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RICKETS-LIKE DISEASES IN PEDIATRIC PRACTICE: CHALLENGES IN DIFFERENTIAL DIAGNOSIS AND CURRENT OPPORTUNITIES (A LITERATURE REVIEW AND CASE OBSERVATIONS)

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"Rare diseases are considered rare not because they occur infrequently,
but because we fail to diagnose them properly.
The rarity of a disease is determined not by its actual incidence,
but by our imperfection in diagnosing it."
V.Kh. Vasylenko

The relevance and significance of the differential diagnosis of rickets-like diseases in modern pediatrics and endocrinology cannot be overstated. Although these disorders are rare and occur less frequently than classical nutritional rickets, they are characterized by a much more severe clinical course and require fundamentally different therapeutic approaches. Differential laboratory diagnosis of rickets-like diseases is a key stage of evaluation, since the clinical manifestations, particularly skeletal deformities, are often similar, whereas the underlying pathogenic mechanisms and treatment strategies differ substantially. Most rickets-like disorders lead to progressive skeletal deformities and disability in affected children. Differential diagnosis enables pathogenetically targeted therapy while accounting for the specificities of treatment for various rickets-like disorders. For example, renal tubular acidosis requires continuous correction of acidosis and potassium imbalance. Fanconi syndrome necessitates treatment of the underlying disease (e.g., cystinosis) together with replacement therapy for lost substances. Vitamin D–dependent rickets type II requires extremely high doses of active vitamin D metabolites or even intravenous calcium administration, since conventional doses are ineffective. Such an approach helps prevent therapy-related adverse effects. In hypophosphatasia, vitamin D is strictly contraindicated because it may aggravate the existing hypercalcemia, potentially leading to renal and neurological complications. In X-linked hypophosphatemia, vitamin D monotherapy is ineffective, and long-term phosphate supplementation is required. Most of these conditions are hereditary, including X-linked, autosomal recessive, and autosomal dominant forms. Accurate diagnosis enables determination of the risk of recurrence in subsequent children and early screening of siblings to initiate treatment before visible skeletal deformities develop. Timely diagnosis also helps prevent systemic complications such as nephrocalcinosis and renal failure in renal tubular acidosis, premature tooth loss in hypophosphatasia, as well as alopecia and endocrine abnormalities in vitamin D–dependent rickets. Laboratory markers remain the only reliable tools for the early identification of rare genetic disorders masquerading as common rickets and for their subsequent genetic confirmation.

Key words: *rickets-like diseases, classification, phosphate diabetes, renal tubular acidosis, children, differential diagnosis.*

Connection of the publication with planned research work.

This work is part of the research project "Clinical and pathogenetic significance of systemic and local metabolic disorders in rheumatic diseases: the role of comorbid conditions and the development of optimal treatment methods," state registration number 0119U001448.

Introduction.

The relevance of rickets-like diseases (RLDs) stems from the fact that these disorders manifest in early childhood and are accompanied by severe skeletal deformities, growth retardation, delayed physical development, and potentially life-threatening electrolyte disturbances [1–4]. The similarity between the clinical manifestations of classical rickets and RLDs often leads to misdiagnosis. In clinical practice, verification of a specific disease subtype is frequently delayed, which negatively affects prognosis [1, 4–7].

Furthermore, molecular genetic studies indicate that RLDs exhibit considerable genetic heterogeneity. Currently, definitive diagnosis is based on the identification of mutations in the corresponding genes using sequencing technologies. However, conventional Sanger sequencing remains relatively expensive and time-consuming, as it requires separate analysis of each individual gene. At the same time, timely diagnosis and early initiation of appropriate pathogenetically targeted therapy help slow the progression of rachitic skeletal deformities, improve growth dynamics, and increase the child's physical activity. This approach helps prevent complications, reduce the risk of disability, and significantly improve patients' quality of life [8–10].

The aim of the study.

To analyze the current state of the problem of hereditary RLDs in children, with a focus on an in-depth investigation of this issue, timely diagnostic algorithms, and individualized treatment approaches. Given the genetic diversity, it is particularly important to perform differential diagnosis of these diseases and to formulate and present an appropriate approach to early diagnosis of RLDs.

Object and research methods.

The article presents an analysis of data on hereditary RLDs in children published in open-access sources and on the official websites of peer-reviewed medical journals over the past 10 years. Cases from the authors' own clinical observations are also presented.

Main part.

Definition. Hereditary rickets-like diseases (RLDs) are a group of genetically determined disorders of phos-

phorus, calcium, and vitamin D metabolism that clinically manifest as rickets but are not associated with vitamin D deficiency [1, 11, 12].

Classification [1, 13–16]. RLDs belong to the group of tubulopathies, which are hereditary disorders affecting the renal tubules. Currently, there is no single universally accepted classification of tubulopathies that fully reflects the diversity of genetic abnormalities and clinical manifestations. Several hereditary forms are of greatest importance in pediatric practice, including vitamin D–resistant hypophosphatemic rickets (phosphate diabetes, PD), Vitamin D–dependent rickets, renal tubular acidosis (RTA), and Fanconi syndrome. Progressive skeletal deformities, resistance to therapeutic doses of vitamin D, and impaired physical development are the main features of RLDs.

According to their pathogenesis, RLDs are classified into the following groups [1, 13–16] **(fig. 1)**:

1. Phosphate diabetes (hypophosphatemic rickets), vitamin D–resistant rickets, associated with reduced renal phosphate reabsorption, leading to hypophosphatemia and impaired bone mineralization.

2. Vitamin D–dependent rickets, characterized by impaired vitamin D metabolism due to defective synthesis of its active form or reduced receptor sensitivity.

3. Hypophosphatasia, caused by deficiency and decreased activity of alkaline phosphatase (ALP), resulting in impaired mineralization of bones and teeth.

4. Disorders associated with impaired renal tubular function:

- Renal tubular acidosis (types I and II)
- Fanconi syndrome (de Toni–Debré–Fanconi syndrome)

In these disorders, the key pathogenic mechanism is the loss of bicarbonates, phosphates, and other substances, leading to metabolic acidosis and clinical manifestations of rickets.

Hereditary Phosphate Diabetes

Definition. Hereditary phosphate diabetes (PD) is a heterogeneous group of genetically determined disorders classified as primary tubulopathies and characterized by hypophosphatemia [1, 8, 11, 12].

Pathogenesis. The disorder is caused by a hereditary defect in phosphate reabsorption in the proximal renal tubules, resulting in phosphaturia, decreased serum phosphate levels, skeletal deformities of the lower extremities, and growth retardation in children. The disease requires long-term, often lifelong, therapy, whereas current treatment approaches do not always achieve complete resolution of clinical manifestations and bone deformities [11, 12, 17, 18].

Clinical forms. Hypophosphatemic rickets is classified into FGF23-dependent and FGF23-independent forms.

FGF23-dependent forms:

1. X-linked hypophosphatemic rickets (XLH), vitamin D–resistant rickets. This is the most common form of hereditary phosphate diabetes (approximately 80% of cases). It is most frequently inherited as an X-linked dominant disorder. It is associated with mutations in the **PHEX** *(Phosphate-Regulating Endopeptidase Homolog, X-Linked)* gene located on the short arm of the X chromosome (Xp22.2–p22.1). Inactivating mutations of the **PHEX** gene result in increased circulating levels of fibroblast growth factor 23 (FGF23). This leads to excessive renal phosphate wasting, hypophosphatemia, rickets, skeletal deformities, and growth retardation [1,

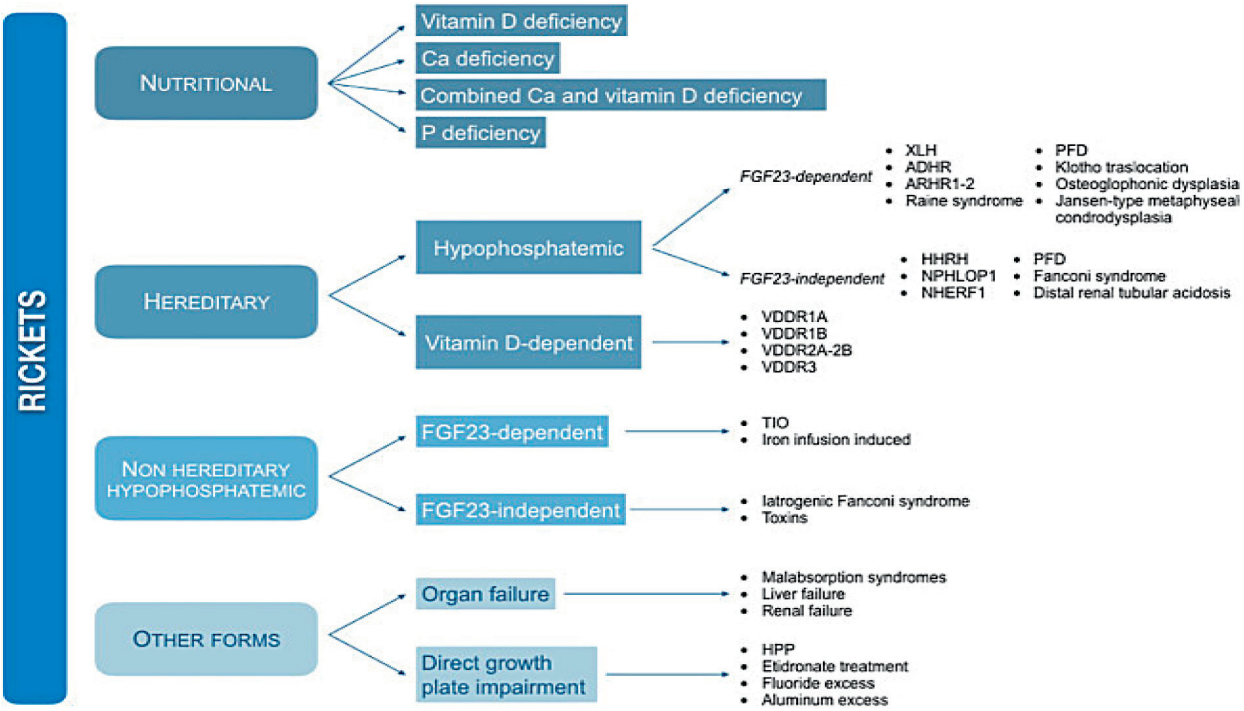

Figure 1 – Classification of the main forms of rickets according to pathogenesis [1].

Notes: XLH – X-linked hypophosphatemic rickets; **ADHR** – autosomal dominant hypophosphatemic rickets; **ARHR1** – autosomal recessive hypophosphatemic rickets type 1; **ARHR2** – autosomal recessive hypophosphatemic rickets type 2; **PFD** – polyostotic fibrous dysplasia; **HHRH** – hereditary hypophosphatemic rickets with hypercalciuria; **NPHLOP1** – nephrolithiasis/osteoporosis-associated hypophosphatemic disorder type 1; **NHERF1** – nephrolithiasis/osteoporosis-associated hypophosphatemic disorder type 2; **VDDR1A** – vitamin D–dependent rickets type 1A; **VDDR1B** – vitamin D–dependent rickets type 1B; **VDDR2A** – vitamin D–dependent rickets type 2A; **VDDR2B** – vitamin D–dependent rickets type 2B; **VDDR3** – vitamin D–dependent rickets type 3; **TIO** – tumor-induced osteomalacia; **HPP** – hypophosphatasia.

2, 12, 19, 20]. To date, more than 130 mutations associated with hereditary phosphate diabetes have been described, most commonly involving loci on the X chromosome (Xp22.2–p22.1), chromosome 12 (12q12–q14), and chromosome 5 (5q35) [8, 10, 11]. Clinically, the disease manifests in early childhood, most often after the onset of walking, with bowing deformities of the lower extremities (genu varum or genu valgum), growth retardation, muscular hypotonia, and a waddling gait. A characteristic feature is **resistance to treatment with standard doses of vitamin D** [19–22].

2. Autosomal dominant hypophosphatemic rickets (ADHR). This form is associated with mutations in the **FGF23 gene** located on chromosome 12 (12p12–p13.3). Mutations in the FGF23 gene lead to increased circulating levels of fibroblast growth factor 23 (FGF23). In addition, the altered hormone becomes resistant to proteolytic cleavage and is not adequately degraded by enzymes, resulting in its accumulation in the body. This leads to impaired renal reabsorption of inorganic phosphate and excessive urinary phosphate loss. ADHR is characterized by variable clinical manifestations, including skeletal deformities, bone pain, and muscle weakness. The disease may manifest in either childhood or adulthood; however, the clinical presentation depends on the age of onset. In adult-onset disease (14–45 years of age), patients commonly present with pain, fatigue, pseudofractures, or spontaneous fractures, while lower extremity deformities are usually absent. In childhood-onset disease (1–3 years of age), the phenotype resembles that of X-linked hypophosphatemic rickets, with leg bowing after walking onset but without significant growth impairment. In some cases, phosphate wasting resolves after puberty. A characteristic feature of this syndrome is the development of periodontal disease. The clinical course is generally milder, and the prognosis is relatively favorable [1, 8, 11].

3. **Autosomal recessive forms (ARHR1 and ARHR2).** Mutations in the ***DMP1*** or ***ENPP1*** **genes** also result in secondary overproduction of FGF23. A mutation in the DMP1 gene (Dentin Matrix Acidic Phosphoprotein 1), which is important for osteocyte maturation, causes osteocytes to secrete excessive amounts of FGF23. In addition to the classical manifestations of rickets, patients may present with defects of the dental enamel and dentin. A mutation in the ENPP1 gene (Ectonucleotide Pyrophosphatase/Phosphodiesterase 1) also leads to elevated levels of FGF23. In addition to signs of rickets, ARHR2 is often accompanied by ectopic ossification of soft tissues [1, 8, 11].

FGF23-independent forms (normal or decreased hormone levels):

4. Hereditary hypophosphatemic rickets with hypercalciuria (HHRH). This is a rare autosomal recessive disorder associated with mutations in the **SLC34A3 and SEPN1 genes (9q34)**. Serum FGF23 levels are usually normal or decreased. A distinctive feature of this disorder is the presence of hypercalciuria despite normal serum calcium levels, along with a 2–4-fold increase in serum $1,25(OH)_2D_3$ concentrations and low parathyroid hormone (PTH) levels. Renal phosphate wasting is the main pathogenic mechanism underlying elevated serum $1,25(OH)_2D_3$ levels. Increased calcitriol concentrations lead to enhanced intestinal calcium absorption, resulting in hypercalcemia and hypercalciuria. Clinical manifestations of rickets in this disorder may be mild, completely absent, or may present later in life. Heterozygous carriers of SLC34A3/NPT2c mutations may exhibit an adult-onset phenotype characterized by severe nephrolithiasis, multiple fractures, and osteoporosis. Accurate diagnosis of hypophosphatemic rickets with hypercalciuria is of considerable therapeutic importance. In this condition, treatment with phosphate salts alone may lead to complete remission, whereas the addition of active vitamin D metabolites may result in complications such as hypercalcemia and nephrocalcinosis. Nephrocalcinosis has been reported in more than 50% of cases [1, 23–25].

5. Rare clinical forms: hypophosphatemic rickets with hyperparathyroidism (13q13.1, KLOTHO gene, α-klotho), McCune–Albright syndrome (22q13.3, GNAS1), Raine syndrome (7p22.3, FAM20C), hypophosphatemic nephrolithiasis/osteoporosis type 1 (5q35.3, SLC34A1), hypophosphatemic nephrolithiasis/osteoporosis type 2 (17q25.1, SLC9A3R1), Dent disease type 1 (Xp11.22, CLCN5), Lowe syndrome (Dent disease type 2) (Xq25, OCRL1), and tumor-induced osteomalacia caused by tumors producing and secreting FGF23 into the bloodstream [1].

Diagnosis [1, 5, 8, 25, 26]. The diagnosis of hereditary PD includes clinical, laboratory, and instrumental investigations.

Biochemical findings: decreased serum phosphate levels (hypophosphatemia), normal or decreased serum calcium levels, elevated alkaline phosphatase activity, increased urinary phosphate excretion (phosphaturia), and normal or mildly elevated parathyroid hormone levels. Additional findings include increased renal phosphate clearance and the absence of aminoaciduria and glucosuria (in contrast to Fanconi syndrome).

Radiological findings: osteoporosis, widening and irregularity of the metaphyses, skeletal deformities, and pseudofractures.

Genetic testing enables the identification of mutations in genes such as PHEX, FGF23, DMP1, SLC34A3, SEPN1, and others.

Treatment [1, 2, 12, 27–35]. Treatment is individualized and depends on the specific form and severity of the disease. Combination therapy is recommended and includes phosphate preparations (Phosphate-Sandoz, France; Reducto-spezial, Germany) together with active vitamin D metabolites (calcitriol, alfacalcidol), while serum and urinary calcium and phosphate levels require regular monitoring. Such therapy helps increase serum phosphate levels, improve bone mineralization, and slow the progression of skeletal deformities. Potential treatment-related complications include hypercalciuria, nephrocalcinosis, and secondary hyperparathyroidism [12, 27–30, 32]. Standard therapy for RLDs in children with growth retardation also includes growth hormone (somatotropin) administration [5, 11, 26, 28, 31].

In 2018, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved a fundamentally new drug for the treatment of X-linked hypophosphatemia – Burosumab (Crysvita®, Crystal®, Japan), a fully human monoclonal antibody targeting FGF23. The drug normalizes serum phosphate levels, reduces the severity of rickets, and improves growth and physical functioning. It may be administered to children older than one year at an initial dose of 0.4 mg/kg sub-

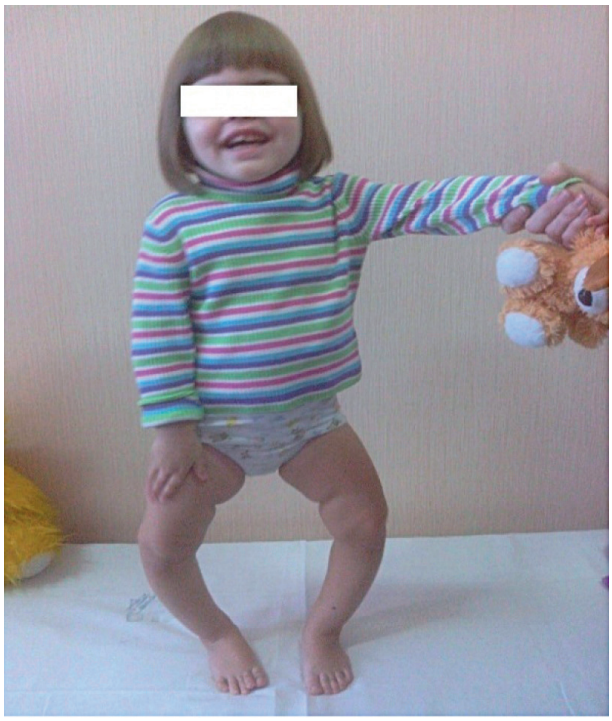

Figure 2 – Three-year-old child with genu valgum deformity of the lower extremities.

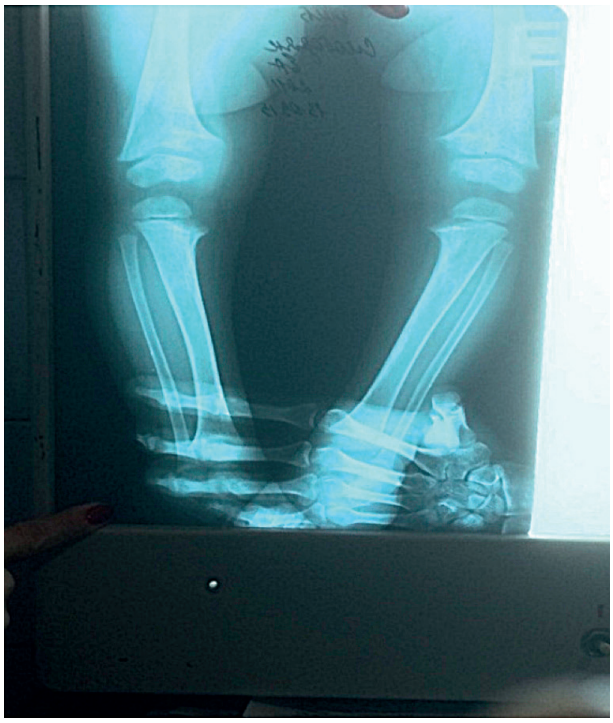

Figure 3 – Anteroposterior radiographs of the knee joints and lower legs. Radiographic findings characteristic of rickets.

cutaneously every two weeks [28–30, 32–35]. The use of burosumab in children with XLH demonstrated significantly greater clinical efficacy, including growth velocity and correction of biochemical abnormalities, compared with conventional therapy [32, 35]. However, despite its high efficacy, the long-term prognosis and safety of burosumab treatment over decades remain subjects of ongoing investigation [26, 28, 30].

When necessary, children with hereditary phosphate diabetes undergo orthopedic treatment; however, the optimal timing of surgery remains controversial because of the possible recurrence of deformities if surgical correction is performed before completion of active growth [36].

Prognosis. Disease activity may decrease with age; nevertheless, short stature, skeletal deformities, and gait abnormalities often persist. Surgical correction of deformities is considered most appropriate after 12 years of age, when the disease process becomes more stable [1, 8, 11, 36].

We present a case from our own clinical observation. The parents of patient K. first consulted a pediatrician when the child was 1.5 years old, reporting a characteristic waddling gait and deformities of the lower extremities. Subsequently, the child developed complaints of rapid fatigability while walking, progressive limb deformities, and growth retardation.

Past medical history. The girl was born from the first pregnancy, which was complicated by early gestational toxicosis. Delivery was the first, full-term, at 37–38 weeks of gestation. Birth weight was 3390 g, and body length was 52 cm. In the maternity hospital, the patient was diagnosed with congenital heart defects (CHD): ventricular septal defect (VSD), patent ductus arteriosus (PDA), and patent foramen ovale (PFO). She was breastfed until she was 1 year and 10 months old. Family history was unremarkable. Due to CHD, the patient was followed by a pediatric cardiac surgeon. At the age of 3 years, echocardiography revealed a small aneurysm of the membranous portion of the interatrial septum. VSD, PFO, and PDA were no longer visualized, while cardiac chamber dimensions, hemodynamics, and myocardial contractility remained within normal limits.

History of the present illness. Deformities of the lower extremities first appeared at 9 months of age, when the child began standing independently. Independent walking started at 1 year and 4 months of age. The deformities progressed with age **(fig. 2)**. Primary teeth erupted at 9 months, followed later by enamel discoloration. From the age of 1 year and 10 months, the patient was followed by an orthopedic specialist at the Regional Clinical Traumatology Hospital for rachitic genu varum deformity of the lower extremities. At the age of 2 years, radiographs of the knee joints and lower legs in the anteroposterior projection demonstrated deformities of the proximal metaphyses of the tibiae and distal metaphyses of the femora, characterized by irregular contours, widening, and heterogeneous structure. The growth plates of the femoral and tibial bones were widened and indistinct. Varus deformity and osteoporosis were also noted. The radiographic findings were characteristic of rickets **(fig. 3)**. At the age of 3 years, pelvic radiographs with hip joints revealed indistinct subchondral regions of the proximal femoral metaphyses, varus deformity of the proximal femora, and osteoporosis. The patient received vitamin D3 supplementation, electrophoresis with $CaCl_2$, paraffin therapy, massage, physical therapy exercises, nighttime orthotic splints, and orthopedic footwear. According to the orthopedic specialist's assessment, the patient remained under observation for rachitic varus deformity of the lower extremities; however, no positive response to treatment was observed.

Physical examination. The girl's general condition was satisfactory. Marked bowing deformities of the lower extremities (genu varum), gait disturbance with a characteristic waddling gait, and growth retardation

(height 92 cm at the age of 3 years) were noted. Cranial bone deformities were present due to hyperplasia of the frontal and parietal eminences, with frontal bossing, depressed nasal bridge, and left-sided cranial flattening (the child predominantly slept on the left side). Dysplastic tooth growth and enamel discoloration were also observed. No significant abnormalities of the internal organs were detected.

Investigations. Blood test results at the age of 2 years and 11 months showed: total calcium (Ca) – 2.26 mmol/L (reference range 2.15–2.65 mmol/L), phosphorus (P) – 0.9 mmol/L (reference range 1.29–2.26 mmol/L), 25-hydroxycholecalciferol (25OHD) – 20.9 ng/mL (reference range 30–50 ng/mL), parathyroid hormone (PTH) – 62.4 pg/mL (reference range 15–65 pg/mL), and osteocalcin (OCN) – 82.7 ng/mL (reference range 11–43 ng/mL). At the age of 3 years and 1 month, laboratory findings were as follows: total Ca – 2.26 mmol/L, P – 0.72 mmol/L, ionized calcium (Ca^{2+}) – 1.05 mmol/L (reference range 1.12–1.32 mmol/L), 25OHD – 71.4 nmol/L (reference range 75–144 nmol/L), alkaline phosphatase (ALP) – 767 U/L (reference value <297 U/L). Urinalysis revealed urinary phosphate excretion of 50.26 mmol/day (reference range 19–25 mmol/day) and urinary calcium excretion of 0.53 mmol/day (reference range 1.5–4 mmol/day). A rickets-like disease was suspected, and calcium glycerophosphate therapy was initiated. During calcium glycerophosphate treatment, laboratory parameters were as follows: total Ca – 2.47 mmol/L, P – 1.33 mmol/L, Ca^{2+} – 1.03 mmol/L, 25OHD – 86.3 nmol/L, ALP – 1062 U/L; urinalysis showed urinary phosphate excretion of 10.19 mmol/day and urinary calcium excretion of 0.69 mmol/day. At the age of 4 years, blood test results demonstrated: P – 0.85 mmol/L, Ca^{2+} – 1.33 mmol/L, 25OHD – 52.72 ng/mL, ALP – 622 U/L, and PTH – 6.92 pmol/L (reference range 1.6–6.9 pmol/L). The patient received repeated courses of calcium glycerophosphate and alfacalcidol (Alpha-D3-Teva).

Thus, the onset of the first clinical manifestations after the age of 1 year, when the child began walking, together with progressive limb deformities, growth retardation, and a characteristic waddling gait; laboratory findings including hypophosphatemia, hyperphosphaturia, elevated alkaline phosphatase activity, normal serum calcium, parathyroid hormone, and vitamin D levels, absence of glucosuria and hyperaminoaciduria; radiographic changes in the bones of the lower extremities; lack of positive response and ineffectiveness of standard vitamin D doses; as well as improvement in laboratory parameters following treatment with calcium glycerophosphate and alfacalcidol (Alpha-D3-Teva), suggested the presence of hereditary phosphate diabetes in the child. However, genetic confirmation was required. Molecular genetic testing was performed at the age of 4 years and 4 months and revealed a heterozygous mutation c.2059–2062dupAGTT p.Y688X in the PHEX gene. The obtained results confirmed the diagnosis of vitamin D–resistant hypophosphatemic rickets. Continued treatment with alfacalcidol (Alpha-D3-Teva) and phosphate preparations (Reducto-special, Phosphate-Sandoz) was recommended under regular monitoring of serum and urinary calcium and phosphate levels, alkaline phosphatase activity, and parathyroid hormone levels. Hospitalization to the traumatology department for temporary epiphysiodesis was also recommended.

Renal tubular acidosis

Definition. Renal tubular acidosis (RTA) is a clinico-laboratorial symptom complex that results from a defect in the reabsorption of bicarbonates in the proximal tubules or a disturbance of acidogenesis in the distal tubules, characterized by the metabolic acidosis and the decrease in the ability of the kidneys to acidate the urine. One of the leading signs of RTA are changes in skeletal skeleton resembling the rachitic [4, 37].

At the heart of RTA are disturbances of one of the most important functions of the kidneys – maintaining the acid-base balance (ABB). Maintenance of ABB is carried out by active secretion of hydrogen ions H^+ tubular cells, which leads to acidification of urine. The mechanism of secretion is reduced to the following. The hydrogen ions H^+ and bicarbonate ions are formed of carbon dioxide and water in the cells of the proximal and distal sections of the tubules. H^+ ions are actively secreted into the tubular fluid in exchange for sodium ions that enter the cells passively, and bicarbonate ions diffuse into the plasma. Secreted H^+ ions in the lumen of the tubule interact with filtered bicarbonate, forming a carbonic acid, which in its turn is dehydrated with a help of carbonic anhydrase enzyme and carbon dioxide diffuses into the cell. Thus, the secretion of H^+ ions is accompanied by the reabsorption of an equivalent amount of sodium and bicarbonate [4, 37].

There are **primary (hereditary) and secondary forms of RTA** [4, 37]. Hereditary RTA is a genetically heterogeneous disease having various types of hereditary transmission (distal – localization of genes – 17q21–q22, 7q33–q34, 2cen–q13, proximal – localization of genes – 8q22, 4q21). The hereditary RTA can be combined with hearing damage (localization of genes – 7q33–q34, 2cen–q13) and ocular pathology (localization of genes – 4q21). Hereditary forms of distal RTA are caused by mutations in at least three different genes: **SLC4A1, ATP6V1B1,** and **ATP6V0A4.** Heterozygous carriers of mutations in the ATP6V1B1 and ATP6V0A4 genes may have an increased risk of developing nephrolithiasis and nephrocalcinosis in adulthood, respectively [9, 37–39].

They expose: **RTA-I** – classical, distal, hypokalemic, Battler-Albright syndrome; **RTA-II** – children's, proximal, Lightwood syndrome; **RTA-III**, which is based on a combined proximal and distal RTA; **RTA-IV** – generalized, hyperkalemic – due to a deficiency of mineralocorticoids – aldosterone or resistance to it [4, 7, 16, 37]. Hereditary forms of RTA occur much less frequently than acquired forms (e.g., drug-induced – NSAIDs, connective tissue diseases such as SLE and Sjögren's syndrome, diabetes, chronic kidney disease, etc.) [37, 40–42]. Proximal RTA (type 2) is less common than distal RTA (type 1), and Fanconi syndrome as a primary disorder is extremely rare [37].

Pathogenesis of RTA I type. The disease is transmitted by autosomal dominant and autosomal recessive type, X-linked, sporadic cases are possible, more common in girls.

Distal tubular acidosis occurs because of disorder of production or transport of hydrogen H^+ ions. The main pathogenetic link is an impairment in ability of the kidneys to establish a gradient of the concentration of H^+ ions between the blood and the tubular fluid, which leads to metabolic hyperchloremic acidosis. The causes of disturbance of acidogenesis in the I type of RTA are

discussed in a number of hypotheses, which include: a decrease in the activity of H^+ secretion by cells; defect in the energy mechanism (H^+-ATPh-ase, H^+/ K^+-ATPh-ase), lack of transport systems, etc. In this connection, the distal tubule cannot create a definite gradient of the concentration of H^+ ions between the blood and the tubular fluid. The content of H^+ in the distal tubules, NH_4 in urine, the titrated acidity decrease. In such patients, the urine pH doesn't usually drop below 6,0; the pH of the urine, more often it is 6,8–7,5. A characteristic of this form of acidosis is that bicarbonates constantly release into the urine, instead of which the chlorine ions diffuse into the blood to protect the osmotic pressure, as the result the hyperchloremia and the blood hydrocarbonates deficiency develop. Bicarbonates release in the urine, the renal excretion of acids and ammonia decrease. With acidosis, increased excretion of sodium causes polyuria. Hypernatriuria leads to hyponatremia, and as a consequence – secondary aldosteronism and hypokalemia. The loss of large amounts of calcium with alkaline urine, hypocitruturia, are the cause of the deposition of oxalate and phosphatolic calcium stones in the kidneys. The resulting stones are deposited in the interstitial tissue, in the lumen of the tubules. There is a bilateral nephrocalcinosis by 3–5 years. This creates conditions for the occurrence of a secondary urinary tract infection. Calcium deficiency leads to osteoporosis and osteomalacia, i.e. hypocalcemia stimulates the production of parathyroid hormone (PTH). Secondary hyperparathyroidism leads to bone resorption and calcium enters the bloodstream, which explains normocalcemia [37–39, 43–45].

Pathogenesis of RTA II type is the defect of reabsorption of bicarbonates in the proximal tubules with preservation of acidogenesis. Pathogenesis is explained by the descrease or lack of production of carbonic anhydrase II-(C); a decrease in the activity in the blood of carbonic anhydrase I-(B); decrease in the activity of mitochondrial HCO_3^-ATPh-ase in membranes of the epithelium of the proximal tubules. The proximal variant of the lesion is more severe than the distal one. Type of inheritance – sporadic cases, boys of an early age are more often ill. In a healthy kidney, the filtered bicarbonates are reabsorbed in the proximal tubule in 85% of cases. If the level of bicarbonate in the plasma exceeds the renal threshold concentration, the reabsorption of bicarbonates doesn't completely occur. The renal threshold concentration of bicarbonates in children is 22–24 mmol/l. Patients with a proximal type of RTA have a decrease in the renal threshold concentration of bicarbonates, so the excretion of bicarbonates in the urine is sharply increased – more than 10–15% of the filtered amount (norm 0–2%). The renal threshold of reabsorption of bicarbonates falls below 22–20 mmol/l. This form of tubular acidosis is characterized by the preservation of the ability to reduce the pH of urine and excrete H^+. The mechanism of urinary acidification in the distal tubules isn't disturbed, urine can have an acidic reaction (pH less than 5,5). The presence of unreabsorbed bicarbonates in the proximal tubules during the flow through the distal tubules leads to stimulation of the aldosterone's secretion, which increases sodium reabsorption and potassium excretion. There are kalyuria, hypokalemia [4, 37]. The differential diagnosis of type I and type II RTA is presented in Table 1 **(table 1).**

Clinical picture of RTA [4, 9, 16, 37, 39, 43]. Clinical manifestations of enumerated biochemical disorders are as follows:

1. Developmental delay and retardation growth, often accompanied by rachitic, osteoporotic changes in bones. This is a consequence of chronic acidosis (reduces the secretion of the growth hormone) and hypercalciuria, hypocalcemia. Among the rachitic manifestations is more often valgus deformity of the legs, difficulty in walking, pain in the bones, pathological fractures, deformation of the chest and others.

2. The consequences of hypernatremia are polyuria, polydipsia, hypoisostenuria, a decrease in the concentration ability of the kidneys.

3. Nephrocalcinosis (bilateral) is due to hypercalciuria, alkaline pH of urine, hypocitruturia. Further – UTI, pyelonephritis, ULD, CRF.

4. The consequences of hypokalemia are muscular hypotension, hyporeflexia, weakness, adynamia, paresis, constipation, lowering of blood pressure, tachycardia.

5. Hyperchloremia, in parallel with disbalance of sodium and water, is manifested by dehydration, dehydration crises, vomiting, subfebrile, fever of unknown origin, lack of appetite, muscular adynamia.

It is generally believed that RTA of the I type is firstly detected not earlier than 2–3 years of life, and even in adults, where the definition appeared as the "adult type" of RTA. Sometimes the only symptom of the disease may be a delay in physical development, and in children 2–3 years old – rickets-like *changes in the osseous system. The complete clinical and laboratory symptom complex of RTA is formed by the age of 3–4 years.*

In distal RTA, the clinical presentation can vary significantly: ranging from mild symptoms, such as moderate metabolic acidosis and the incidental discovery of kidney stones, to severe manifestations like growth retardation, pronounced metabolic acidosis, and neph-

Table 1 – Biochemical parameters of blood and urine with RTA [1, 4, 37]

Laboratory data	I type of RTA	II type of RTA
Acidification of urine	It is always impaired, pH cannot be below 6,8	It isn't impaired, pH can be below 6.8; more often < 5.5
Excretion H^+	It is always impaired, sharply reduced	It isn't impaired
Kidney threshold reabsorption of bicarbonate's ions	Normal (22-24 mmol/l)	Sharply reduced (19-20 mmol/l)
Urinary excretion of bicarbonates	Normal (0-2% of the filtered amount)	Sharply increased (10-15% of the filtered amount)
Heredity	Recessive, dominant, linked to the X-chromosome	Sporadically, boys of the young age are ill
Therapy	Dose of bicarbonates – 2-3 mmol/kg/day	High doses of bicarbonates - 10 mmol/kg/day
Complications	Urolithiasis disease (ULD), nephrocalcinosis, chronic renal failure (CRF)	May be absent, delay in growth.

Figure 4 – Before the manifestation of the disease.

rocalcinosis. Progressive hearing loss develops in the majority of patients with recessive distal RTA (caused by mutations in the *ATP6V1B1* and *ATP6V0A4* genes) [9, 37, 39, 43].

RTA of the II type – in the first months of life there is periodic vomiting, anorexia, an increase in the temperature of an unknown genesis, hypotrophy develops, children lag behind in physical development, rickets-like changes in the bone system occur early, and nephrocalcinosis rarely develops. But, despite the severity of clinical manifestations, spontaneous recovery is possible for this type [16, 37].

As a result of generalized dysfunction of the proximal renal tubules, a pathological condition develops that leads to proximal renal tubular acidosis and massive losses of amino acids, glucose, potassium, sodium, phosphates, bicarbonate, uric acid, and water due to impaired reabsorption – Fanconi syndrome (de Toni–Debré–Fanconi) [37].

Treatment [16, 37, 43, 44]. The treatment is oriented to the correction of disturbances peculiar to RTA **–** restoration of electrolyte balance. It is allowed to do gymnastics, massage, potato-cabbage diet, restriction of proteins of animal origin, alkalinizing drink, increasing the amount of liquid to 2,5 liters per day. Drug therapy: correction of acidosis (citrate mixtures, sodium hydrogencarbonate), hypokalemia, hypocalcemia, treatment of osteomalacia (vitamin D 50 thousand IU/day, calcium preparations – gluconate, chloride, glycerophosphate). Rickets-like disorders (phosphate diabetes, RTA, Fanconi syndrome) are characterized not only by bone deformities but also by significant growth delay. Even with adequate pathogenetic therapy, many children do not reach their genetically determined height; therefore, growth hormone is prescribed [5, 11, 26, 28, 31].

The **prognosis** is favorable for the II type, severe in the I type with the development of CRF [37, 39, 43, 45].

We present a case of our own clinical observation.

The girl E., at the age of 4,5 years entered the children's neurological department with complaints of weakness in the legs, rapid fatigue, gait disturbance, inability to run, jump.

Past Medical History. A child from the I pregnancy, normal childbirth, in a period of 39-40 weeks. Weight at birth 3200g, height 51cm. Early anamnesis is without features. Began to go with 10 months **(fig. 4)**. Hereditary anamnesis is not burdensome.

History of the present illness. At the age of 3,5 years in the kindergarten, she poisoned herself with herring, was treated in the children's infectious disease department. After discharge from the hospital, bloating of the abdomen, polyuria, recurrent acidic conditions, episodes of fever increased. Parents paid attention to the change in gait, there was weakness in the legs, fast fatigue, the girl stopped running and jumping. The enumerated complaints progressed. Significant pains in the lower extremities were associated, loss of weight was noted (at 3,5 years –18 kg, at 5 years –14 kg), growth retardation (at 3,5 years –104 cm, at 5 years –104 cm), X-shaped deformation of the lower extremities was formed.

Neurological status. State of the disease of moderate severity. Muscle tone is sharply reduced in the limbs, more in the legs. She lags behind in growth and weight. The Barre test for the upper limbs is negative, for the lower is doubtful. Tendon reflexes from hands are alive D <S, knee and Achilles are enliven D <S. In the Romberg position is stable. The pointing test performs satisfactorily. Meningeal symptoms are negative. The expressed X-shaped deformation of the lower extremities, flat-valgus feet **(fig. 5)**. The lumbar lordosis is smoothed. Paraparetic gait, waddling gait, she cannot jump, run, walk the stairs. The electromyogram (EMG) was made in the department: Diffuse neuronal level of disorders. In the regional medical genetic center, a study was carried out on the SMN gene, the result is negative. The magnetic resonance tomography (MRT) of the brain and

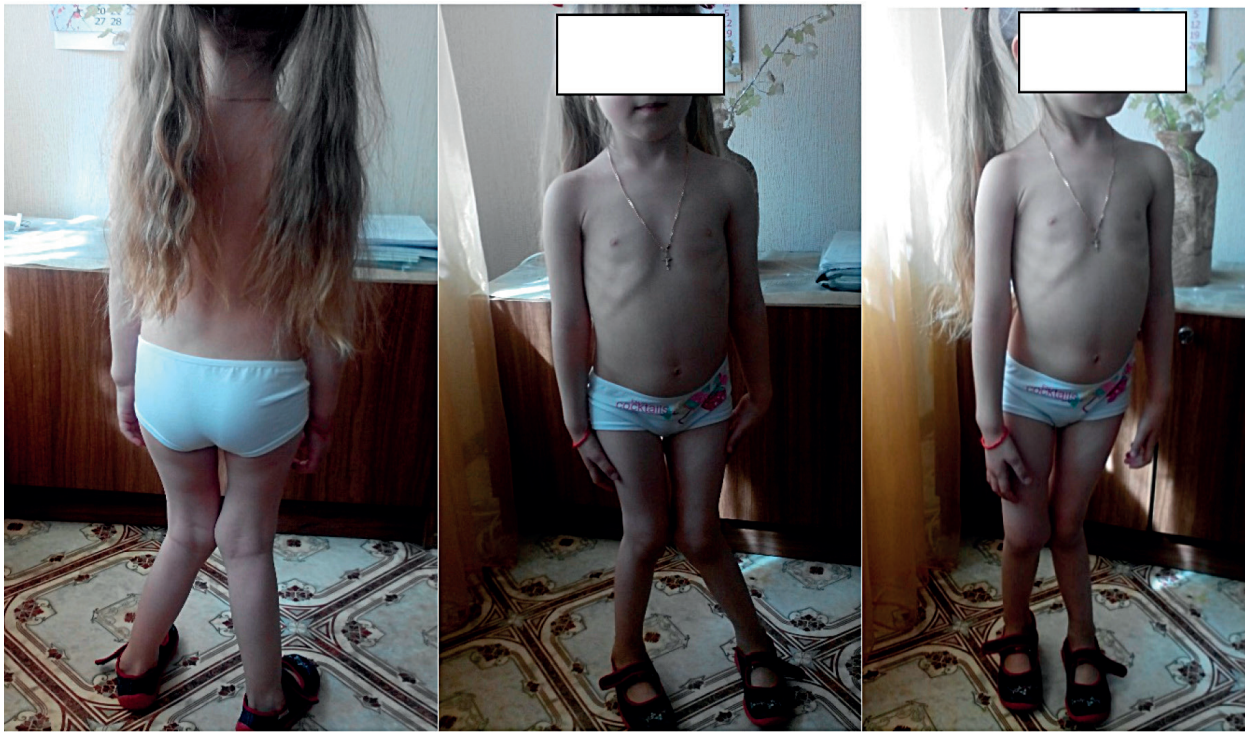

Figure 5 – The child is 5 years old, in the acute phase of the disease.

spinal cord was performed: the defeat of the brain and spinal cord was not detected. Diaginosis: Mitochondrial encephalopathy with lower paraparesis, with the disturbance of walking function. It is recommended EMG in dynamics, to investigate blood lactate, in therapy – cerebrum compositum, coenzyme compositum.

The state of the child has significantly improved against the background of ongoing metabolic therapy. But, after courses of massage therapy at home, a significant deterioration of the state was noted. There was difficulty in walking. At the age of 5 years the girl practically stopped walking on her own. EMG: the myopathic pattern of disturbances predominates. Blood lactate – 8.10 mmol/L **–** 2.09 mmol/L (reference range: 0.5–2.20 mmol/L).

To clarify the nature of metabolic abnormalities, she was sent to **the Kharkiv Specialized Medical Genetic Center (KhSMGC),** where she **was examined:**

1. Organic urine acids: changes in metabolites of ketosis, decrease in metabolites of the Krebs cycle;

2. **24-hour urine** analysis: volume – 2100 mL (reference range: 0.7–1.2 L), creatinine – 1.1 g/day (reference range: 0.27–0.415 g/day), Ca – 2.6 mmol/day (reference range: 0.5–3.8 mmol/day), P – 28.2 mmol/day (reference range: 10–30 mmol/day), urea – 401 mmol/day (reference range: 133–200 mmol/day), uric acid – 2.7 mmol/day (reference range: 0.6–3.0 mmol/day), hydroxyproline – 63 mg/day (reference range: 21.1–51.3 mg/day), total urinary glycosaminoglycans (GAGs) – 41.6 CPC units/g (reference range: up to 198 CPC units/g).

3. Blood biochemical analysis: homocysteine – 8.13 µmol/L (reference range: up to 5 µmol/L), lactate, Fe^{3+}, total Ca, and Ca^{2+} – within normal range, **P – 0.77 mmol/L (reference range: 1.45–1.78 mmol/L)**, Mg^{2+}, Na^{+}, Zn^{2+}, K^{+}, Cu^{2+}, Cl^{-}, and Se^{4+} – within normal range, creatinine – 22.13 µmol/L (reference range: 27–62 µmol/L), uric acid – 0.7 U/L (reference range: 1.68–3.84 U/L), cholesterol, glucose, bilirubin, triglycerides, urea, ALT, AST, GGT, CPK, and proteinogram – within reference values.

4. Liquid thin-layer chromatography amino acids in the blood – a decrease in serine, histidine, glycine, alanine, tyrosine, cystine, methionine, phenylalanine, leucine. The level of the metabolites studied is within the normal range. Liquid thin-layer chromatography amino acids in the urine – increased arginine, cystine, lysine. The level of carbohydrates in urine is the norm. Urinalysis – test for cystine – negative.

Diagnosis: Combined defect of oxidative phosphorylation, insufficiency of respiratory chain complexes with primary lesion of renal tubules (renal tubular dysfunction). Secondary dysfunction of parathyroid glands. Hyperhomocysteinemia.

Assigned: diet (a sufficient number of plant proteins and fluids, limiting acidogenic – sulfur-containing amino acids, enriching with phosphates and alkalinizing products – potato and potato-cabbage diets); for the normalization of the processes of homocysteine remethylation in methionine – stomach support, P5P, folacin; energotropnaya therapy – coenzyme compositum, ubiquinone compositum, korilip.

Considering the changes in the skeletal, muscular, and urinary systems associated with secondary dysfunction of the parathyroid glands, examination at the nephrology department of the **National Children's Specialized Hospital "Ohmatdyt"** was recommended (at the age of 5 years and 7 months). The patient underwent the following examinations:

1. Blood test – Erythrocytes – 4,3T/L, Hb – 143 g/L, Leukocytes – 6,1 G/L, eosinophil – 2%, stabs neutrophils – 3%, segmented neutrophils – 59%, lymphocytes – 31%, monocytes – 5%, Platelets – 273 G/L, ESR – 8 mm/h;

2. Blood biochemical analysis: proteinogram, cholesterol, glucose, bilirubin, urea, creatinine, ALT, AST, CRP, ASO, Na^{+} and K^{+}, and GFR – within reference values, Ca^{2+} – 1.28 mmol/L, **P – 0.75 mmol/L, ALP – 897 U/L,**

acid–base status (ABS): pH – 7.29 (reference range: 7.36–7.42), HCO_3^- – 13.8 mmol/L (reference range: 21–26 mmol/L), BE – –11.2 mmol/L (reference range: ±2 mmol/L); follow-up ABS: pH – 7.31, HCO_3^- – 16.8 mmol/L, BE – –8.3 mmol/L.

3. Urine analysis: urine calcium – 4.7 mmol/day, urine phosphate – 17.7 mmol/day; **PH of urine – 8.1;** the common analysis of urine, Nechiporenko's method – without features; Zimnitsky's test – specific gravity –1011–1016;

4. Consultations of specialists. Neuropathologist: Myopathic syndrome on the background of the main disease. Orthopedist: Osteoporosis. Epimetaphyseal dysplasia due to tubulopathy. Valgus deformity of the shins. Geneticist: To exclude a congenital metabolic disease, blood and urine tests for the amino acid spectrum are recommended.

5. Kidney ultrasound: The kidneys are enlarged – the right one is 9.6×4.0 cm, the left one is 10.6×4.3. The renal parenchyma is compacted, the contours of the pyramids are compacted, thickened. In the projection of pyramids, multiple calcifications up to 5 mm are visualized. Ultrasound of other abdominal organs without features. Ultrasound of the thyroid and parathyroid glands – there are no structural changes. Thyroid calcitonin is within normal limits.

6. Plain abdominal radiography: signs of **nephrocalcinosis** were identified in the projection of the kidneys.

7. Molecular genetic study (Institute of Molecular Biology and Genetics, Kyiv): there are no mutations in the genes SMN1, SMN1, NAIP (genes of spinal muscular atrophy).

Carried out therapy – diet, soda-buffer, alpha-D_3-Teva, calcium-D_3 nicomede, magnerot, dimephosphon, osteogenone, phisical therapy, massage, tutor-bandages on the legs.

Diagnosis: Tubulopathy. Renal-tubular acidosis of the I type. CRF (tubular). Nephrocalcinosis. Subnanism somatogenic. Osteoporosis. Epimetaphyseal dysplasia due to tubulopathy. Valgus deformity of the lower legs.

At the age of 6 years and 7 months, the girl was treated at the pediatric traumatology department in Kyiv. The conclusion of the lower extremity radiography revealed shortening of the left lower extremity, pelvic tilt to the right, left-sided coxa valga, severe valgus deformity of both lower legs, and valgus deformity of the feet **(fig. 6)**.

Surgical correction of the valgus deformity of both lower legs was performed by epiphysiodesis, followed by removal of screws from the distal thirds of both femora and the proximal thirds of the tibiae.

Follow-up examination was performed at the pediatric nephrology department in Kyiv. Complete blood count, blood biochemical analysis including proteinogram, urea, creatinine, glucose, bilirubin, ALT, and AST; urinalysis, Nechiporenko urine test, and bacteriological urine culture were within normal limits.

1. Blood biochemical analysis: K^+ – 3.8 mmol/L, Na^+ – 141 mmol/L, total Ca – 2.48 mmol/L, P – 1.69 mmol/L, Cl^- – 110 mmol/L, PTH – 27.3 pg/mL, ALP – 299 U/L, blood acid–base status (ABS): pH – 7.26, HCO_3^- – 19.0 mmol/L, BE – –7.9 mmol/L; GFR – 173 mL/min.

2. Zimnitsky urine test: urine specific gravity fluctuations – 1010–1014; urinary Ca excretion in 24-hour urine – 2.8 mmol/day.

3. Kidney ultrasonography: signs of nephrocalcinosis.

The following recommendations were provided: diet therapy; long-term sodium bicarbonate buffer therapy; Alpha D3-Teva; Calcium-D3 Nycomed administered in 2-month courses; Magnerot; Agvantar (L-carnitine); dimephosphon; Osteogenon (later replaced with Aleandra); Blemaren (later replaced with Smart Omega); growth hormone (Somatin) administered subcutaneously at 4 IU once daily, 5 days per week; physical therapy; and massage.

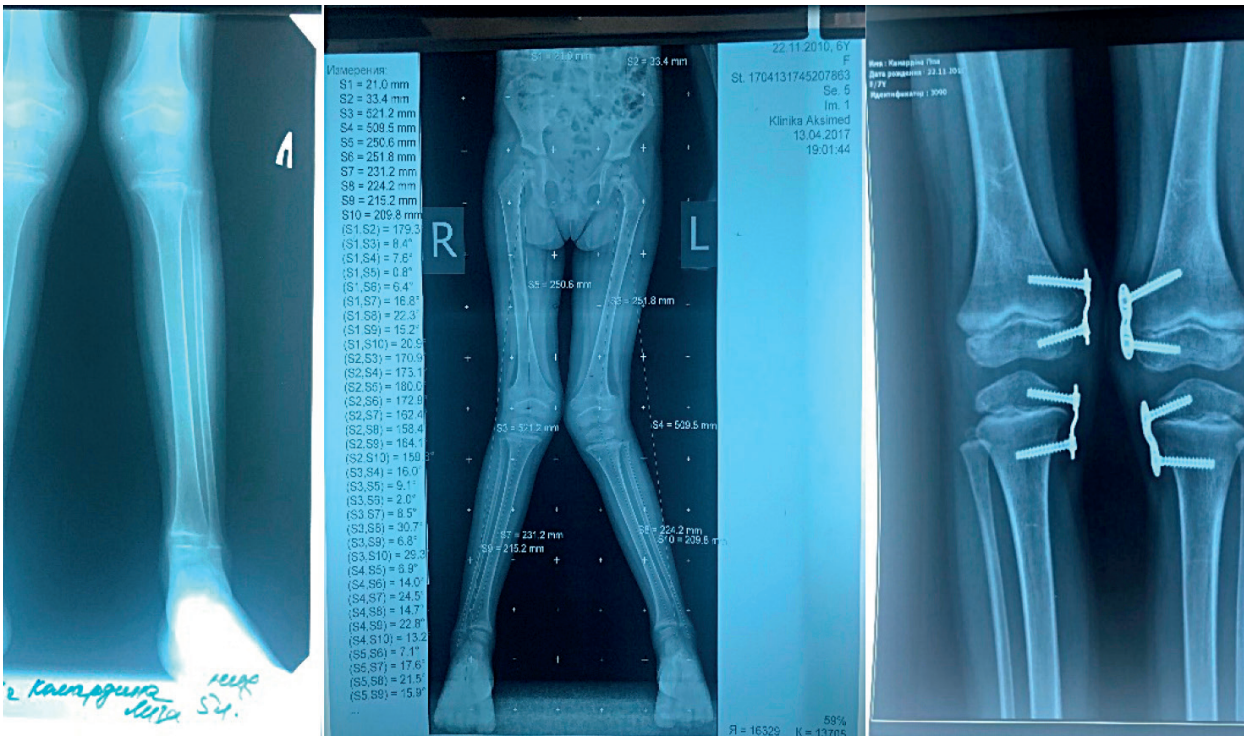

Figure 6 – Radiographs of the lower extremities before surgery and after surgical correction of the valgus deformity of both lower legs.

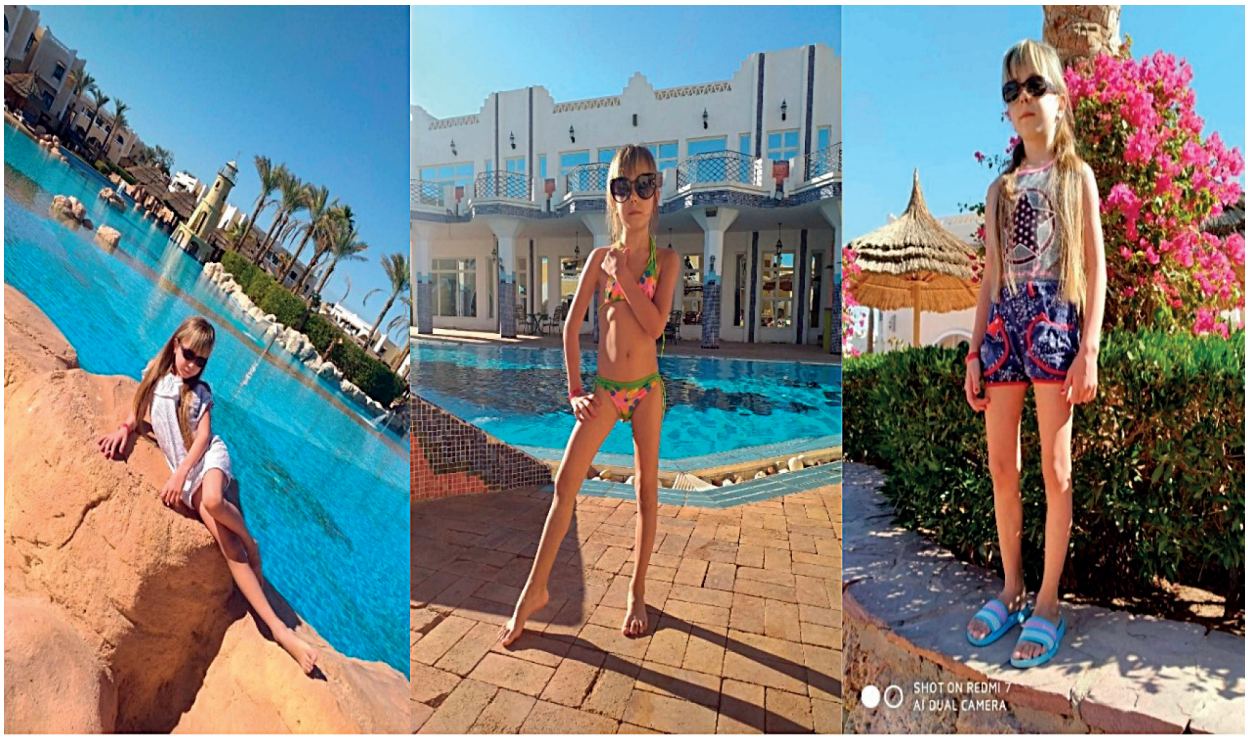

Figure 7 – The girl is 10 years old.

The child is 8 years old. The survey was conducted **in the National Children's Specialized Hospital "Ohmatdyt", in the Center for Orphan Diseases:**

1. Urinary screening: protein test – negative; The Fehling's test is negative; Sulkovich's test – (+); test for hyperaminoaciduria – negative; The Benedict's test is negative; sample with dinitrophenylhydrazine (DNFG) – negative; The Obermeer's test is negative; The Legal's test is negative; test for cystine – negative.

2. Thin layer chromatography of carbohydrates in urine is the norm;

3. Common glucosaminoglycans (GAG) in the urine of CPC – test – 45/213 from CPC/g creatinine.

4. Chromatomass spectrometry (TMS) (content of amino acids and acylcarnitines): the level of the studied metabolites is within the reference values.

5. Highly effective liquid chromatography of amino acids in blood: no abnormalities in the concentration of amino acids in the blood;

6. Genetic consultation: Diagnosis – tubulopathy associated with skeletal involvement. This condition requires differential diagnosis with cystinosis, De Toni–Debré–Fanconi syndrome, and RTA. No evidence sugges-

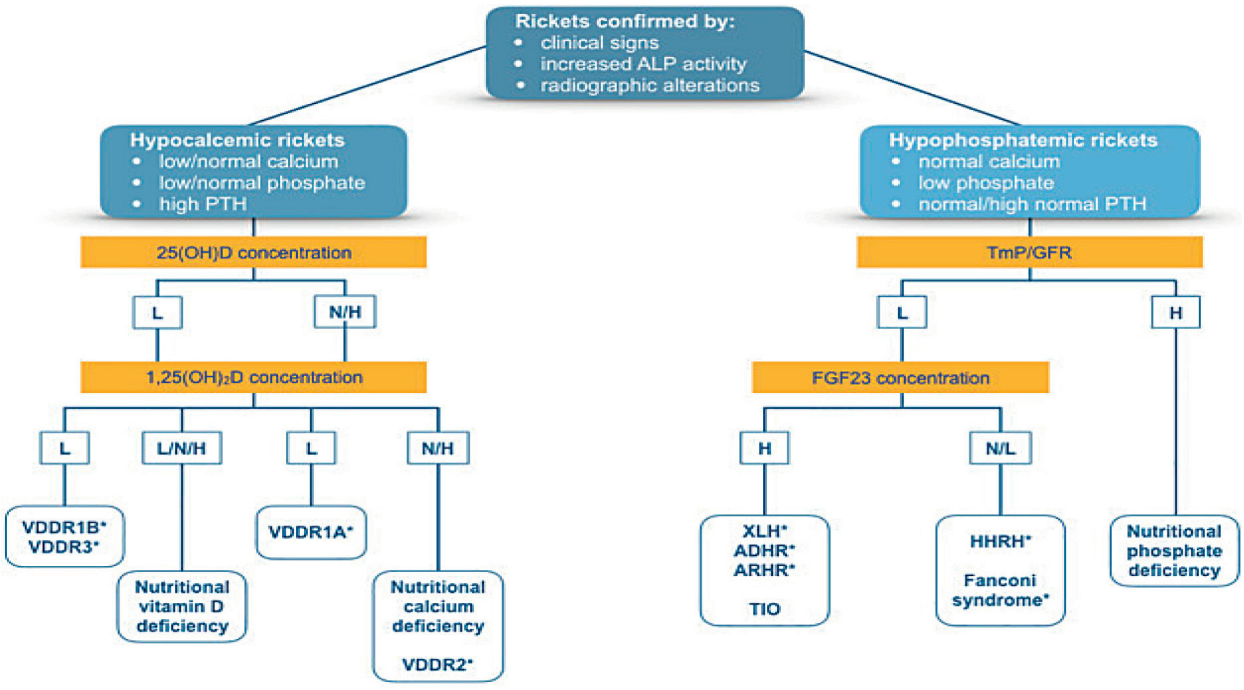

Figure 8 – Primary differential diagnosis [1].

Notes: see **fig. 1**; **L –** low values, **N –** normal values, **H –** high values.

Table 2 – Differential diagnosis of hereditary rickets-like diseases [1, 4, 11, 37]

Feature	Phosphate diabetes	Renal tubular acidosis	de Toni–Debré–Fanconi syndrome	Vitamin D–dependent rickets	Hypophosphatasia
Type of inheritance	X-linked, AD	Sporadic / AD / AR	Most commonly AR	AR	AD or AR
Age at onset	1–1.5 years	5–6 months to 2–3 years	2.5–3 years	Early childhood	At any age
Initial manifestations	Marked leg deformities, waddling gait, delayed tooth eruption, enamel defects	Polyuria, polydipsia, irritability, severe muscular hypotonia	Polyuria, polydipsia, unexplained fever, muscle pain	Seizures, growth retardation	Early tooth loss, skeletal deformities
Specific features	**Progressive, predominantly varus deformity of the legs**	Polyuria, polydipsia, **severe muscular hypotonia**, ↓ blood pressure, **valgus deformity of the legs**	**Unexplained fever**, skeletal deformities, ↓ blood pressure, constipation	Alopecia (type II)	Impaired mineralization, bone fragility
Physical development	↓ height, normal body weight	↓ height, significant ↓ body weight	↓ height, significant ↓ body weight	↓↓ height	Variable
Serum calcium	Normal low-range or ↓	Normal or mildly ↓	Normal or ↓	↓↓↓ very low in type II	Normal or ↑
Serum phosphorus	**Markedly ↓↓↓**	↓	↓↓	↓	Normal or ↑
Potassium, sodium	Normal	↓ or normal	↓	Normal or ↓	Normal
Acid–base balance	Normal	**Metabolic acidosis, pH <7.35**	Metabolic acidosis	Normal	Normal
Aminoaciduria	Absent	Absent	**Marked + glucosuria + proteinuria**	Absent or minimal	Absent
Phosphaturia	**Marked ↑↑↑**	Moderately ↓	**Marked**	Absent	Absent
Calciuria	Normal	**Marked ↑↑↑**	↓	Normal	↑
Alkaline phosphatase	↑	↑	↑↑	↑	**Markedly ↓, low ALP activity**
PTH	Upper normal range or ↑	Mildly ↑	Normal or ↑ (secondary)	↑↑↑ markedly elevated in type II	Normal
Vitamin D	Normal or ↓	Normal or mildly ↓	Normal or ↓	↓/↑ type I – low $1,25(OH)_2D_3$ with normal $25(OH)D_3$; type II — normal $25(OH)D_3$ with elevated $1,25(OH)_2D_3$	Normal
Underlying defect	Renal phosphate wasting	Metabolic acidosis	Loss of phosphates, bicarbonates, amino acids, and glucose	↓ synthesis of active vitamin D / resistance to vitamin D	ALP deficiency, **decreased enzyme activity**

tive of inherited disorders of amino acid or acylcarnitine metabolism was identified.

7. Genetic research (laboratory "EUROLAB"): By direct automatic sequencing, the coding sequence of the CTNS gene (DNA) was studied, the mutation in which is responsible for cystinosis nephropathic. Pathogenic variants are not found.

Against the background of the administered therapy, significant positive dynamics were observed **(fig. 7)**. Calcium and phosphorus levels in the blood and urine normalized. Changes in ABS and insufficient fluctuations in urine specific gravity, as assessed by the Zimnitsky test, persisted. According to the kidney ultrasonography findings, signs of nephrocalcinosis did not progress. After 6 months of growth hormone (Somatin) therapy, the patient grew by 12 cm (height: 116 cm) and gained 5 kg in body weight (weight: 20 kg). The girl can run, jump, and dance. No weakness in the legs, fatigue, or pain in the lower extremities was reported. Acetonemic episodes did not recur.

Thus, the diagnosis and treatment of RTA is a complex task, the solution of which is possible with knowledge of the issues of clinical polymorphism of the debut and the course of the disease, thorough the diagnostic search, and the timely appointment of therapy.

Differential Diagnosis of Rickets-Like Diseases

Differential laboratory diagnosis of RLDs is a crucial stage of evaluation, since the clinical manifestations, particularly skeletal deformities, are often similar, whereas the underlying pathogenic mechanisms and treatment approaches differ substantially [1, 11, 37]. The diagnosis is established on the basis of confirmed clinical manifestations, typical radiographic findings characteristic of rickets, and elevated serum **alkaline phosphatase** activity. We further propose a diagnostic algorithm that takes into account **hypocalcemia** and **hypophosphatemia (fig. 8)**. Serum concentrations of Ca, P, and PTH are key biochemical parameters for differentiating hypocalcemic and hypophosphatemic forms of rickets [1, 37]:

• **Hypocalcemic forms of rickets** are usually characterized by decreased serum Ca levels, low or normal serum P concentrations, and elevated PTH levels.

• **Hypophosphatemic forms of rickets** are characterized by marked hypophosphatemia in the presence of normal serum calcium levels and normal PTH concentrations.

We present the differential diagnostic features of hereditary RLDs that are most important in pediatric practice, namely vitamin D–resistant hypophosphatemic rickets (phosphate diabetes, PD), vitamin D–dependent rickets, renal tubular acidosis (RTA), and Fanconi syndrome **(table 2)**.

Special attention should be paid to the major distinguishing features of RLDs. In vitamin D deficiency rickets, children usually respond well to vitamin D therapy and demonstrate positive clinical dynamics. In PD, characteristic findings include marked hypophosphatemia, normal serum calcium levels, elevated ALP activity, phosphaturia, normal or mildly elevated PTH levels, and the absence of aminoaciduria and glucosuria. In RTA, metabolic acidosis and electrolyte disturbances predominate in the clinical presentation. Fanconi syndrome is characterized by multiple urinary losses, including glucose, amino acids, and phosphates.

In vitamin D–dependent rickets, the underlying problem is not vitamin D deficiency itself, but rather impaired vitamin D metabolism or receptor dysfunction. Low serum calcium and low active vitamin D levels are characteristic of vitamin D–dependent rickets type I, whereas low serum calcium combined with elevated active vitamin D levels is typical of type II vitamin D–dependent rickets. The key diagnostic marker of hypophosphatasia is deficiency and decreased activity of alkaline phosphatase.

Serum levels of Ca, P, ALP, PTH, and vitamin D metabolites are **fundamental parameters for the differential diagnosis of various forms of rickets** [1, 4, 11, 37]. The key indicators and their diagnostic significance are as follows:

• **Alkaline phosphatase (ALP).** Elevated ALP activity is observed in all forms of rickets except hypophosphatasia (HPP).

• **Hypocalcemia.** This is the principal biochemical marker in patients with severe vitamin D deficiency as well as in vitamin D–dependent forms of rickets.

• **Hypophosphatemia.** In the presence of normal serum calcium concentrations, hypophosphatemia is a specific feature of **hypophosphatemic rickets**. However, hypophosphatemia may also occur in severe vitamin D deficiency, usually in combination with hypocalcemia, as a consequence of secondary hyperparathyroidism. In all forms of rickets, hypophosphatemia is considered a "common denominator."

• **Hypercalciuria.** This is an important diagnostic criterion in patients with **hereditary hypophosphatemic rickets with hypercalciuria (HHRH)**.

• **Secondary hyperparathyroidism.** This is a characteristic biochemical feature of hypocalcemic forms of rickets. In contrast, in hypophosphatemic variants, PTH levels are usually normal or only mildly elevated. An exception is **HHRH**, in which serum PTH concentrations may be low or even suppressed.

• **Fibroblast growth factor 23 (FGF23).** Elevated FGF23 levels are observed in **FGF23-dependent** forms of rickets. An FGF23 concentration above **40 pg/mL** in the presence of hypophosphatemia is considered a key marker for the early diagnosis of **X-linked hypophosphatemic rickets (XLH)** in children.

Biochemical parameters are essential for the accurate differentiation of various forms of pathology and for selecting appropriate therapy. However, when clinical, biochemical, and radiological findings suggest a genetic form of rickets, specific molecular genetic testing becomes necessary.

Conclusions.

Rickets remains a major challenge in modern pediatric healthcare systems. The application of validated clinical and biochemical algorithms is a fundamental prerequisite for the timely identification of patients suspected of having this pathology. Early diagnosis and appropriate treatment are primary strategic objectives that make it possible to prevent severe irreversible complications in the future. A key stage in determining treatment strategy is differential diagnosis and the clear distinction between nutritional and genetically determined forms of the disease. Each type of rickets requires a personalized diagnostic approach, specific therapeutic regimen, and multidisciplinary patient management. To optimize the diagnostic process, a review of current literature was performed, diagnostic algorithms were proposed, and contemporary treatment approaches for patients with rare hereditary forms of rickets based on current recommendations were presented.

Prospects for further research.

Given that RLDs represent a diagnostically challenging pathology in children, further in-depth investigation of this problem is planned, including optimization of diagnostic and differential diagnostic algorithms, as well as the development of individualized treatment approaches.

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РАХІТОПОДІБНІ ЗАХВОРЮВАННЯ В ПРАКТИЦІ ПЕДІАТРА: ТРУДНОЩІ ДИФЕРЕНЦІЙНОЇ ДІАГНОСТИКИ ТА СУЧАСНІ МОЖЛИВОСТІ (ОГЛЯД ЛІТЕРАТУРИ ТА ВЛАСНІ СПОСТЕРЕЖЕННЯ)

Конюшевська А. А.

Резюме. Стаття присвячена сучасному стану проблеми спадкових рахітоподібних захворювань у дітей, генетично зумовлених порушень обміну фосфору, кальцію та вітаміну Д. Представлено літературний огляд патогенезу, клінічних проявів рахітоподібних захворювань.

Результати молекулярно-генетичних досліджень свідчать, що рахітоподібні захворювання мають виражене генетичне різноманіття. Тому остаточне підтвердження діагнозу базується на ідентифікації мутацій у відповідних генах, яке є дуже коштовним та тривалим. Тому особливо важливим є проведення диференціальної діагностики цих захворювань. Рання діагностика та вчасне призначення патогенетичної терапії будуть сприяти уповільненню розвитку рахітичних деформацій скелета, забезпечувати позитивну динаміку росту, попереджувати розвиток ускладнень, запобігати інвалідизації дитини.

У статті розглянуто основні ознаки рахітоподібних захворювань у дітей – виражені прогресуючі деформації скелета, резистентність до лікувальних доз вітаміну Д. Проведена диференціальна діагностики захворювань, які мають найбільше значення в педіатричній практиці, а саме, – вітамін Д-резистентний гіпофосфатемічний рахіт, вітамін Д-залежний рахіт, нирковий тубулярний ацидоз та синдром де Тоні–Дебре–Фанконі.

Докладно висвітлено дані щодо можливості лікування рахітоподібних захворювань. Наприклад, класичне комбіноване лікування при гіпофосфатемічних рахітах - препарати фосфатів, активні форми вітаміну Д, за потребую – гормон росту, хірургічне лікування скелетних деформацій. Описано новий препарат для лікування Х-зчепленої гіпофосфатемії – буросумаб (Burosumab), людське моноклональне антитіло проти FGF23, який нормалізує концентрацію сироваткового фосфору. Медикаментозна терапія при нирковому тубулярному ацидозі включає корекцію ацидозу, гіпокаліємії, гіпокальціємії, лікування остеомаляції.

Наведено випадки власного клінічного спостереження дитини з вітамін-Д-резистентним гіпофосфатемічним рахітом і дитини з нирковим тубулярним ацидозом.

Ключові слова: рахітоподібні захворювання, класифікація, фосфат-діабет, нирковий тубулярний ацидоз, діти, диференційна діагностика.

RICKETS-LIKE DISEASES IN PEDIATRIC PRACTICE: CHALLENGES IN DIFFERENTIAL DIAGNOSIS AND CURRENT OPPORTUNITIES (A LITERATURE REVIEW AND CASE OBSERVATIONS)

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Abstract. The article is devoted to the current state of the problem of hereditary rickets-like diseases in children, which are genetically determined disorders of phosphorus, calcium, and vitamin D metabolism. A literature review of the pathogenesis and clinical manifestations of rickets-like diseases is presented.

The results of molecular genetic studies indicate that rickets-like diseases are characterized by considerable genetic heterogeneity. Therefore, definitive diagnosis is based on the identification of mutations in the corresponding genes, which remains both costly and time-consuming. Consequently, the differential diagnosis of these disorders is particularly important. Early diagnosis and timely initiation of pathogenetically targeted therapy may help slow the progression of rachitic skeletal deformities, promote positive growth dynamics, prevent complications, and reduce the risk of disability in affected children.

The article discusses the main manifestations of rickets-like diseases in children, including severe progressive skeletal deformities and resistance to therapeutic doses of vitamin D. Differential diagnosis of the disorders most relevant to pediatric practice was performed, namely, vitamin D–resistant hypophosphatemic rickets, Vitamin D–dependent rickets, renal tubular acidosis, and Fanconi syndrome.

The paper also provides a detailed overview of current treatment options for rickets-like diseases. For example, conventional combination therapy for hypophosphatemic rickets includes phosphate supplementation, active vitamin D metabolites, and, when indicated, growth hormone therapy and surgical correction of skeletal deformities. A novel treatment for X-linked hypophosphatemia, Burosumab, a fully human monoclonal antibody against fibroblast growth factor 23 that normalizes serum phosphate concentrations, is also described. Pharmacological treatment of renal tubular acidosis includes correction of acidosis, hypokalemia, hypocalcemia, and treatment of osteomalacia.

Cases from the own clinical observations of a child with vitamin D–resistant hypophosphatemic rickets and a child with renal tubular acidosis are presented.

Key words: rickets-like diseases, classification, phosphate diabetes, renal tubular acidosis, children, differential diagnosis.

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3D-СКАНУВАННЯ В ОРТОПЕДИЧНІЙ СТОМАТОЛОГІЇ: ПЕРЕВАГИ, НЕДОЛІКИ ТА ПЕРСПЕКТИВИ РОЗВИТКУ

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Концепція автоматизованого проектування та виготовлення зубних протезів, відома як CAD/CAM технології, запатентована та запроваджена наприкінці XX століття. Поширення методу інтраорального сканування дозволяє підвищити ефективність діагностики та лікування при наявності дефектів твердих тканин коронкової частини зуба, порушенні безперервності зубного ряду, визначенні етапності лікування для забезпечення стійкого результату з позитивною динамікою. У зв'язку з удосконаленням сканерів методи діагностики набувають більшої точності, оперативності та доступності при стоматологічному ортопедичному лікуванні. В результаті поширюються можливості лікарів при плануванні та виконанні маніпуляцій на клінічному прийомі, значно покращується ефективність лікування пацієнтів. Інтраоральне сканування дозволяє швидко без дискомфорту для пацієнта порівняно з традиційним одержанням відбитків, отримувати зображення зубів з високоточною інформацією про їх стан, здійснювати вибіркове сканування окремих ділянок, мати можливість легко повторити процедуру та скоротити тривалість отримання відбитків, а також передачу інформації зубному техніку. Попри перспективність методу інтраорального сканування деякі дослідження свідчать про менш точне відтворення дистальних поверхонь зуба порівняно з мезіальними, а також верхньої щелепи порівняно з нижньою. Складним є процес сканування беззубих щелеп за неможливості відтворення функціонального стану слизової оболонки, зокрема її піддатливості. Відпрацювання послідовності дій із стратегією сканування напряму залежить від підготовки та досвіду лікаря, що здійснює процедуру. Отже, сучасні інтраоральні технології сканування мають значний потенціал, забезпечують високу точність, надійність діагностики та лікування ортопедичної стоматологічної патології, складають конкуренцію традиційним методам протезування. Перспективи застосування 3D-сканування в ортопедичній стоматології передбачають подальшу оптимізацію досліджень при різних патологічних станах, а також доступність різних методів сканування.

Ключові слова: *CAD/CAM-системи, цифрові відбитки, 3D-сканування, інтраоральне сканування, ортопедична стоматологія.*

Зв'язок публікації з плановими науково-дослідними роботами.

Наукова робота авторів є частиною ініціативної НДР кафедри ортопедичної стоматології з імплантологією «Застосування новітніх технологій для діагностики та лікування функціональної патології зубощелепної системи», номер державної реєстрації 0121U113817.

Вступ.

Ортопедична стоматологія посідає важливе місце серед напрямків сучасної стоматології, оскільки охоплює діагностику, профілактику та лікування порушень функціонування жувального апарату, зумовлених частковою чи повною втратою зубів. Одним із ключових аспектів цієї галузі є використання сучасних технологій 3D-сканування, що забезпечують отримання високоточних тривимірних моделей зубів, щелеп та м'яких тканин ротової порожнини пацієнта.

Актуальність дослідження методів сканування в стоматології постійно зростає у зв'язку з інтенсивним розвитком технологій і появою більш досконалих інноваційних рішень. Щороку підвищуються вимоги до точності та якості цифрових даних, що зумовлює необхідність поглибленого вивчення можливостей новітніх сканерів, аналізу та вдосконалення існуючих підходів.

Початок розвитку сканування в ортопедичній стоматології припадає на кінець XX століття, коли з'явилися перші пристрої для одержання тривимірних зображень. Так, у 1971 році у Франції розпочалися роботи над створенням системи для проєктування та виготовлення штучних зубних коронок. У 1973 році Ф. Дюре у своїй дисертації запропонував новаторську концепцію автоматизованого проєктування та виготовлення зубних протезів, відому як CAD/CAM. Згодом, у 1989 році на конференції в Чикаго було представлено патент на розроблений ним CAD/