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ПЕДИАТРИЯ

НАУЧНО-ПРАКТИЧЕСКИЙ ЖУРНАЛ

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ УЗБЕКИСТАНА
ТАШКЕНТСКИЙ ПЕДИАТРИЧЕСКИЙ МЕДИЦИНСКИЙ ИНСТИТУТ

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Адрес редакции:
100140, Республика Узбекистан,
г.Ташкент, ул.Богишамол, 223
тел.: +99871 260-28-57;
факс: +99871 262-33-14
сайт: tashpmi.uz/ru/science/journal_pediatry
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Республикамизнинг таниқли олимаси, Ўзбекистон фанини халқаро миқёсда юксалишига катта хизмат кўрсатган фан арбоби, тиббиётимизнинг, олий таълимнинг фидокор устози, маърифат- маънавиятнинг жонкуяр тарғиботчиси, ватанпарвар олима - профессор **САНЪАТ СОБИРОВНА АЗИЗОВА** қалбимизда ва хотирамизда доимо сақланиб қоладилар.

Akhmedova D.I., Abidova M.D.

MODERN ASPECTS OF RICKETS-LIKE DISEASES IN CHILDREN

Tashkent Pediatric Medical Institute

Rickets-like diseases (RLD) encompass a diverse group of hereditary disorders characterized by metabolic disturbances, primarily affecting the renal tubules and phosphorus-calcium metabolism. These disorders lead to compromised bone mineralization and various multi-organ complications. RLD falls under the category of tubulopathies, representing inherited abnormalities of the renal tubules [10].

RLD remains a significant medical and social concern, necessitating continuous updates in knowledge for pediatricians and medical professionals in other fields. The clinical presentation of RLD is highly heterogeneous, featuring pronounced skeletal deformities, delayed physical development, hypotension, respiratory failure, convulsive episodes, frequent fractures, premature tooth loss, alopecia, among others.

In some instances, delayed diagnosis and consequent lack of appropriate therapy contribute to disease progression, leading to severe disabling complications and, potentially, early childhood mortality.

In recent decades, substantial progress has been made globally in understanding the etiopathogenetic mechanisms of RLD. These advances underscore the pivotal role of molecular genetic diagnostics in identifying the underlying causes of rickets [3].

Genetically determined RLD includes:

Vitamin D-resistant rickets (VDRR) or phosphate diabetes (PD) - affecting approximately 1 in 20,000 children.

Vitamin D-dependent rickets (VDD) - with an incidence rate of 1-5 in 10,000 children.

Renal tubular acidosis (RTA) - occurring in approximately 1 in 40,000 children.

De Toni–Debre–Fanconi syndrome - affecting roughly 1 in 350,000 newborns [10].

Vitamin D-resistant rickets (VDRR), also known as hypophosphatemic rickets, is a subset of rare hereditary diseases affecting children [2]. It remains a pressing issue in pediatrics, with an incidence rate of 1:20,000 children [1,21].

VDRR is characterized by genetic heterogeneity and is associated with hypophosphatemia, skeletal abnormalities, stunted growth, and multi-organ complications. Untreated, it invariably leads to disability [6]. The disease's clinical and biochemical features, as well as its treatment, largely depend on its etiology [31].

First distinguished from typical rickets in 1935 by F. Albright, A.M. Butler, and E. Bloomberg, VDRR was further characterized in 1937 [6]. Molecular genetic studies have since identified several nosological forms, with the X-linked dominant form being the most prevalent, accounting for 80% of cases [24].

The X-linked dominant form is associated with the PHEX gene on chromosome Xp22.1-p22.2, which encodes a phosphate-regulating protein affecting phosphate reabsorption and vitamin D metabolism [5].

Impaired phosphate reabsorption in renal tubules and absorption in the small intestine results from this genetic defect [4]. Recent studies have implicated fibroblast growth factor-23 (FGF-23) in the pathogenesis of X-linked hypophosphatemic rickets [21].

Clinical manifestations range from isolated hypophosphatemia to severe lower limb deformities, with characteristic "duck gait" and delayed physical development [21].

Bone changes, visible on X-rays, include generalized osteoporosis and metaphyseal irregularities, becoming more pronounced over time [7].

Biochemical indicators typically include hypophosphatemia, elevated alkaline phosphatase activity, normal calcium and parathyroid hormone levels, low calcitriol (1.25 (OH)2-D3), and hyperphosphaturia [21].

Vitamin D-dependent rickets is an autosomal recessive inherited disease characterized by early onset, myopathic syndrome, and reduced levels of calcium and phosphorus in the blood. Coined by American scientists D. Fraser and R.B. Salter in 1958, the term "vitamin D-dependent rickets" was further detailed in 1961 [19]. It is also known as pseudovitamin D-deficient rickets or hypocalcemic vitamin D-resistant rickets. Currently, there are several types: vitamin D-dependent rickets type I (Prader type) and vitamin D-dependent rickets type II (Brooks type), each further divided into two subtypes, based on various genetic defects and distinct clinical and laboratory characteristics [14, 22].

The disease is caused by mutations of the CYP27B1 gene located on the long arm of chromosome 12 (12q13.1–q13.3). The CYP27B1 gene comprises 9 exons, and to date, 78 mutations have been described [30]. The enzyme 1α-hydroxylase is involved in converting 25(OH)D3 into the biologically active form, calcitriol 1,25(OH)2 D3. Defects in this enzyme result in low hormone levels in the blood serum [12, 13, 32].

Calcitriol 1,25(OH)2 D3 plays a crucial role in maintaining calcium homeostasis by enhancing calcium and phosphorus absorption in the small intestine and compensating for hypocalcemia. Calcitriol deficiency reduces calcium absorption in the intestine, leading to hypocalcemia, secondary hyperparathyroidism, impaired phosphorus-calcium metabolism, ricket-like skeletal deformities, and osteomalacia [11].

The disease typically manifests in children aged 3-6 months with functional changes in the central nervous system, followed by increasing muscle weakness and hypotension [15]. Characteristic features include "rickety rosaries" at the border of bony and cartilaginous parts of the ribs, chest compression, Harrison's furrow along the diaphragm attachment line, rickety kyphosis, and scoliosis. Limb deformities include "rickety bracelets" in the hands and forearms, "strings of pearls," and O- or X-shaped lower limbs, often accompanied by flat feet. Patients may experience delayed tooth eruption, enamel defects, and hypoplasia. Muscle hypotonia, joint laxity, "frog belly," and abdominal muscle divergence are common. Disease progression may lead to motor development and growth delays, osteomalacia, and fractures [9].

Laboratory findings in vitamin D-dependent rickets include hypocalcemia, hypophosphatemia, low serum 1.25(OH)2 D3 levels with normal 25(OH)D3, increased alkaline phosphatase activity, high serum parathyroid hormone (PTH) levels, and hyperaminoaciduria [17]. With 9 exons, the CYP27B1 gene has been associated with 78 mutations, but no common mutations have been identified [11].

Renal tubular acidosis (RTA) is among the rickets-like diseases (primary tubulopathies) characterized by persistent metabolic acidosis, reduced bicarbonate levels, and increased blood chloride concentration [29]. Alongside impaired renal function, RTA is associated with hearing impairment and ocular pathology.

RTA is an autosomal recessive disease, although sporadic cases with an autosomal dominant inheritance pattern have been reported. The disease is classified into two main types based on the primary disorder localization: type I, also known as Butler-Albright syndrome, and type II, or Lightwood syndrome. Type I, distal renal tubular acidosis, is characterized by hydrogen ion accumulation in the body due to reduced excretion in the distal renal tubules and typically manifests in preschool-age children. Type II is proximal renal tubular acidosis, caused by inadequate bicarbonate reabsorption in the proximal renal tu-

bules, resulting in hyperchloremia [29].

Different variants of RTA are distinguished based on the genetic defect:

Distal renal tubular acidosis with/without hemolytic anemia (OMIM 179800 and OMIM 611590) – caused by mutations in the SLC4A1 gene (17q21-q22), which comprises 20 exons. 137 mutations have been identified, with the S773P mutation being the most common. This mutation frequently occurs in the region spanning from the 589th to the 628th codon [30].

Distal renal tubular acidosis with late-onset sensorineural hearing loss (OMIM 605239) – associated with mutations in the ATP6V0A4 gene (7q33-q34), which consists of 22 exons. 80 mutations have been reported.

Distal renal tubular acidosis with sensorineural hearing loss (OMIM 267300) – linked to mutations in the ATP6B1 gene (2p13.1) or ATP6V1B1 gene, consisting of 14 exons. 55 mutations have been identified, including common variants such as R157C, M174R, and G364S.

Distal renal tubular acidosis with nephrocalcinosis, growth retardation, and mental retardation (OMIM 611555) – primary genetic defect undetermined.

Familial proximal renal tubular acidosis – primary genetic defect undetermined.

Proximal renal tubular acidosis with glaucoma, cataracts, keratopathy, and mental retardation (OMIM 604278) – associated with mutations in the SLC4A4 gene (4q21), which comprises 23 exons. 19 mutations have been described.

Proximal renal tubular acidosis with osteopetrosis (OMIM 259730) – linked to mutations in the CA2 gene (8q22), which consists of 7 exons. 30 mutations have been described.

Renal tubular acidosis type III, an atypical form (OMIM 267200) – primary genetic defect undetermined.

Renal tubular acidosis type IV with hyperkalemia – primary genetic defect undetermined [25].

The disease typically presents with reduced appetite, vomiting, constipation, hypotrophy, muscular hypotension, polyuria, polydipsia, fatigue, and delayed physical development in the first year of life. In the second year, these symptoms are joined by rickety deformities of the skull (frontal and parietal tubercles), rachitic "rosaries" and "bracelets," and hallux valgus changes of the lower extremities. Systemic osteoporosis, as well as kidney diseases such as pyelonephritis, nephrocalcinosis, and urolithiasis, may accompany RTA. Distal forms are primarily associated with deafness, while proximal forms are linked to ocular abnormalities and osteoporosis. Early hearing assessment is necessary [20].

Laboratory findings in RTA include metabolic acidosis, moderate hypophosphatemia, hypocalcemia, elevated chloride and alkaline phosphatase levels in the blood, alkaline urine pH, reduced citrate excretion, and increased urinary excretion of ammonia, sodium, potassium, calcium, and bicarbonates. Moderate proteinuria and leukocyturia may be observed. Radiological examination typically reveals systemic osteoporosis, while scintigraphy shows radioisotope accumulation in areas of active rachitic processes [25]. A comprehensive comparison of clinical and molecular genetic data is necessary to better understand disease pathogenesis and determine appropriate treatment [28].

De Toni-Debre-Fanconi syndrome was initially described in 1933 by Italian pediatrician G. de Toni in a child exhibiting hypophosphatemic rickets and glucosuria. The French physician R. Debre documented the syndrome in 1934. Swiss pediatrician G. Fanconi hypothesized the tubular nature of the disease in 1936. This syndrome is characterized by three main laboratory signs: glucosuria, generalized hyperaminoaciduria, and hyperphosphaturia, all of which arise due to combined tubulopathy [16].

De Toni-Debre-Fanconi syndrome represents the most severe form of pathology with rickets-like skeletal changes among all hereditary tubulopathies of mixed type. The genetic defect and primary biochemical product of the disease have not been fully elucidated. Currently, four genetically heterogeneous variants

of De Toni-Debre-Fanconi syndrome have been identified, differing in inheritance type (autosomal recessive and autosomal dominant), the extent of impaired intestinal calcium absorption, and the severity of the condition [18]:

Fanconi syndrome type 1 (OMIM 134600) – associated with the FRTS1 gene (15q15.3). Pathogenic mutations have not been described in databases; the gene has only been studied using polymorphic markers.

Fanconi syndrome type 2 (OMIM 613388) – linked to the SLC34A1 gene (5q35.3), which comprises 13 exons. 26 mutations have been reported.

Fanconi syndrome type 3 (OMIM 615605) – caused by mutations in the EHHADH gene (3q27.2), which consists of 7 exons. Only one mutation has been described.

Fanconi syndrome type 4 (OMIM 616026) – associated with the HNF4A gene (20q13.12), comprising 10 exons. 155 mutations have been identified. This variant of the disease is characterized by diabetes mellitus (MODY*) and early aging.

De Toni-Debre-Fanconi syndrome can manifest as either complete or partial, with reabsorption disorders affecting only certain components of the renal filtrate. Studies suggest a disruption in transmembrane glucose, phosphate, and amino acid transport in the proximal renal tubules. Skeletal deformities develop due to a combination of hypophosphatemia and acidosis or isolated hypophosphatemia [16]. The disease is presumed to be either enzyme-deficient or caused by abnormalities in renal tubular transport proteins. Recent hypotheses have also connected the pathology to mitochondrial abnormalities in renal tubules.

The disease's main clinical features typically emerge in the first year of life, presenting as increased thirst (polydipsia), polyuria, subfebrility, and vomiting. As the disease progresses, affected children experience delayed physical development, muscle hypotonia, and by age 5-6, they may lose the ability to walk independently. Spontaneous fractures are sometimes observed. Teeth are dystrophic and erupt considerably later than usual. By the second year of life, children become more susceptible to infections, often experiencing pneumonia, otitis media, and acute respiratory viral infections. With ongoing tubular dysfunction, chronic renal failure typically develops by age 10-12 [23].

Radiographically, pronounced bone deformities of the lower extremities (either hallux valgus or varus), chest and skull abnormalities, and changes in the upper extremities are observed. Bone tissue structure alterations, osteoporosis, and epiphyseal separations may also be seen.

Morphological examination of bone biopsies reveals disrupted bone beam structure, lacunae, and weak bone mineralization. Nephrobiopsy shows characteristic proximal tubular patterns (resembling a "swan's neck"), epithelial atrophy, and interstitial fibrosis. Glomerular involvement occurs at later stages of the disease [18].

Biochemical abnormalities include hypophosphatemia and hypocalcemia, increased alkaline phosphatase levels, metabolic acidosis, and increased organic acid excretion. Moderate tubular proteinuria (involving light chains of immunoglobulins and lysozyme in the urine) and mild leukocyturia are common. Bicarbonate loss in urine results in metabolic acidosis. With worsening acidosis, calciuria increases, exacerbating the phosphorus-calcium imbalance. Other findings include glucosuria, generalized hyperaminoaciduria (without a concurrent increase in blood amino acid levels), polyuria, increased urine pH, decreased sodium and potassium levels, and elevated blood lactic and pyruvic acid levels. Increased sodium and potassium excretion leads to hypoisostenuria [27].

The rarity of individual forms and their similarity to other metabolic diseases, caused by various hereditary and environmental factors (toxins, drugs, chemicals, etc.), pose significant challenges to the early diagnosis of diseases in this group. Delayed diagnosis and treatment often lead to irreversible consequences [25]. Accurate diagnosis is crucial not

only for timely treatment but also for providing appropriate medical and genetic counseling to affected families, calculating genetic risks, as rickets-like diseases have different inheritance patterns, prognoses, and treatment approaches.

This group of diseases shares significant similarities with classic vitamin D-deficient rickets, complicating diagnosis and often leading to delayed identification and treatment. Hence, a comprehensive analysis of clinical, laboratory, and genetic features is necessary [2].

Molecular genetic studies have revealed significant genetic heterogeneity among rickets-like diseases. Several hereditary forms are particularly relevant in pediatric and medical genetic practice, including hypophosphatemic vitamin D-resistant rickets (phosphate diabetes), vitamin D-dependent rickets, renal tubular acidosis, and de Toni-Debre-Fanconi syndrome [5].

Rickets remains a pressing issue in childhood due to its widespread occurrence and severe clinical consequences. Rickets-like diseases comprise a heterogeneous group, stemming from various etiological factors and pathogenetic mechanisms. This diversity must be considered when prescribing treatment and implementing preventive measures. The similarity between classical rickets and rickets-like diseases often leads to diagnostic errors, with the diagnosis often occurring late.

Accurate diagnosis is currently achievable only through the identification of gene mutations responsible for the pathology using sequencing methods. Sequencing allows the simultaneous analysis of numerous genes.

Despite extensive research on the clinical and genetic features of rickets-like diseases in children, specific gene mutations characteristic of our country has not yet been identified. These mutations should account for the clinical and functional disorders most frequently associated with hereditary rickets-like diseases in children.

Attention to these diseases in our country has increased significantly in recent years. This has led to the adoption of measures to enhance medical and social care for children with rare (orphan) and other hereditary genetic diseases at the legislative level.

It is imperative to conduct clinical, paraclinical, and molecular genetic studies to identify diagnostically and prognostically significant biochemical and hormonal markers, including vitamin D levels. Establishing gene mutations characteristic of our country and developing an algorithm for diagnosing and prognosticating the most frequently identified hereditary rickets-like diseases in children are vital steps. These studies will enable the early diagnosis of the most common hereditary rickets-like diseases in Uzbekistan, allowing for timely treatment initiation and patient management. This, in turn, will improve their quality of life and reduce mortality.

The lack of data on the structure of rickets-like diseases in Uzbekistan, the necessity of identifying diagnostic and prognostic markers, and the development of clear clinical, diagnostic, and molecular genetic criteria and management recommendations for patients with rickets-like diseases could serve as a basis for conducting a dissertation scientific research.

Therefore, investigating the clinical, functional, and molecular genetic characteristics of rickets-like diseases in children is of particular interest.

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Ахмедова Д.И., Абидова М.Д.

СОВРЕМЕННЫЕ АСПЕКТЫ РАХИТОПОДОБНЫХ ЗАБОЛЕВАНИЙ У ДЕТЕЙ

Рахитоподобные заболевания представляют собой разнообразную группу наследственных расстройств, создающих значительные трудности в педиатрической практике. В данном обзоре рассматриваются последние достижения в диагностике, лечении и понимании рахитоподобных заболеваний у детей. Молекулярно-генетические исследования выявили высокую генетическую гетерогенность этих заболеваний, подчеркивая важность точной диагностики с помощью выявления мутаций генов с использованием методов секвенирования. Несмотря на проведенные обширные исследования, специфические генетические мутации, характерные для определенных регионов и популяции, остаются неидентифицированными, что подчеркивает необходимость дальнейших исследований. В данном обзоре подчеркивается значимость клинических, параклинических и молекулярно-генетических исследований для выявления диагностических и прогностических маркеров, установления четких диагностических критериев и разработки рекомендаций по лечению этих сложных состояний. Путем углубленного изучения рахитоподобных заболеваний можно улучшить раннюю диагностику, оптимизировать стратегии лечения и в конечном итоге повысить качество жизни и снизить смертность среди детей.

Ahmedova D. I., Abidova M. D.

BOLALARDA RAXITGA O'XSHASH KASALLIKLARNING ZAMONAVIY JIHATLARI

Raxitga o'xshash kasalliklar irsiy kasalliklarning bir guruhi bo'lib, pediatriya amaliyotida sezilarli qiyinchiliklarni yuzaga keltiradi. Ushbu maqolada bolalarda raxitga o'xshash kasalliklarni tashxislash, davolash va tushunishdagi so'nggi yutuqlar aks ettirilgan. Molekulyar-genetik tadqiqotlar orqali ushbu kasalliklarning yuqori genetic geterojenligini aniqlagan bo'lib, sekvestratsi ya texnikasi yordamida gen mutatsiyalarini aniqlash va aniq tashxis qo'yish muhimligini isbotlanmoqda. O'tkazilgan keng qamrovli tadqiqotlarga qaramay, ma'lum mintaqalar va populyatsiyalarga xos bo'lgans petsifikgenetik mutatsiyalar aniqlanmagan bo'lib qolmoqda, bu esa tadqiqotlar zarurligini ta'kidlaydi. Ushbu maqolada diagnostic va prognostik belgilarni aniqlash, aniq diagnostika mezonlarini belgilash va ushbu murakkab sharoitlarni davolash bo'yicha tavsiyalar ishlab chiqish uchun klinik, paraklinik va molekulyar genetik tadqiqotlarning ahamiyatiga alohida e'tibor qaratilgan. Raxitga o'xshash kasalliklarni chuqur o'rganish orqali erta tashxisotni yaxshilash, davolash strategiyalarini optimallashtirish va oxir-oqibat hayot sifatini yaxshilash va bolalar o'limini kamaytirish mumkin.

Pazilova S.B.

OSHQOZON–ICHAK TRAKTI MIKROFLORASINING AHAMIYANI VA UNING TARKIBIDAGI BUZILISHLARNI TUZATISH TAMOYILLARI

Toshkent pediatriya tibbiyot instituti

A. Levenguk bakteriyalar dunyosini kashf qilganidan beri olimlarni insonning o'z i ichidagi va atrof-muhitdagi mikroorganizmlar bilan oz'aro munosabatlariga bog'liq bo'lgan savollar qiziqtirib kelmoqda. Bundan tashqari, agar dastlab olimlar mikroorganizmlarni faqat kasallikni chaqiruvchi «tajovuzkorlar» sifatida qabul qilishgan bo'lsa, unda buyuk rus olimi I. I. Mechnikovning olib brogan ishlaribizning organizmga ulkan ta'sir ko'rsatadigan «simbiont mikroflorasi» va bioterapiya haqida yangi ta'limotning asosi bo'lib xizmat qildi va bioterapiya- bir qator patologik jarayonlarni davolash, salomatlikni mustahkamlash va natijada hayotni uzautirishga olib keldi.

Ma'lumki, mikroflora har qanday biosferaning ajralmas qismidir. Barcha tabiiy tizimlarda mikroorganizmlar murakkab ko'p komponentli jamoalar-biotsenozlar shaklida mavjud bo'lib, ularning ichida xarakterli munosabatlar shakllanadi, bu mikrob populyatsiyalarining hayotiyligini saqlashgayordamberadi. Biotsenoz -ovqatlanish zanjirida o'zaro bog'liq bo'lgan va ma'lum bir hududda yashaydigan tirik organizmlardir.

Ular insonning barcha tashqi yuzalarini va bo'shliqlarini to'ldirib, o'zaro manfaatli simbiotik munosabatlarning ko'p qirrali kengaygan mexanizmiga ega bo'lgan yagona ekologik tizimni yaratadilar.

Makroorganizmning alohida biotoplarida turli mikrob populyatsiyalarining tarqalishining o'ziga xos xususiyatlari u erda mavjud bo'lgan mikroorganizmlarning yashash sharoitlari bilan bog'liq.

Eng zich joylashtirilgan ekotizim yogon ichak biotopidir, unda barcha mikrofloraning taxminan 60% to'plangan. Odamning oshqozon–ichak traktida son-sanoqsiz mikroblar yashaydi, ular lokalizatsiyasi, yashash davomiyligi va funktsiyalari jihatidan juda katta darajada farqlanadi. Ribosomal RNK16s fragmentining tuzilishi bo'yicha o'tkazilgan tadqiqotlar natijalari shuni ko'rsatdiki, ichak mikroflorasining ko'p shtammlari hali etishtirilmagan, yani kultivatsiyalanmagan, lekin ular asosan guanin va sitozin miqdori past (taxminan 20%) yoki yuqori (taxminan 50%) gramm-musbat bakteriyalarga hos. Shunisi qiziqki, probiyotiklarning aksariyati gram-musbat bakteriyalar bo'lib, ular tarkibida guanin va sitozin miqdori past (Lactobacillus casei DN–114001, L. Shirota, L. Plantarum 299v, L. rhamnosus GG, L. johnsoni La1) yoki guanin va sitozin miqdori yuqori (Bifidobacterium lactis BB12). Oshqozon-ichak traktining normal mikroflorasi quyidagi tarkibiy qismlarga bo'linadi: indigen yoki

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