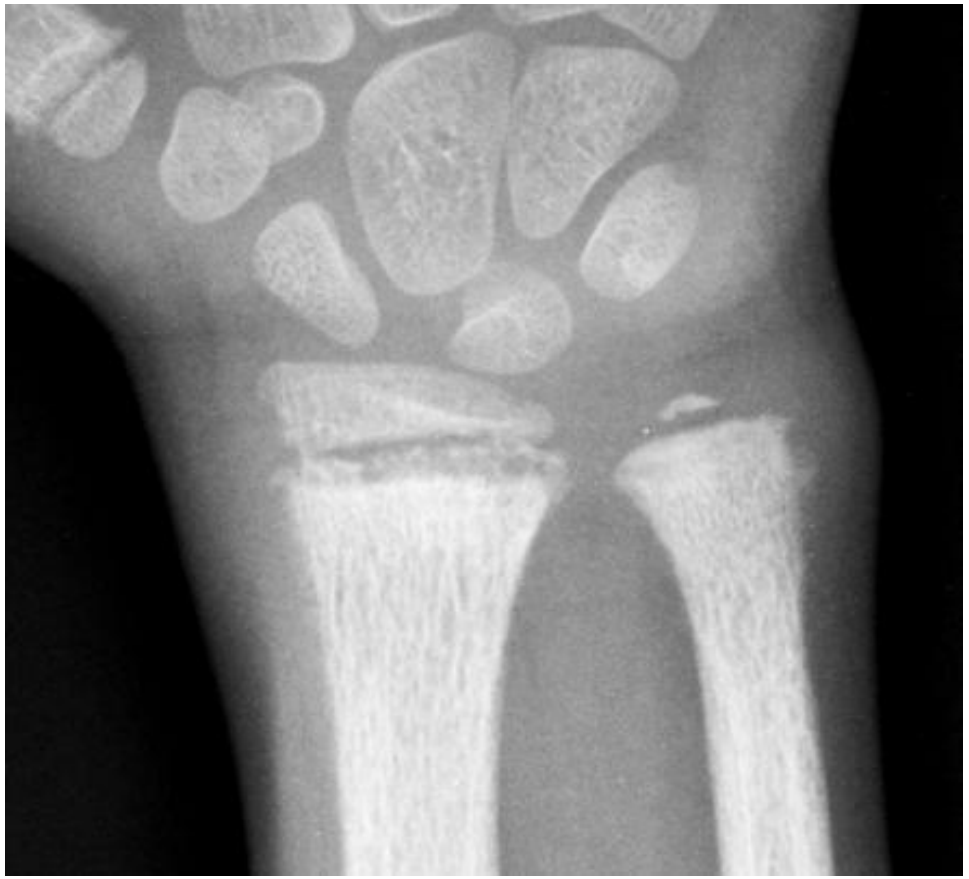
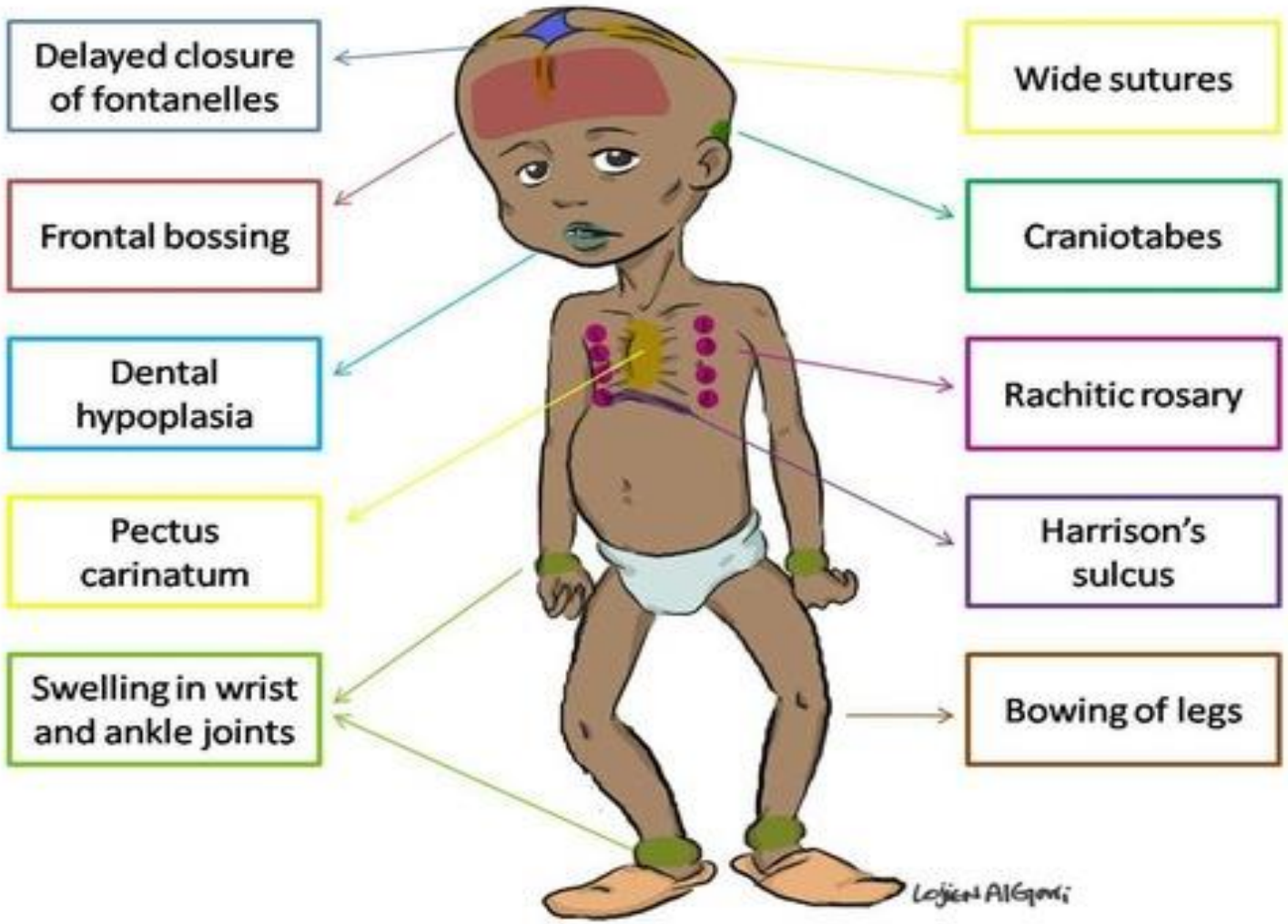


10 important clinical features in Rickets



Deformities of the spine, pelvis, and legs result in reduced stature, rachitic dwarfism.

Ligaments. Relaxation of ligaments helps to produce deformities and partly accounts for knock-knees, overextension of the knee joints, weak ankles, kyphosis, and scoliosis.

Muscles. The muscles are poorly developed and lack tone. As a result, children with moderately severe rickets are late in standing and walking. Potbelly depends to a large extent on weakness of the abdominal muscles; weakness of the gastric and intestinal walls may contribute.

Diagnostic criteria

I. Clinical:

1. syndrome of affection of nervous system is observed in 100% of cases and is revealed at initial period of disease as excitability, interrupted sleep, sweating, and quick persistent red dermographism. At the height of disease flaccidity, lag of motor development or rarely nervous-psychical retardation (only in graveforms of disease);
2. syndrome of lesion of osseous system is revealed in100% of cases. There are the following symptoms:

- symptoms of osteomalacia which manifest in form of softening of the big fontanel's edges, craniotabes, softening of ribs (Harrison's groove), kyphosis, bandy and baker's legs;

- symptoms of hyperplasia of osteoid tissue - increase of frontal and occipital tubers, costohondral prominence ("rachitic rosary"), bracelets on the upper and lower extremities, threads of pearls on finger's phalanges;
- symptoms of hypoplasia of osseous tissue - tardy closing of fontanels, delayed dental eruption, in severe cases - lag of growth of tubular bones in length. In acute course of rickets symptoms of osteomalacia prevail, in subacute - symptoms of hyperplasia of osteoid tissue;

3. muscular hypotonia is seen in 98,8% of patients. Its development leads to delay of statical abilities;
4. changes of internal organs: cardio-vascular system, respiratory tract, digestive tract and so on, increase of liver and spleen.

Diagnostic criteria

2. Laboratory:

- common blood analysis - hypochromic anemia;
- biochemical analyses of blood:
- increase of alkaline phosphatase at the initial period of disease;
- hypophosphatemia of a slight degree at the initial period of disease but marked at its height (normal level of phosphorus in blood - 0,97-1,62 mmol/l);
- hypocalcemia of moderate or high degree at the height of disease (normal level of calcium in blood is 2,25-2,75 mmol/l);

Diagnostic criteria

X-ray: disorders of periostal and enchondral ossification in the bone's growth zone are revealed. Bone becomes low contrasted, cortical stratum becomes thinner, zones of enlightenment appear (Loozer's zones). Strip of preliminary calcification disappears (preparatory zone), the edge becomes illegible, loosened. Growth zone dilates, becomes fungus-like or glass-like. Epiphyseal nucleus appears lately.

Differential diagnosis:

1. Vit D-dependent rickets of I type: defect of 25-hydroxyvitamin D-l-hydroxylase in kidney lays in its basis. Laboratory signs are following: hypocalcemia, hypophosphatemia, high levels of parathormone in blood, increased activity of alkaline phosphatase, aminoaciduria, gllucosuria. Usual doses of vit D are ineffective.
2. Vit D-dependent rickets of II type: almost the same, but total alopecia and retarded growth are present; level of 1,25 (OH)2 D3 is normal, but hypocalcemia and hypophosphatemia are preserved.

3. Phosphat-diabetes: defect is not quite clear, but it concerns reabsorption of phosphates in renal tubules and decreased activity of convertion of 25 (OH) D3 in 1,25 (OH)2 D3. There are O-shaped legs; hypophosphatemia may be revealed by chance from the 1st month of life, signs of hypocalcemia, hyperplasia of osteoid tissue, myopathy are absent, level of blood Ca is normal or slightly decreased, parathormone in blood is normal, alkaline phosphatase elevated a little bit.

4.Hypophosphatasia. the length of tubular bones is diminished, there are disorders of ossification of all skeletal bones; activity of alkaline phosphatase in blood is very low. Hypercalcemia, nephrocalcinosis, renal insufficiency may be seen.
Differential diagnosis is also made with congenital fragility of the bones, Down's disease, chondrodystrophy, hypothyrosis, phosphatic diabetes, syndrome of De Toni-Debre-Fanconi, renal tubular acidosis.

Treatment.

Common measures in rickets treatment irrespective of it form are the following:

- adequate feeding, regimen and walks;
- massage and curative physical training;
- complex of vitamins A,B,C with microelements.

In initial stage of rickets 1,500-2000 IU of vit D2 is enough (total dose 100-120 000 IU) during 30-40 days. In moderate and severe rickets it's necessary to prescribe 3-5 000 IU/d (200-400 000 ID) during 30-40 days. Criterion of finishing the treatment is normalization of laboratory findings. Dose of calcifediol (25(OH)D3) and calcitriol (1,25(OH)2D3) are 10 and 1 mcg/d correspondently during two 10 days courses with 2 weeks' interval between them. After the course of treatment it's necessary to give preventive dose (500 IU/d). UV irradiation is effective. Prescription of citrates is of great use.

Treatment Curative therapy (schemes):

- Mild and medium forms:-oral daily administration -2000-4000 IU Vitamin D for 6-8 weeks and then returned to prophylactic - typically for 6 months each 1000 IU / day).
- Severe forms: manifest hypocalcemia(convulsions) and children with malabsorption.-administration of 3 doses of 100 000 UI D3 intramuscularly every 3 days, then a dose of 200 000 IU after 30 days oral or i.m.

In endogenic cases of deficient rickets doubled doses may be used. As a rule active metabolites of vit D are prescribed.

If hypocalcemia is seen the initial dose of vit D must be doubled. Besides, calcium must be given (orally, parenterally, or electrophoresis).

Vitamin D (cholecalciferol) is well stored in the body and is gradually released over many weeks. Because both calcitriol and calcidiol have short half-lives, these agents are unsuitable for treatment, and they bypass the natural physiologic controls of vitamin D synthesis. The single-day therapy avoids problems with compliance and may be helpful in differentiating nutritional rickets from familial hypophosphatemia rickets (FHR). In nutritional rickets, the phosphorus level rises in 96 hours and radiographic healing is visible in 6-7 days. Neither happens with FHR. If severe deformities have occurred, orthopedic correction may be required after healing. Most of the deformities correct with growth. A consultation with a pediatric endocrinologist is recommended.

Prevention of Rickets

Prevention may be antenatal and postnatal, specific and non-specific.

1. Prenatal prevention of rickets is carried out by obstetricians. Specific prevention is not indicated in women older than 35 years, because of excessive Ca deposits in placenta and fetal hypoxia, atherosclerosis in women.

2. Postnatal specific prevention with vit D is provided by doses 500 IU/d, that is the physiological necessity of a child's organism. Oily solutions of vit D (ergocalciferol) are used more often. Use of total 2-5 daily doses in one intake (correspondingly every 2-5 days). In summer the vitamin is not given. Premature infants need the administration of vit D from 2 weeks by doses 1000-1500 IU/d. Prophylactic course of vitamin D may be interrupted by UV irradiation. Specific prevention isn't carried out in the children receiving formula feeding.

3. Specific postnatal prevention we begin from 2nd week with 500 IU of vit D all year round + vit C 0.03 g + B, B2 - 0,001 g, B5 0.003 g 2 weeks in a month. It is possible to alternate vit D with UV irradiation, after course of which it is not necessary to give vit D 3-4 weeks. Once in 2-3 weeks it is necessary to provide test of Sulkowitz; if it is positive, vit D must be abolished.

Non-specific prevention signifies rational feeding, individual care, sufficient stay outdoors, gymnastics, massage.

Title of the seminar: Neonate tetany. Etiopathogenesis, symptoms, diagnosis, differential diagnosis, treatment and prevention.

Name of the tutor: Olena Debretseni

Duration: 90 min

Audience: 4rd course students

Goals:
General: To master skills in diagnostics neonate tetany. Diagnosis based on the learning of the clinical and laboratory data, treatment and prevention activities on different stages of child's development.

Special goals:
• Knowledge: to learn the main symptoms in neonate tetany and history-taking.
• Practical skills: physical examination, analyze clinical and laboratory data, be able to evaluate information on the preliminary diagnosis, using a standard procedure based on the results of laboratory and instrumental studies.

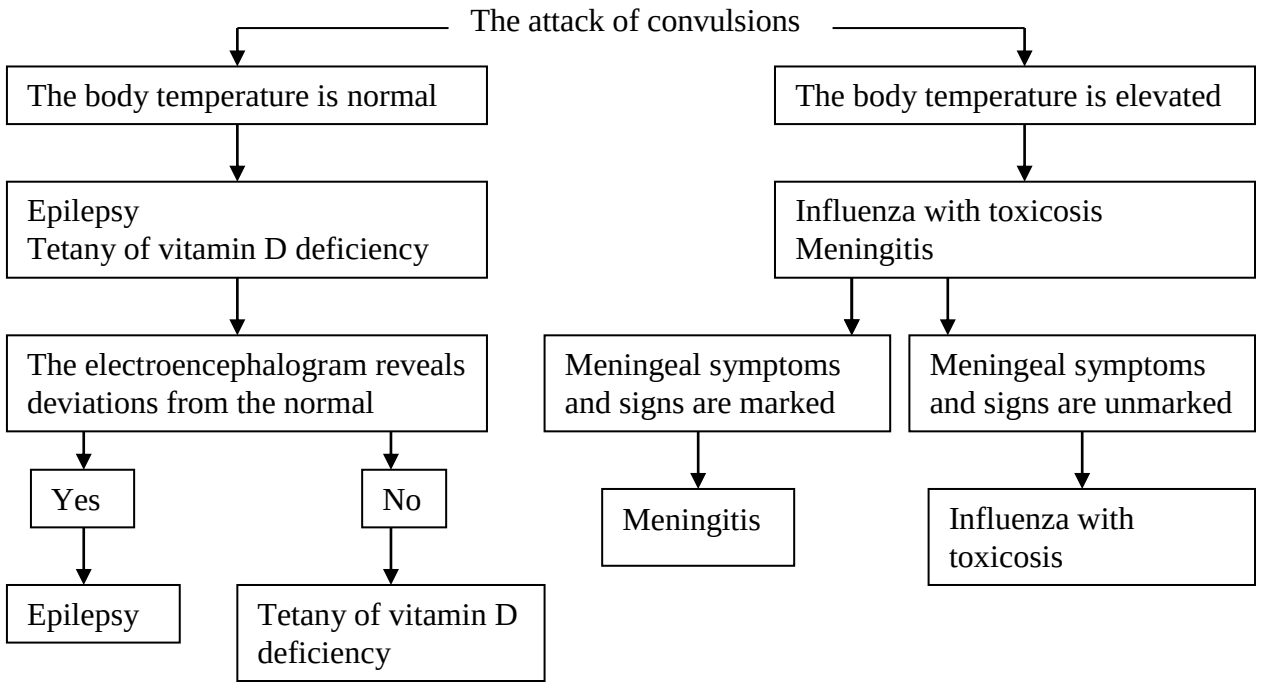
Methodology of the seminar:
5 minutes Short introduction
5 minutes Ice breaker
20 minutes Theory presentation (Power Point presentation)
35 minutes Interactive
Use of “OPEN” QUESTIONS and ROLE-PLAY TEACHING METHODS in the “history-taking” part of the class.
Practical training of collect data on patient complaints, medical history, life history, conduct and evaluate the results of physical examination (on patients, on each other)
15 minutes Control – verbal interview
10 minutes Feedback from each participant: take home notes: “What was new for me today? What did I learn/practice? What will I introduce into my future practice?”
Results: we expect each participant:

- Master the basics of history-taking collecting data on patient complaints, medical history, life history, conduct and evaluate the results of physical examination patients with rickets
- Practice to perform physical examination, analyze clinical and laboratory data, evalueiting information on the preliminary diagnosis, using a standard procedure based on the results of laboratory and instrumental studies.

Neonate Tetany, the state of hyperexcitability of the central and peripheral nervous systems, results from abnormal concentrations of ions in the fluid bathing nerve cells. These abnormalities may include decreases of H + (alkalosis), Ca 2+ , or Mg 2 . When the serum calcium concentration falls below 7-7.5 mg/dL, muscular irritability occurs, apparently owing to the loss of the inhibitory control that serum ionized calcium exerts on the neuromuscular junctions.

Tetany due to deficiency of vitamin D occasionally accompanies rickets. It occurs most frequently between the ages of 4 mo. and 3 yr. The prognosis is good unless treatment is delayed. Death rarely occurs, though it may result from laryngospasm and possibly from cardiac dilatation, so-called cardiac tetany. Tetany is a disease stipulated by the disturbances of mineral metabolism, hypofunction of parathyroid glands and manifesting with elevated excitability of nervous-muscular apparatus and development of clonotonic convulsions.

Diagnostic Algorithm for Tetany.



Diagnostic criteria

1. Anamnestic data:

Wrong formula feeding, abuse of cow milk, goats and flour meals, insufficient stay at the fresh air, absence of rickets' prevention are revealed in the case history.

2. Clinical signs:

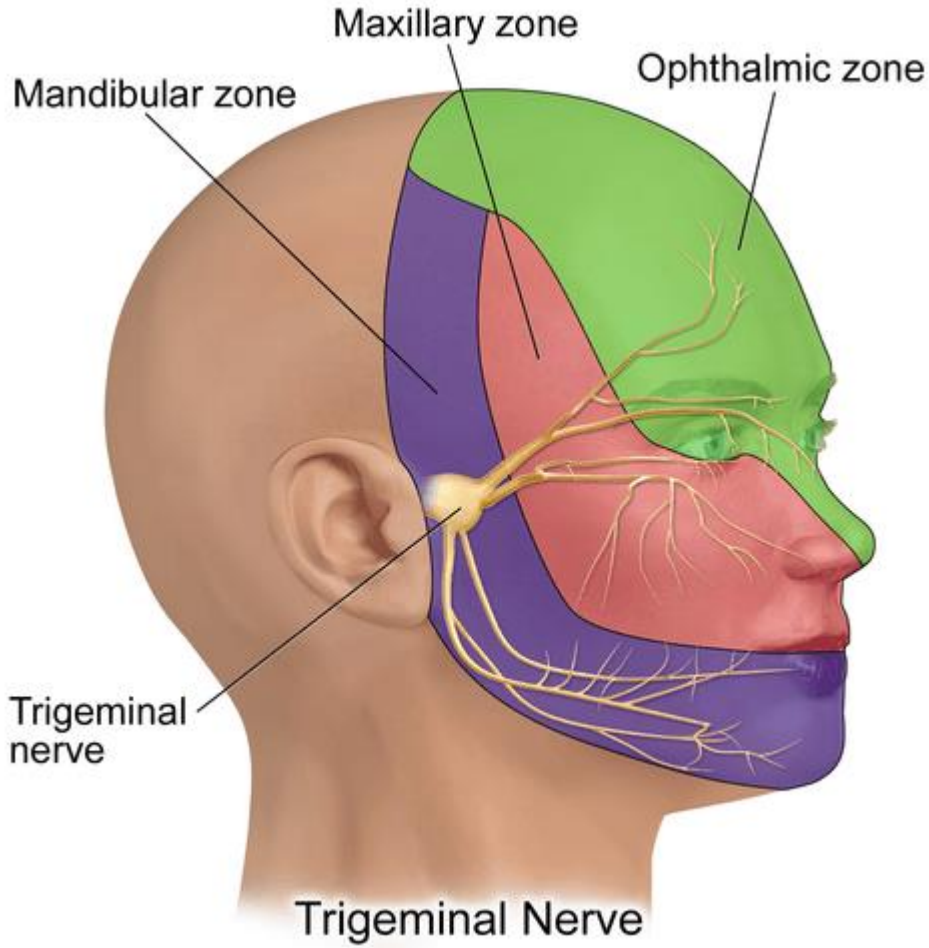
Tetany develops in children suffering from rickets. As a rule, children younger than 2-3 years may be ill both with rickets and tetany.

Clinically we can distinguish latent and manifest tetany.

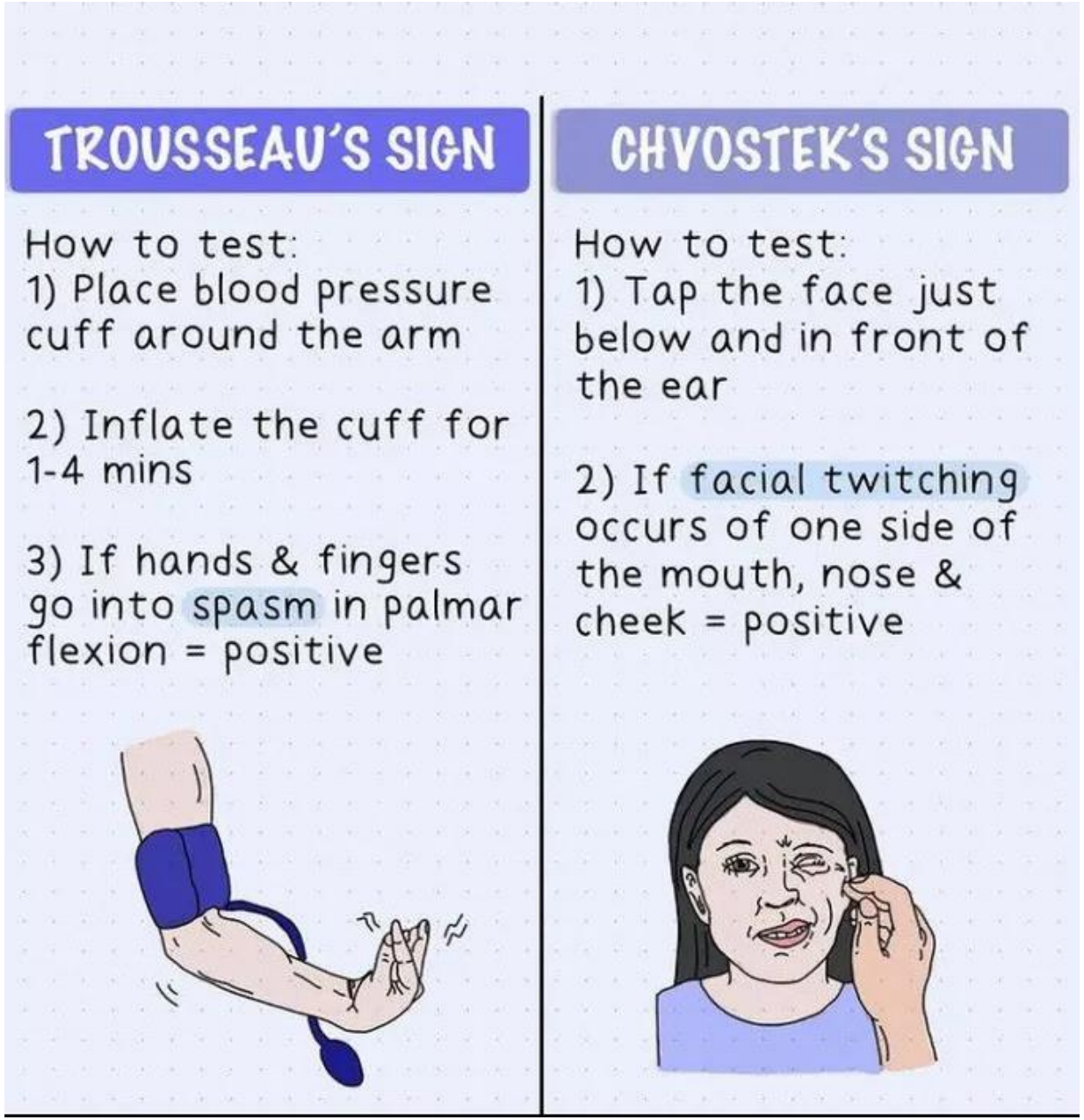
Symptoms of latent tetany:

1. Chvostec’s symptom - symptom of facial nerve, tapping on the place of outlet of facial nerve causes spastic contraction of mimic facial muscles;

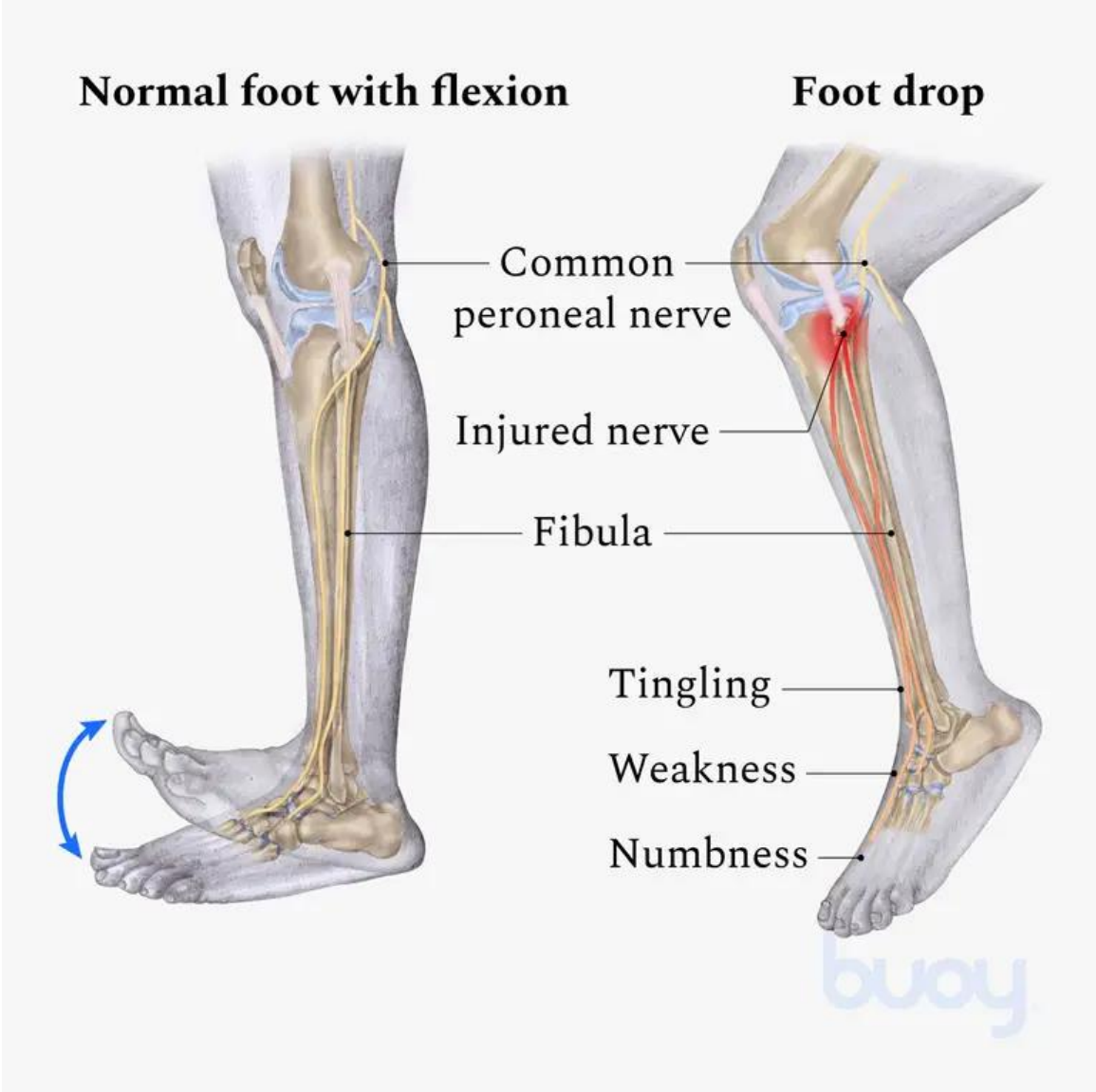
2. Weis's symptom
- irritation of the place of outlet of trigeminal nerve (near the external acoustic meatus) leads to contraction of mimicry muscles;



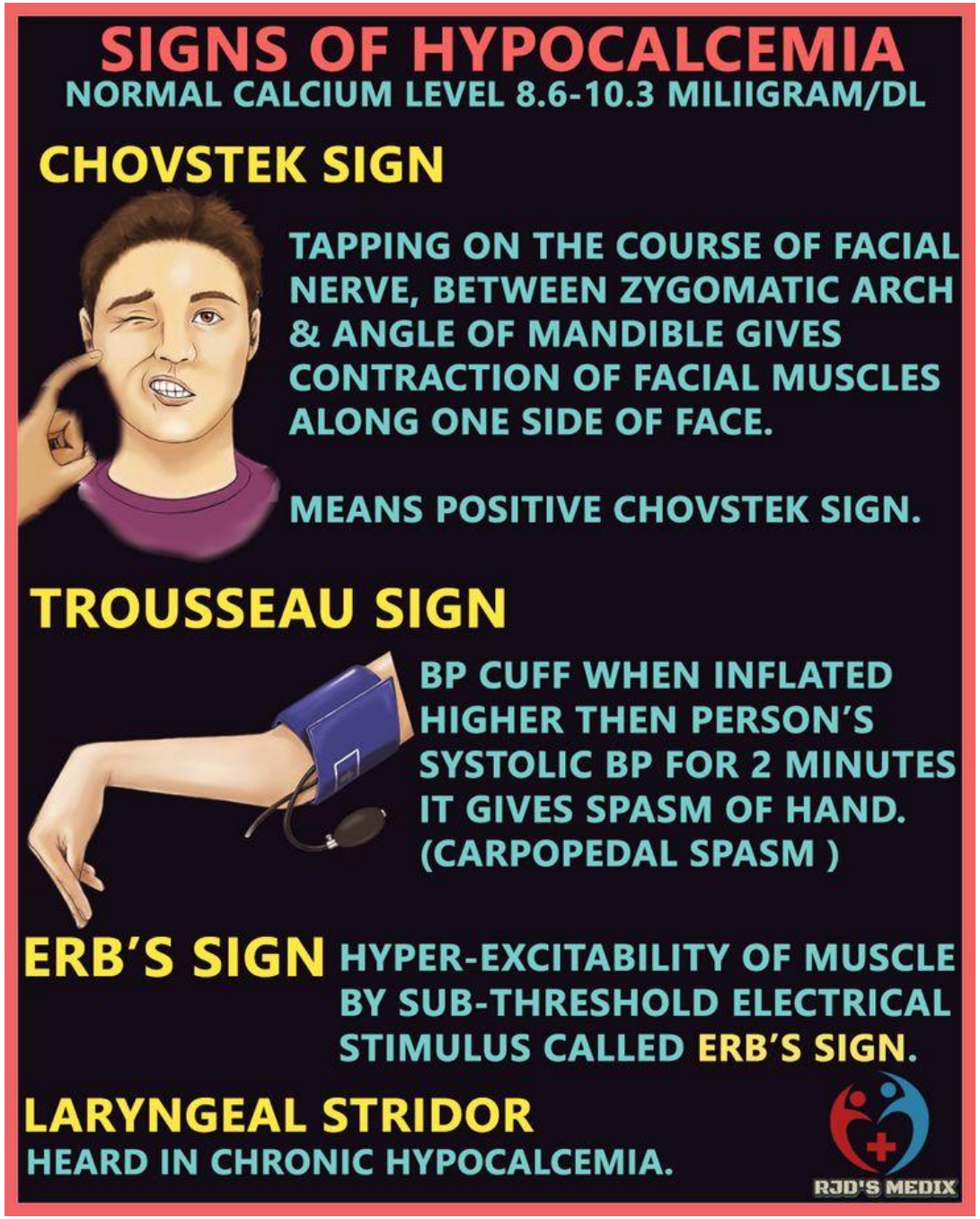
3. Trousseau’s symptom - squeezing of nerve-vascular bundle on the shoulder causes spastic contraction of hand’s muscles - "obstetrician’s hand";



4. Lust’s symptom - peroneal symptom, tapping lower the head of the fibula causes dorsal flexion and opening of feet’s fingers;

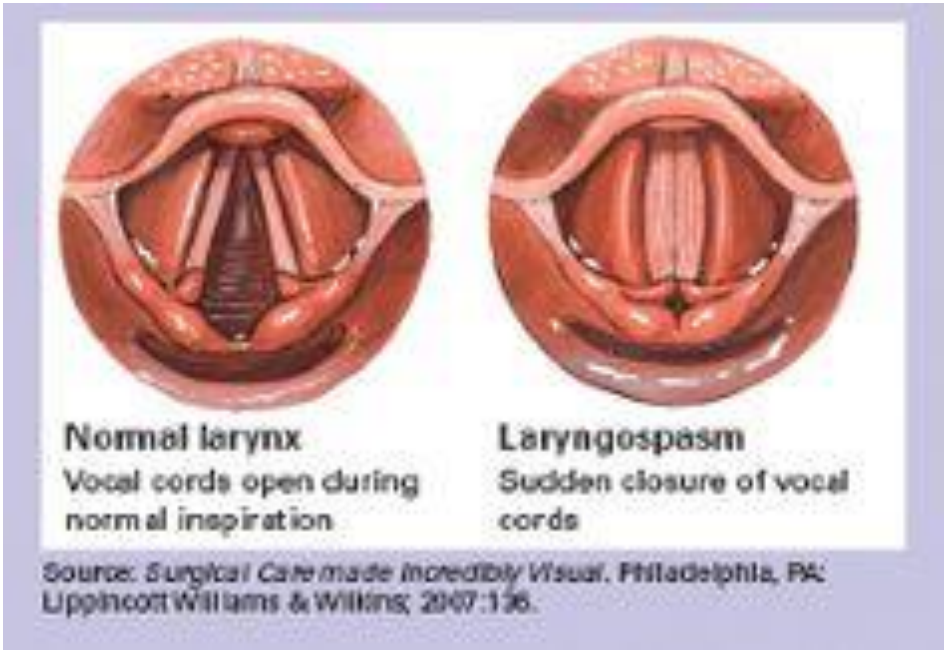


5. Maslov’s symptom - prick on the heel causes apnoe instead of quickening of breathing;
6. Erb’s symptom - closing of cathode on the muscle leads to its spasm while strength of the current is less than 5 mA.



Symptoms of manifest tetany:

1. laryngospasm - convulsive spasm of true glottis during inspiration accompanied by "cock-cry" and development of cyanosis attack;



2. carpo-pedal spasm - tonic convulsions of extremities’ muscles;

4. expiratory apnoe - stop of respiration on expiration with development of attack of general cyanosis.
Convulsive spasm of a heart muscle leading to child’s death is possible.

3. Laboratory diagnostics:

Hypocalcemia (to 1,2-1,5 mmol/l), quantity of inorganic phosphorus is relatively elevated. Alcalosis is seen in some children.

Table 25. Age-Specific Normal Ranges of Blood Ionized Calcium, Total Calcium and Phosphorus

Age	Ionized Calcium (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)
0-5 mo	1.22-1.40	8.7-11.3	5.2-8.4
6-12 mo	1.20-1.40	8.7-11.0	5.0-7.8
1-5 y	1.22-1.32	9.4-10.8	4.5-6.5
6-12 y	1.15-1.32	9.4-10.3	3.6-5.8
13-20 y	1.12-1.30	8.8-10.2	2.3-4.5

Adapted with permission[121]; Specker.[524]

Conversion factor for calcium and ionized calcium: mg/dL × 0.25 = mmol/L.

Conversion factor for phosphorus: mg/dL × 0.323 = mmol/L.

Differential diagnosis is conducted with:

- hyperthermic convulsions
- complicated pneumonia
- meningitis
- viral diseases
- epilepsy

Treatment of Tetany

It is desirable to substitute formula feeding for breastfeeding. If it is impossible one has to limit the quantity of cow’s milk and increase the quantity of vegetables.

Infants with latent tetany may respond to oral calcium gluconate (5%) or calcium chloride (1-2%) - 1 teaspoonful x 3 times a day.

Infants with clinical manifestations of tetany require i.v. calcium gluconate (10%) 2 ml/kg given slowly while monitoring ECG (bradycardia, arrhythmia).

In convulsions it is necessary to inject i.v. seduxen (0,1 ml/ kg of 0,5% solution), $MgSO_4$ (0,5 ml/kg of 25% solution), sodium oxybutyrate (0,5 ml/kg of 20% solution), oxygen inhalations.

3-4 days after convulsions it is necessary to prescribe vit D3 2000-4000 IU twice a day.

If laryngospasm is diagnosed it is necessary to try to create a dominant focus of stimulation in the brain by irritation of nasal mucosa, skin, or vestibular analyzer.

Title of the seminar: Hypervitaminosis D. Etiopathogenesis, symptoms, diagnosis, differential diagnosis, treatment and prevention.

Name of the tutor: Olena Debretseni

Duration: 90 min

Audience: 4rd course students

Goals:
General: To master skills in diagnostics hypervitaminosis D.. Diagnosis based on the learning of the clinical and laboratory data, treatment and prevention activities on different stages of child's development.

Special goals:
• Knowledge: to learn the main symptoms in hypervitaminosis D. and history-taking.
• Practical skills: physical examination, analyze clinical and laboratory data, be able to evaluate information on the preliminary diagnosis, using a standard procedure based on the results of laboratory and instrumental studies.

Methodology of the seminar:
5 minutes Short introduction
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Results: we expect each participant:
• Master the basics of history-taking collecting data on patient complaints, medical history, life history, conduct and evaluate the results of physical examination patients with rickets
• Practice to perform physical examination, analyze clinical and laboratory data, evalueiting information on the preliminary diagnosis, using a standard procedure based on the results of laboratory and instrumental studies.

Hypervitaminosis D

Hypervitaminosis D is a disease, which is caused by the toxic action of vitamin D and is characterized with intoxication of different degree, affection of organs and systems and development of hypercalcemia. It may results from excessive intake of vitamin D or may be due to hypersensitivity to vitamin D. Hypervitaminosis D is a disease, which is stipulated by the toxic action of vitamin D and is characterized with intoxication of different degree, affection of organs and systems and development of hypercalcemia.

Diagnostic criteria

1. Clinical:

1. Syndrome of toxicosis:

Toxicosis of 1 degree - decrease of appetite, irritability, disorders of sleep, delay of weight increase, subfebrile temperature.

Toxicosis of 2 degree - pallor of skin, vomits, decreases of weight, functional disorders of internal organs and systems.

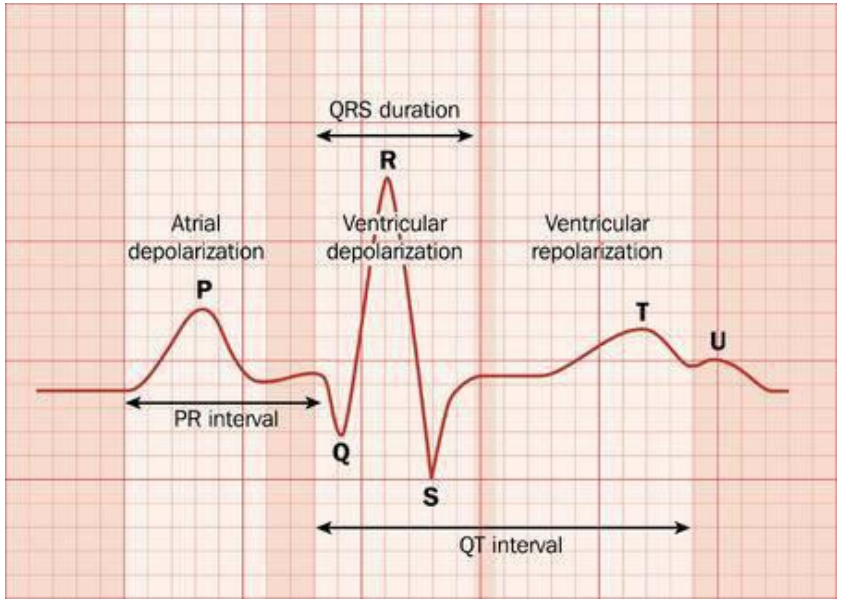
Toxicosis of 3 degree - anorexia, persistent vomits, dehydration, considerable loss of weight, complications such as pneumonia, pyelonephritis, myocarditis, and pancreatitis.

2. Syndrome of functional disorders of nervous system:

1. flaccidity,
2. apathy,
3.alternating with excitability,
4. irritability,
5. drowsiness,
6. hyperesthesia,
7. sweating,
8. meningism,
9. encephalitic reactions,
10. depression of consciousness,
11. convulsions.

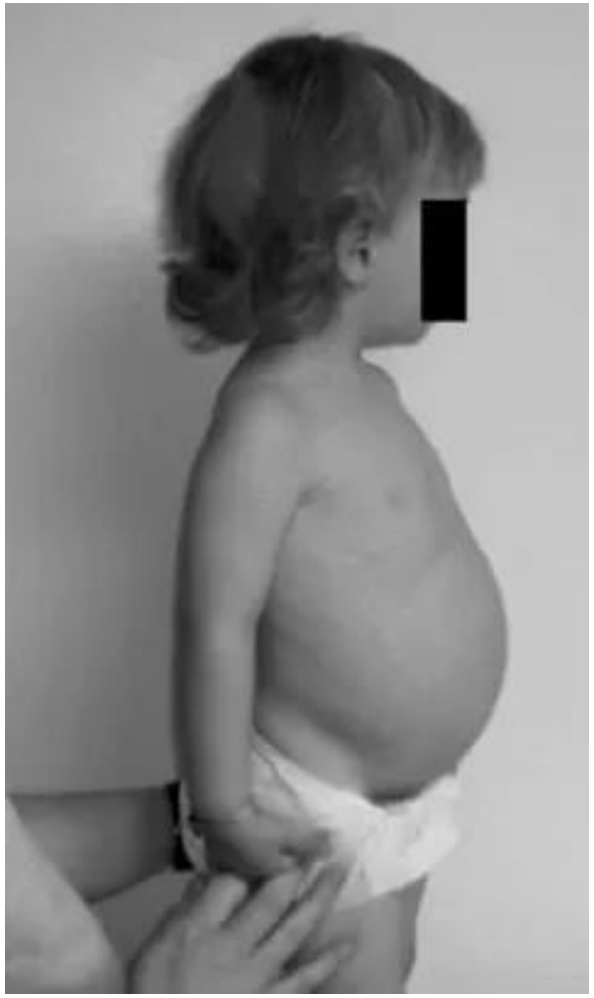
3. Cardio-vascular syndrome:

tachycardia, muffled cardiac sounds, systolic murmur, cyanosis, dyspnea, enlargement of liver, edemas. ECG disorders
- dilation of QRS-complex, lengthening of PQ interval, smoothing of T-wave, diphase T-wave in lead V4.



4. Gastro-intestinal syndrome:

decrease of appetite up to anorexia, vomit, persistent constipation, rarely diarrhea, enlargement of liver and spleen.

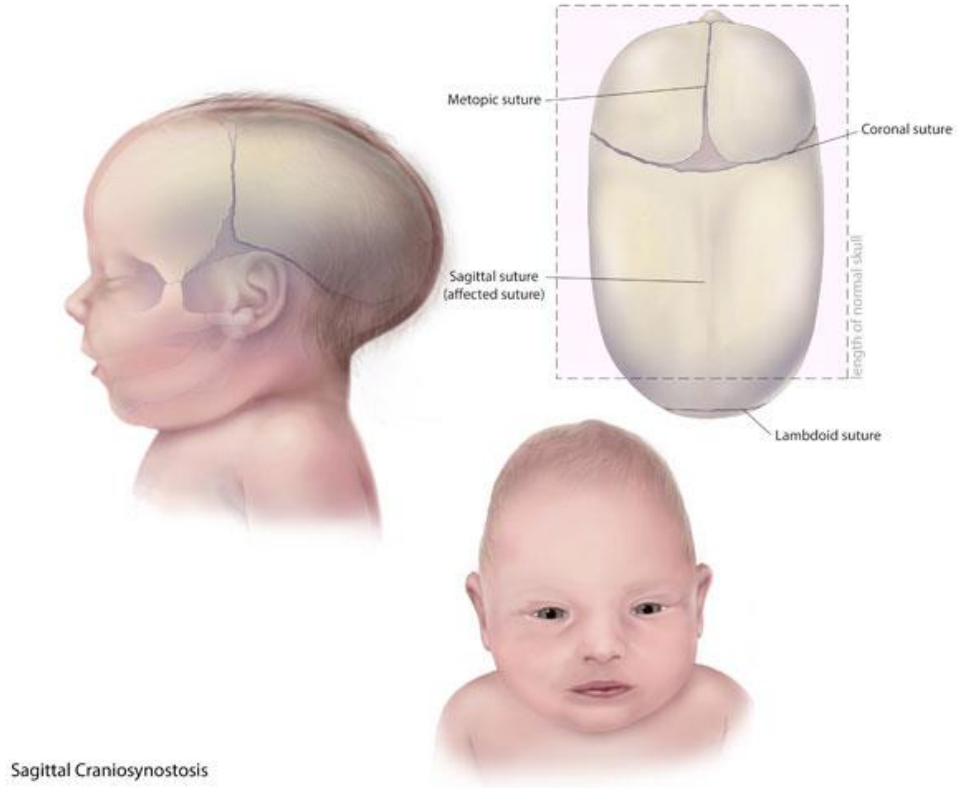


5. Renal syndrome:

dysuric symptoms, polyuria, probably oliguria up to anuria, azotemia.

6. Changes in osseous system:

consolidation of the skull bones, early closure of big fontanel, craniostenosis.



Sagittal Craniosynostosis

2. Laboratory:

- blood: leucocytosis, elevated ESR;
- biochemical changes: hypercalcemia, hypophosphatemia, hypomagnesemia, hypokalemia, elevated levels of citrates and cholesterin;

- urine: increase of calcium, Sulkowitch’s test is positive;
- stool: neutral fat;
- acid-base equilibrium - metabolic acidosis.

Acid Base Disorders

Disorder	pH	$[H^+]$	Primary disturbance	Secondary response
Metabolic acidosis	↓	↑	↓ $[HCO_3^-]$	↓ pCO_2
Metabolic alkalosis	↑	↓	↑ $[HCO_3^-]$	↑ pCO_2
Respiratory acidosis	↓	↑	↑ pCO_2	↑ $[HCO_3^-]$
Respiratory alkalosis	↑	↓	↓ pCO_2	↓ $[HCO_3^-]$

Classification of Hypervitaminosis D

Course	Form	Period
Acute (as neurotoxicosis or toxicosis with dehydration of 1-3 degree)	Gastro-intestinal Cardio-vascular	Clinical manifestations Residual signs
Chronic		
	Nervous Renal	

Treatment of Hypervitaminosis D

This depends upon the severity of general condition.

Intensive detoxicative therapy includes:

- 1.i.v. injections of 5% albumin,
- 2. 5% solution of glucose with Ringer's solution,
- cocarboxylase, vit C,
- prednisolone,
- vit E,
- furosemid (1 mg/kg 3 times/d),

- thyreocalcitonin (75-150 U i.m. every day),
- 3% solution of ammonium chloride (teaspoonful 3 times a day),
- almagel,
- Trilon B 50 mg/kg 2-3 times/d.

It is necessary to exclude food with high concentration of calcium (milk, curds).

Title of the seminar: Iron deficiency anemia. Etiopathogenesis, symptoms, diagnosis, differential diagnosis, treatment and prevention.

Name of the tutor: Olena Debretseni

Duration: 90 min

Audience: 4rd course students

Goals:
General: To master skills in diagnostics Iron deficiency anemia. Diagnosis based on the learning of the clinical and laboratory data, treatment and prevention activities on different stages of child's development.

Special goals:
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Methodology of the seminar:
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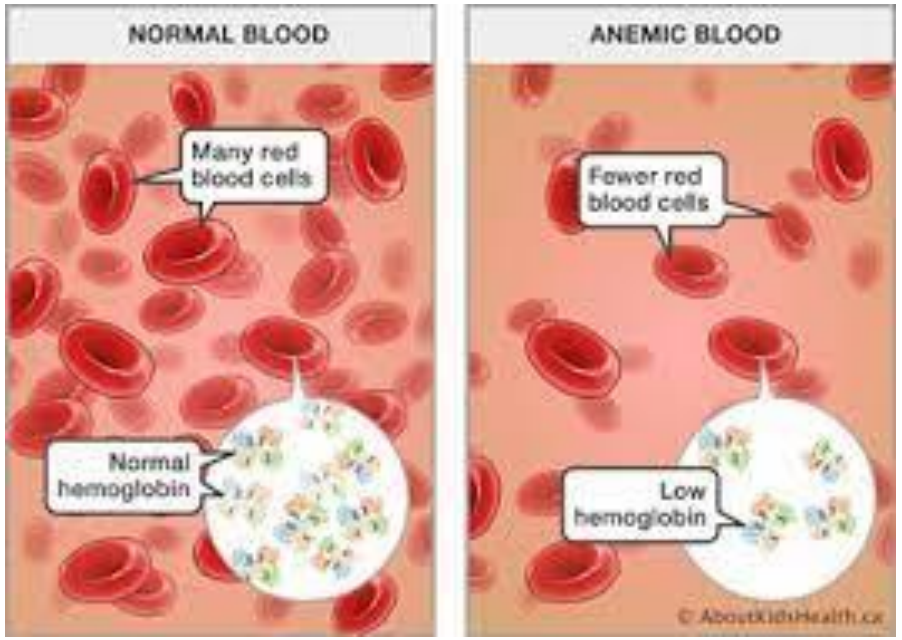
• Practice to perform physical examination, analyze clinical and laboratory data, evalueiting information on the preliminary diagnosis, using a standard procedure based on the results of laboratory and instrumental studies.

Iron deficiency is the most common nutritional deficiency worldwide and an important public health problem especially in developing countries. Since the most important indicator of iron deficieny is anemia, the terms “iron deficiency” and “iron deficiency anemia” are often used interchangeably. However, iron deficiency may develop in the absence of anemia and the tissues may be affected from this condition.

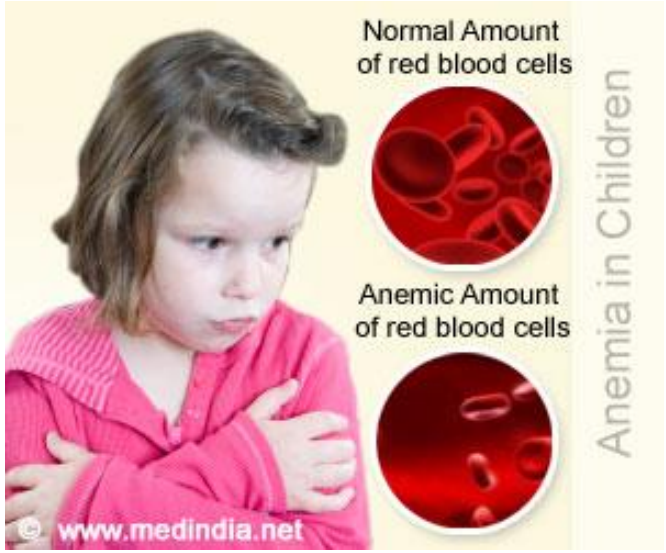
The most common causes of iron deficiency in children include insufficient intake together with rapid growth, low birth weight and gastrointestinal losses related to excessive intake of cow's milk. If insufficient intake can be excluded and there is insufficient response to oral iron treatment in patients with iron deficiency especially in older children, blood loss should be considered as the underlying cause.

There is no clear data about how many individuals are affected by iron deficiency worldwide, but it is estimated that ID is present in most of the pre-school children and pregnant women in developing countries and in at least 30–40% in developed countries when anemia is used as an indirect indicator of ID (24).

According to the 2001 World health Organization (WHO) data, 30% of the children aged between 0 and 4 years and 48% of the children aged between 5 and 14 years are anemic in developing countries (24). In our country, the frequency of iron deficiency anemia (IDA) has been reported to range between 15.2% and 62.5% in different studies conducted with children (25–28).



Reduced erythrocyte count or a hemoglobin (Hb) value 5 percentile below the normal hemoglobin value specified for that age in healthy individuals is defined as anemia. When defining anemia, the lower limit of the normal value for different age groups and genders should be determined.



Lower limits for hemoglobin and hematoctrit values specified by the World Health Organization by age and gender

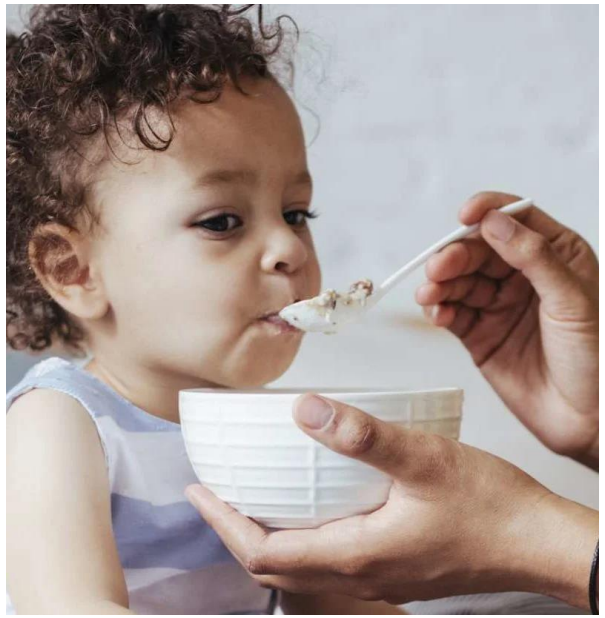
Groups by age and gender	Hemoglobin (g/dL)	Hematocrit(%)
Children aged between 6–59 months	11	33
Children aged between 5–11 years	11.5	34
Children aged between 12–14 years	12	36
Girls aged >15 years	12	36
Boys aged >15 years	13	39

Etiology

The most common causes of IDA observed in children include inadequate intake together with rapid growth, low birth weight and gastrointestinal losses due to excessive consumption of cow's milk. In the intrauterine period, the only source of iron is iron crossing through the placenta. In the final period of pregnancy, the total amount of iron in the fetus is 75 mg/kg. Physiological anemia adevelops in the postnatal period and iron stores are sufficient to provide erythropoesis in the first 6 months of life if there is no significant blood loss. In low birth weight infants and in babies with perinatal blood loss, the stores are exhausted earlier, since they are smaller. Delayed umbilical cord clamping may improve the iron status and reduces the risk of iron deficiency (29).

Solid foods given after the 6th month should be rich especially in iron, zinc, phosphorus, magnesium, calcium and vitamin B6. According to the world Health organization data, 98% of the iron requirement in infants aged 6–23 months should be met by solid foods (30, 31). Solid foods should include products rich in meat, fish, egg and vitamin C to meet this iron need. Another mistake made in feeding infants is giving excessive cow's milk at an early time.

In infants, chronic blood loss may be observed in relation with heat-sesitive proteins in cow’s milk. In addition, the absorption of iron in cow’s milk is much lower compared to breastmilk. Cow’s milk will substitute for iron-rich fooods and in addition calcium and caseinophosphopeptides in cow’s milk may disrupt the absorption of iron. If infants are fed with iron-poor foods after the 6th month when they exhaust almost all of their iron stores, iron deficiency develops easily.



In patiens and especially in older children, blood loss as an underlying cause should be considered, if inadequate intake can be excluded or there is inadequate response to oral iron treatment. Chronic iron deficiency anemia which develops with occult bleeding is observed with a relatively lower rate in children and may occur as a result of gastrointestinal problems including peptic ulcer, Meckel's diverticulum, polyp, hemangioma or inflammatory bowel disease. Insensible blood loss may rarely be related with celiac disease, chronic diarrhea or pulmonary hemosiderosis; it is possible to make the differential diagnosis with history.

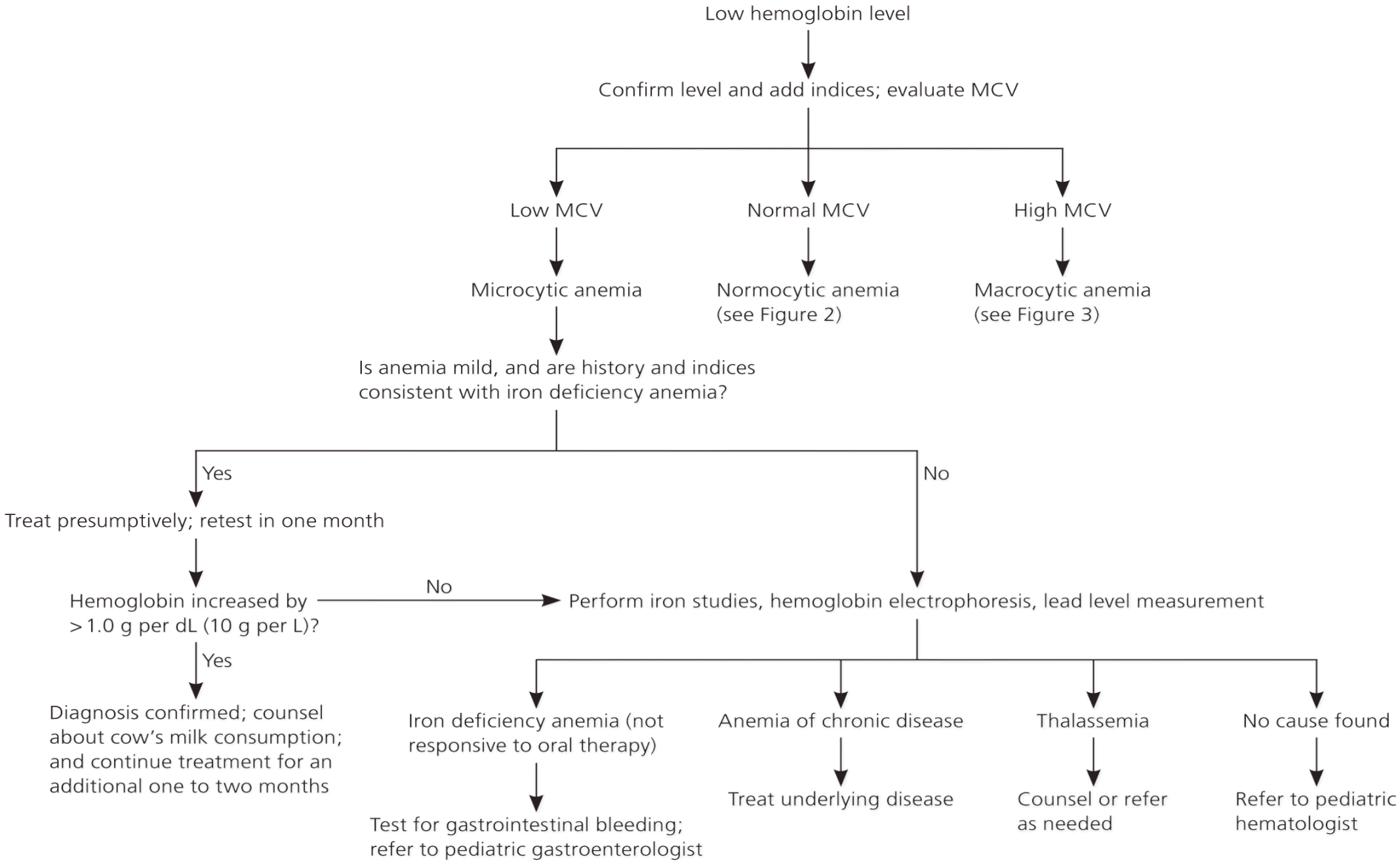
It should be kept in mind that parasitosis may also contribute to iron deficiency especially in developing countries. Iron deficiency anemia is observed in 2% of adolescent girls and it is mostly related with growth spurt and menstruel blood loss (32).
A detailed history of menstruation should be obtained in adolsecent girls and underlying bleeding disorders including von-Willebrand disease should be kept in mind in girls who have bleeding in excess than expected.

Iron deficiency anaemia can also be an issue for infants:

- who were born prematurely
- who are twins or other multiples
- who were very sick as newborns
- whose mothers were iron deficient during late pregnancy.

Clinical findings

Since the majority of iron in the body is used for synthesis of hemoglobin, the most important finding of iron deficiency is anemia. In iron deficiency anemia, clinical findings secondary to anemia may be found as in all anemias or the diagnosis can be made during laboratory investigations in the absense of any clinical finding. Slowly progressing paleness may sometimes be missed by families.


Low hemoglobin level
Confirm level and add indices; evaluate MCV
Low MCV
Normal MCV
High MCV
Microcytic anemia
Normocytic anemia (see Figure 2)
Macrocytic anemia (see Figure 3)
Is anemia mild, and are history and indices consistent with iron deficiency anemia?
Yes
No
Treat presumptively; retest in one month
Hemoglobin increased by >1.0 g per dL (10 g per L)?
No
Perform iron studies, hemoglobin electrophoresis, lead level measurement
Yes
Diagnosis confirmed; counsel about cow's milk consumption; and continue treatment for an additional one to two months
Iron deficiency anemia (not responsive to oral therapy)
Anemia of chronic disease
Thalassemia
No cause found
Test for gastrointestinal bleeding; refer to pediatric gastroenterologist
Treat underlying disease
Counsel or refer as needed
Refer to pediatric hematologist

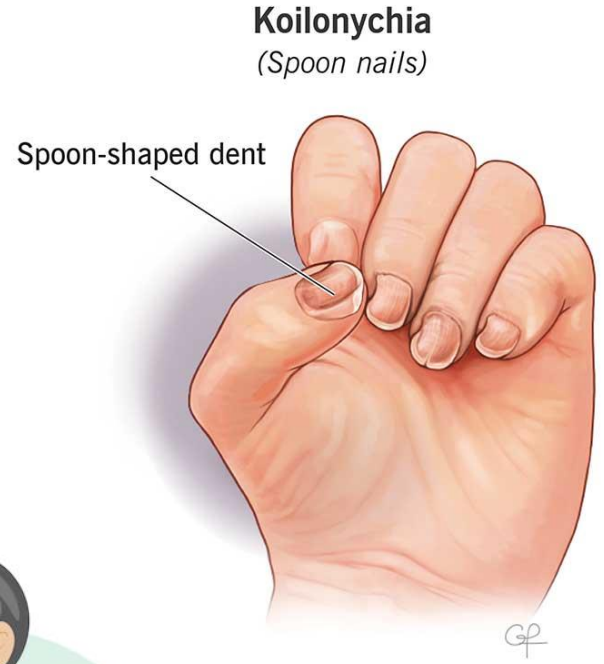
Iron deficiency findings

Skin

- Pale especially around nails, hands and eyelids.
- Nails: Koilonychia (spoon nails)
- Hair loss

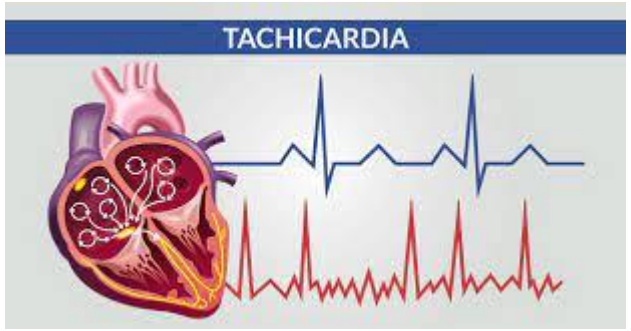
Musculoskeletal system

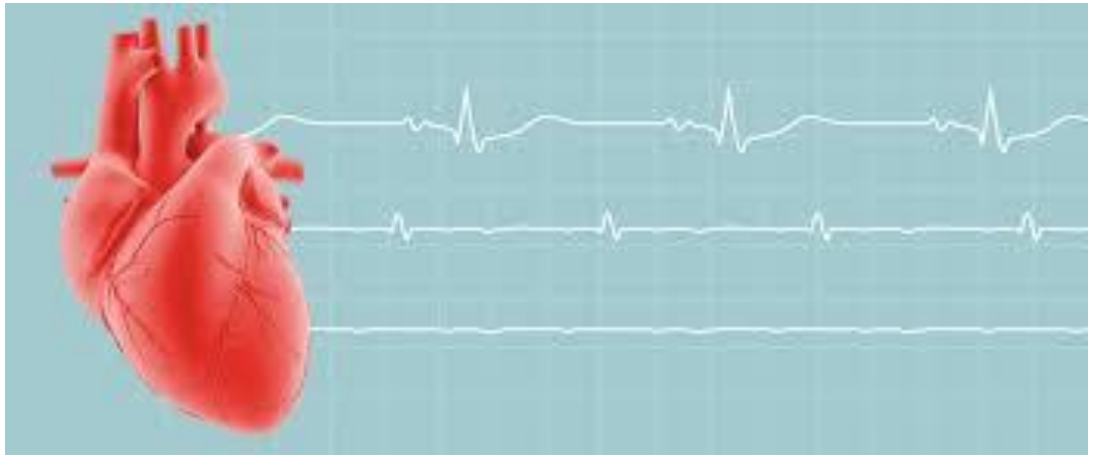
- Decreased effort capacity
- Exercise limitation



Cardiovascular system

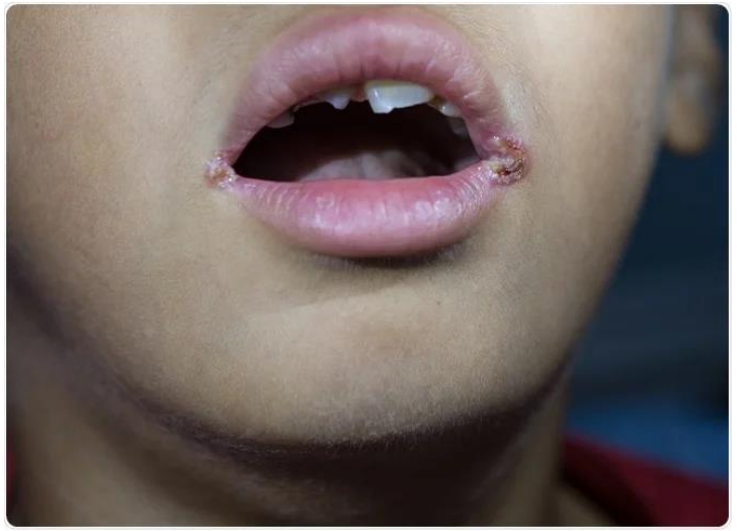
- Increased cardiac output
- Tachycardia
- Cardiomegaly
- Heart failure
- Systolic murmur in apex

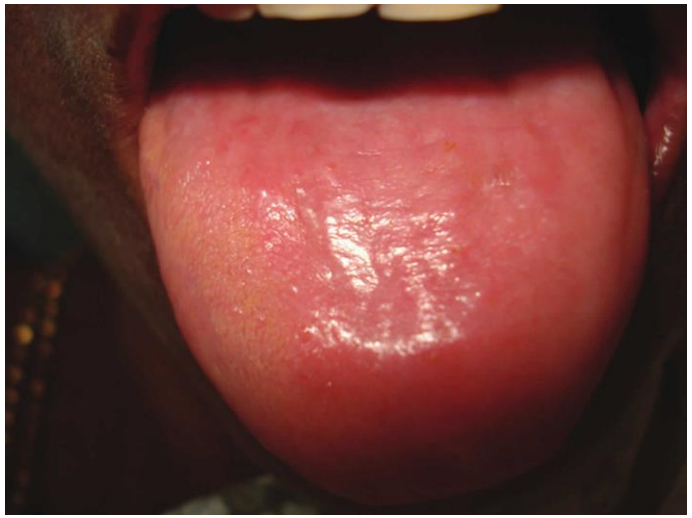




Gastrointestinal system

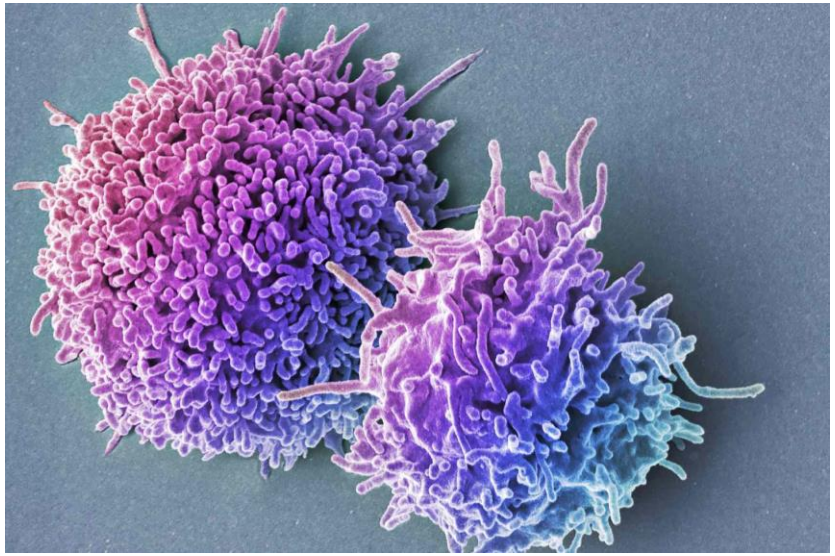
- Loss of appetite
- Angular stomatitis
- Atrofic glossitis
- Dysphagia
- Pica
- Gluten sensitive enteropathy
- Plummer-Vinson syndrome(the classic triad of dysphagia, iron-deficiency anemia and esophageal webs)

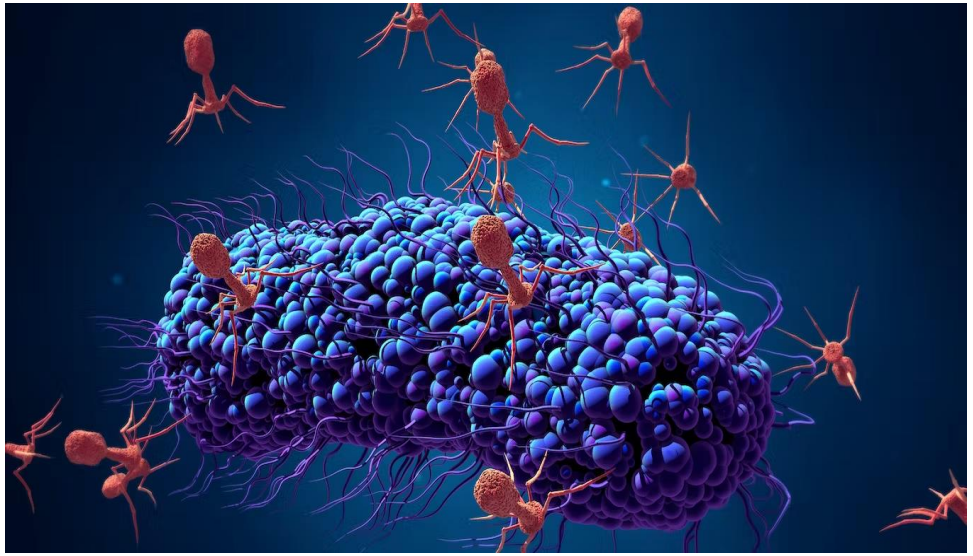




Immune system disorders

- Decreased resistance against infections
- T lymphocyte and polymorphonu-clear leukocyte dysfunction





Central nervous system

- Irritability-malaise
- Fainting
- Papilledema
- Pseudotumor cerebri
- 6th nerve palsy
- Restless leg syndrome
- Breath holding spell
- Sleep disturbance
- Attention deficit
- Learning difficulty
- Behavioral disorder
- Decrease in perception functions
- Retardation in motor and mental developmental tests

Diagnosis and laboratory findings

Investigations which may be oredered in patients in whom iron deficiency is considered:

- Complete blood count
- Peripheral blood smear
- Reticulocyte
- Urea, creatinine
- Serum iron, total iron binding capacity, transferrin saturation index
- Ferritin
- Serum soluble transferrin receptor level(Used with a low rate in practice)

Iron deficiency develops in the body in three stages.

1.Prelatent stage: Iron stores are lowered or absent, serum iron concentration, hemoglobin and hematocrit are normal. This stage of iron deficiency is manifested with reduction or absence of bone marrow iron stores and reduced serum ferritin level.
2.Latent stage: serum iron (SI) and trasferrin saturation are reduced in addition to reduced iron stores. Hemoglobin and hemoctrit are within normal limits.
3.Marked IDA: In addition to the depletion of iron stores, serum iron and transferin saturation hemoglobulin and hematocrit levels are reduced.

The serum ferritin level is the best indicator of the iron stores in the body and the first biochemical variable to change in ID. A serum ferritin level below 10–12 µg/L strongly supports ID, but ferritin is an acute phase reactant and it should be kept in mind that it may be increased in infection and inflammation.

In addition, thrombocytosis in relation with IDA may be observed in complete blood count. The reason of thrombocytosis is cross-reaction of increased erythropoetin in IDE with thrombopoetin receptors in the megakaryocytes which leads to increased platelet count. Although rarely, thromobocytopenia may also be observed in IDA (33).

The leukocyte count is usually normal, but leukopenia may also be observed. However, other diagnoses should be considered primarily in cases of anemia especially accompanied by leukopenia and/or thrombocytopenia. Eosinophilia in complete blood count or peripheral smear may give a clue in terms of underlying parasitosis. At this point, treatment can be started directly, if complete blood count and peripheral smear strongly suggest IDA. If there is suspicion, treatment itself is a good diagnostic tool.

Some new methods have been developed to be used in definite diagnosis because of some defects of hematological and biochemical tests. Addtional tests including zinc protoporphyrine (ZnPP), free erythrocyte protoporphyrine, serum soluble transferrin receptor (sTfR) and reticulocyte hemoglobin content may be helpful (34).

Treatment

The main principles in treatment of iron deficiency anemia include making the diagnosis, investigating the condition which causes to iron deficiency and elimination of this condition, replacement of deficiency, improvement of nutrition and education of patients and families.

Iron is found in two forms in diet; non-heme iron and heme iron. Non-heme iron is found in food products other than meat and heme iron is found in meat and meat products. Absorption of heme iron is much higher, but only 10% of the iron in diet is heme iron. While the absorption of heme iron is affected by enviromental factors with a very low rate, non-heme iron is affected by other food substances and pH of the environment. Therefore, increasing consumption of meat and meat products is very important in prevention and treatment of iron deficiency. The other foods rich in iron include egg, well-done legumes, green vegetables and dry fruit.

The most commonly used treatment dose is 3–6 mg/kg/day. There are different recommendations releated to the dose, in the literature and textbooks. For example, the recommended dose is 3 mg/kg in Nathan and Oski's hematology testbook, 4.56 mg/kg/day in Lanzkowsky's Pediatric Hematology Oncology testbook and 6 mg/kg/day in Williams' Hematology testbook. The Centers for Disease Control in USA recommended use of 3 mg/kg/day elementary iron in 1998 in order to simplify the dose and increase compliance, but this recommendation is based on expert opinion rather than clinical studies. In our own center, we give 3–4 mg/kg/day ferrous iron in two doses 1 hour before or 2 hours after meals in order to increase compliance. There are also different recommendations in relation with dividing the dose. Studies have shown that a singel daily dose was also efficient especially in children who developed gastrointestinal side effects (35).

Ascorbic acid increases absorption of iron, but use of preparation containing vitamin C in combination with iron has a high cost. In Turkey, ferrous fumarate is included in another preparation containing +2 iron for children. It has two forms one of which contains zinc, vitamin C, folic acid and iron and the other one which contains only zinc and iron (Ferrozinc®, Ferrozinc-G®, respectively 1 spoon: 40 mg elementary iron). In a thesis study performed in our center, we showed that zinc deficiency accompanied iron deficiency with a rate of 9% (36).

The rate of iron absorption also depends on the severity of anemia. It reaches the highest values in the first month of treatment. Signs observed in patients including restlessness, loss of appetite and fatigue rapidly disappear with initiation of treatment. An increase in the reticulocyte count is expected on the 7–19th days of treatment. If an increase of 1 g/dL or more is observed in Hb after ten days, the diagnosis is correct. In this case, treatment can be continued for at least 2 months to fill iron stores. The treatment period should not exceed 5 months. If there is an insufficient increase after one-month treatment, incompliance, continuing blood loss despite iron replacement, disruption in absorption of iron, high gastric pH (use of antacids or H2 receptor antagonists), wrong diagnosis or inefficient iron preparation should be considered.

Prevention

The American Academy of Pediatrics, the World Health Organization and other well-known pediatrics organizations have proposed many recommendations for prevention of iron deficiency which is the most common nutritional deficiency in the whole world. These recommendations include enrichment of foods with iron, giving iron-rich formulas when brastmilk is insufficient, avoiding cow's milk in the first year of life, screening infants in the 9–12th months in terms of iron deficiency and giving infants iron prophylaxis (38).

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