CAZ CLINIC

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LOWE SYNDROME OR OCULOCEREBRORENAL SYNDROME: ETIOPATHOGENESIS, CLINICAL PICTURE AND TREATMENT (THE SYNTHESIS). A CLINICAL CASE.

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SUMMARY

Lowe syndrome, also called oculocerebrorenal syndrome, OCRS, is a multisystemic condition characterized by various abnormalities affecting the eye, nervous system (NS) and kidneys. This syndrome (Sm) is a rare disease, with an estimated prevalence in the general population of about 1 in 500000. The syndrome is caused by mutations in the *OCRL* gene mapped on the Xq25-26 locus, and encodes a inositol polyphosphate-5-phosphatase which metabolize phosphatidylinositol 4,5-bisphosphate (PIP_2) in the Golgi apparatus, and, having the X-linked recessive type of inheritance, develops mostly in men. Symptoms suggestive of the disease are bilateral congenital cataract, glaucoma, severe psychomotor retardation and proximal renal Fanconi-type tubulopathy. Enzymatic and molecular tests are used to confirm the diagnosis. Tests for the diagnosing of the disease in the prenatal period may also be available. The treatment is complex, and includes therapeutics as well as interventional approaches. Surgical treatment is applied to correct of ocular problems, e. g., glaucoma, simultaneously with the control of tubular acidosis and administering the drugs which are given to maintain bone function and relieve behavioral problems; as well, physical and speech therapy is indicated. The prognosis is complicated. In this study we present a clinical case of a boy of small age, diagnosed with Lowe Sm, based on congenital cataracts, renal tubular dysfunction and neurological disorders. Genetic analysis found a mutation that causes an amino acid substitution in exon 9 of the *OCRL* gene.

REZUMAT

SINDROMUL LOWE SAU SINDROMUL OCULOCEREBRORENAL: ETIOPATOGENEZA, MANIFESTĂRILE CLINICE ȘI TRATAMENTUL (SINTEZĂ). CAZ CLINIC.

Sindromul (Sm) Lowe, sau Sm oculocerebrorenal (OCRL), este o afecțiune multisistemică caracterizată prin diverse anomalii care afectează ochiul, sistemul nervos (SN) și rinichii. Acest Sm face parte din bolile rare, cu o prevalență estimată în populația generală de aproximativ 1 la 500.000. Sindromul reflectă mutațiile în gena OCRL localizată pe cromozomul Xq25-26, și codifică polyphosphatidylinositol-4,5-biphosphate 5-phosphatase (PIP2) în aparatul Golgi, fiind expresia unei patologii X-lincate recesive. Se întâlnește doar la băieței. Simptomele sugestive bolii sunt: cataracta congenitală bilaterală, glaucom, retardare psihomotorie severă și tubulopatie renală proximală (de tip Fanconi). Pentru confirmarea diagnosticului se aplică testele enzimatice și cele moleculare. La fel, pot fi disponibile și teste pentru depistarea bolii în perioada prenatală. Tratamentul este complex: medicamentos și chirurgical. Tratamentului chirurgical se aplică pentru corectarea problemelor oculare, iar cel sindromologic pentru controlul glaucomului și corijarea acidozei tubulare. De asemenea, se dau preparate pentru menținerea funcției osoase și ameliorarea problemelor de comportament; este indicată terapia fizică și logopedică. Prognosticul este rezervat. În lucrare vom prezenta cazul clinic al unui băiețel, diagnosticat cu Sm Lowe, pe baza cataractei congenitale, a disfuncției tubulare renale și a tulburărilor neurologice. Prin analiza genetică s-a constatat o mutație care determină o substituție de aminoacizi în exonul 9 al genei OCRL.

РЕЗЮММЕ

LOWE СИНДРОМ ИЛИ ОКУЛОЦЕРЕБРОРЕНАЛЬНЫЙ СИНДРОМ: ЭТИОПАТОГЕНЕЗ, КЛИНИЧЕСКИЕ СИМПТОМЫ И ЛЕЧЕНИЕ (СИНТЕЗ). КЛИНИЧЕСКИЙ СЛУЧАЙ.

Lowe синдром (См) или окулоцереброренальный (OCRL) См, является мультисистемным расстройством, характеризующимся различными нарушениями, неврологическими, глазными, почечными. Этот См является одним из редких заболеваний с предполагаемой распространенностью в общей популяции от 1 до 500 000 человек. См отражает мутации в гене OCRL, расположенной на Xq25-26хромосоме, и кодирует полифосфатидилинозитол-4,5-бифосфат-5-фосфатазу (PIP2) в аппарате Гольджи, являясь выражением рецессивной Х-сцепленной патологии, встречающейся только у мальчиков. Симптомами этого заболевания являются: двусторонняя врожденная катаракта, глаукома, тяжелая психомоторная отсталость и проксимальная почечная тубулопатия (тип Фанкони). Для подтверждения диагноза применяются ферментные и молекулярные тесты. Кроме того, могут быть доступны тесты для выявления заболевания в течение дородового периода. Лечение комплексное: лекарственное и хирургическое. Хирургическое лечение применяется для коррекции глазных проблем, а синдромологическое - для лечения глаукомы и коррекции тубулярного ацидоза, а также назначены препараты для поддержания функции костей и улучшения поведенческих проблем, также, физическая и логопедическая терапия. Прогноз неблагоприятный. В статье мы представили клинический случай мальчика с диагнозом Lowe См на основании врожденной катаракты, дисфункции почечных канальцев и неврологических расстройств. Генетический анализ обнаружил генную мутацию OCRL, которая подтверждает аминокислотную замену в 9-ом экзоне.

Introduction.
Lowe Sm, also called oculocerebrorenal syndrome, OCRS, is a multisystemic condition characterized by various abnormalities affecting the eyes, NS and kidneys [1, 2, 3, 4]. For the first time, it was described in its classical form by Lowe U, Terry M and Lachlan E in 1952 [3]. Then, in 1954, another Sm, i. e., Fanconi renal Sm, associated with Lowe Sm [5] was revealed. Later, in 1965, a recessive X-linked type of inheritance was determined characteristic for this disease [6], develops mostly in men. The classical form of the syndrome is characterized by symptomatic triad, i. e., congenital cataracts, severe intellectual deficiency and renal tubular dysfunction with slow progressive renal failure [1, 2, 4]. This rare disease develops as a result of a mutation in the *OCRL1* gene which encodes a inositol polyphosphate-5-phosphatase with phosphatidylinositol activity, the protein 105-kD in weight, which catalyses in Golgi apparatus the formation of phosphatidylinositol 4,5-bisphosphate, also called PIP_2 or $PI(4,5)P_2$, a minor phospholipid component of cell membranes. PIP_2 enriches the plasma membrane, forming a substrate for a number of important protein signaling pathways, being involved in modulating protein function. In Lowe disease, a deficiency of PIP_2 develops in the Golgi apparatus.
Lowe Sm is manifested from the age of the newborn by clinical symptoms caused by congenital neurological, ocular and renal malformations [7]. The patients are born with both eyes severely affected by congenital cataract. Other ocular problems may be present, including glaucoma, found approximately in 1/2 of infants, characterized by increased intraocular pressure [8]. Most newborns have decreased muscle tone from birth, i. e., display severe neonatal hypotonia, as well as impaired tendon reflexes (TR), which can compromise breathing and nutrition, leading to respiratory problems and feeding difficulties in the first period of life. The development of motor skills, such as sitting, getting up and walking, is delayed. Autonomous walking occurs after the third year of life [9]. Seizures and behavioral problems have also been reported in affected children. There was a delay in neuropsychic development, and intellectual capacity varies from normal to severely impaired. Psychomotor retardation is evident in childhood, while behavioral problems and kidney complications occur in adolescence [10]. Both enzymatic and molecular tests are available for diagnosis confirmation and prenatal diagnosis [11]. Treatment includes interventional treatment of cataract, treatment of glaucoma and using the drugs to correct tubular acidosis, bone disease and to address behavioral problems, is indicated also physical and speech therapy [1]. The prognosis depends on the degree of damage of NS and kidneys.

Scope of the study.
Analysis of literature data on ethiopathogenesis, clinical manifestation and treatment of Lowe Sm. Description of a clinical case of a male child with Lowe Sm.

Material and methods.
Analysis the data from the literature on Lowe Sm (34 sources from specialized literature Library of PubMed). Description of a clinical case diagnosed with Lowe Sm in the Neurology Clinic, Department of Pediatrics, confirmed by molecular genetic testing.

Clinical case.
Boy aged 4.5 months, presented to neurology clinic, in 2016, with myoclonic seizures, generalized hypotonia, peripheral edema. Anamnesis of life: child born from the 4th pregnancy, physiological course, 4th birth without pathological peculiarities, at 40 weeks of pregnancy, weighing 2800 g, from birth the presence of hypotonia and bilateral cataract. At the age of 1.5 months the child underwent surgical intervention for cataract with insufficient effect. Family history has been complicated by presence of eye and kidney problems in a maternal uncle, namely, congenital cataract, developmental delay, renal failure and scoliosis. Examination showed peripheral edema, inability to fix or track objects visually, marked hypotonia, delaying in physiological motor abilities, i. e., the child does not hold the head, the movements of the limbs are slow, the child does not catch the toy, diminished TR, horizontal nystagmus, macrocrania, low-set ears, asymmetric in form and position, weight deficiency, i. e., 4100 g. Ophthalmological examination revealed bilateral central nuclear cataract, increased intraocular pressure and corneal edema. Laboratory examinations established tubular metabolic acidosis with hypocaliemia type II (pH – 6,9; pO_2 – 68,32 mm Hg, pCO_2 – 30,13 mm Hg, SO_2 – 92,11%; HCO_3 – 16,88 mmol/L, BEb – 7,8 mmol/L, BE eef – 8,05 mmol/L, as well as hypokalemia. Serum levels of Ca – 2,0 mmol/L, Ca+ – 1,12 mmol/L, P – 3,7 mmol/L, Na – 120 mmol/L, Cl – 96 mmol/L, creatinine – 0,08 mg/dL, BUN – 64 mg/dL, lactate dehydrogenase (LDH) – 1200 U/L, creatine khinase (CK) – 680 U/L. Also, the urine examination found phosphaturia (28,89 mg/kg/d), Ca excretion (7,8 mg/kg/d), proteinuria (1,86 g/24 h). These data were suggestive for the disturbance of renal tubular reabsorption of phosphates and the increase in the index of fractional excretion of phosphate (FeP). On X-ray, abnormalities of radial and ulnar epiphyses were found, that proved of rickets. USG examination and renal scan revealed data suggestive for congenital generalized proximal tubulopathy. Neurological examination showed delay in motor and cognitive functions. Cerebral MRI revealed volume retrocerebellar cystic formation and hypoplasia of corpus callosum. Electromyography - normal appearance. Using molecular genetic analysis one month after initial admission a mutation was detected in exon 9 of the *OCRL1* gene, type c.741G>T p.(Trp247Cys), suggestive of Lowe Sm. Thus, the diagnosis was confirmed as follows: Oculocerebrorenal (Lowe) syndrome, mutation in exon 9 of the *OCRL1* gene. Flaccid tetraplegia. Nephrotic syndrome. Congenital cataract. Renal tubular dysfunction, i. e., congenital tubulopathy. Hypophosphatemic rickets. Delay in physical and neuropsychic development. Large retrocerebellar cyst, hypoplasia of the corpus callosum. For the treatment was recommended to correct tubular acidosis and maintaining bone function, as well as supportive treatment for rickets. The child's condition has improved. Surgery for cataract has been recommended. However, at the age of 9 months, on the background of an acute respiratory disease, the child developed acute renal failure, cerebral edema and pulmonary edema, which could not be controlled, and as a result the patient died. On the morphopathological examination, the diagnosis was confirmed as follows: Oculocerebrorenal syndrome. Renal failure. Cerebral edema. Pulmonary edema. Bilateral congenital nuclear cataract. Congenital generalized proximal tubulopathy. Cortical atrophy, large retrocerebellar cyst, hypoplasia of the corpus callosum.

Discussions.
According to the literature data, there are many synonyms of Lowe Sm, namely, (1) oculocerebrorenal Sm (OCR); (2) Oculocerebrorenal Lowe disease / Sm (OCRL); (3) Lowe disease; (4) Oculocerebrorenal dystrophy [1].
Lowe Sm refers to rare diseases. According to American and Italian associations of Lowe Sm, the prevalence to be approximately 1 to 500000 [7, 12, 13]. In general, the estimated prevalence is between 1 to 10 men per 1000000 [7].

Causes.
Lowe Sm is single gene disease, caused by decreasing of the PIP_2 level. PIP_2 is a minor phospholipid component of cell membranes, which is a substrate of many cell signaling pathways, especially for a number of proteins. The disorder of synthesis processes lead to the imbalance of phospatosides which plays a central role in the reshaping of the cytoskeleton and in the membrane transport, causing of clinical manifestations at birth and possibly late complications. Lowe Sm and other variants of the disease occur as a result of mutations in the *OCRL* gene mapped on the long arm of the X chromosome, namely, Xq 25 – q26, which comprises 24 exons. The *OCRL* gene encodes protein 105 PIP_2. In classic Lowe Sm mutations occurs more often in exons 8 – 23, and in Dent-2 variant of Sm, more light form, only in the first seven exons. Mode of inheritance is X-linked recessive.
Lowe Sm is a multisystem pathology, mainly involving the eyes, CNS and kidneys. Clinical symptoms of the disease are evolutionary and change over time (Table 1). In all children with this Sm is present at birth bilateral congenital cataract, muscular hypotonia and areflexia, and the kidneys initially can be spared. Renal Sm, described as a Fanconi Sm, can manifest in the first months of life and may be different in severity between subjects. In some cases, it may be asymptomatic or clinical presentation may be unusual. As the disease develops, most often in adolescence, appears and symptoms of NS damage, e. g., delay in neuropsychic and motor development, behavioral disorders with stereotypes, disorders of temperament and aggression. Facial dysmorphisms are often present, i. e., ear positioning abnormalities, protruding forehead, enophthalmos, chubby cheeks, etc. [1, 14].

Characteristic clinical symptoms of Lowe Sm ate those described below.
(1) Ocular symptoms. Was described bilateral congenital cataract which is typical of the disease, present from

Table 1. The appearance of symptoms or complications of Lowe syndrome according to age [2].

No	Age of onset	Simptome
1.	Prenatal	Cataract Increasing of the level of alpha-fetoprotein
2.	Neonatal	Cataract Muscular hypotonia Missing deep TR Increasing CK/LDH Proteinuria of small molecular weight proteins
3.	1 – 3 months	Fanconi syndrom
4.	Infants and toddlers	Glaucoma Growth deficiency Retardation of development
5.	Children	Behavioral problems Corneal scars, keloid Tubulointerstitial fibrosis / glomerular sclerosis
6.	Adolescents	Scoliosis
7.	Adults	Arthropathy Final stage of kidney disease
8.	Without specific age of onset (in any age)	Seizures Platelet dysfunction

birth. Usually, cataract develop in utero, in the early embryonic period, as a consequence of migration changes of the embryonic crystalline epithelium [1, 2, 15] and are diagnosed in 90 – 100% of cases [7]. Another ocular symptom is glaucoma, present in less than 50% of patients, frequently occurs in the first year of life, but can occur later in life. Also, during life in 25% of individuals, often after 5 years, develop the scars and keloids of non-traumatic origin, responsible for primary retinal dysfunction [2, 14, 16, 17]. Other ocular symptoms noted are strabismus, horizontal nystagmus, micro- or exophthalmos, blue sclera, pupil constriction, intraocular pressure may be high or normal. Ocular problems often lead to blindness [7].

(2) Nervous system. Major cardinal symptom, the first suggestive sign, related to pathology of the NS is severe neonatal muscular hypotonia, often with the absence of TR and periostal reflexes [1, 2] which may be of different degree of severity, frequently severe. Hypotonia compromises respiration and can cause serious respiratory problems in the first period of life. Often, hypotonia have an impact caused by retardation in the development of motor skills. Affected children acquire independent skills after the age of 6 – 13 years [2, 17], sometimes autonomous walking occurs after the age of 3 years [1]. Intellectual disability is a common symptom in patients with Lowe Sm. Mental retardation can be of any degree, most often of moderate or severe [9], and about 10% of cases present with a mild mental delay [1]. Some children with Lowe Sm may be with normal neuropsychic development and a normal intellect [2]. However, these children may have behavioral disorders throughout their lives [7]. Another common symptom which occurs in 1/2 of cases are seizures, that are not related to a particular type [2, 14], and some patients – less than 9% – can manifest febrile seizures [18]. From the point of view of psychological development, the course of patients with Lowe Sm evolves with a characteristic pattern of behavioral abnormalities, characterized by disorders of conduct with self- and heteroaggression, irritability, tantrums, obsessive-compulsive behavior, complex repetitive aimless movements etc. [2, 18]. Causes of neuropsychic disorders are demyelination of nerve fibers, gliosis, abnormalities in stratification of the cortex, substantial changes in white substance, cystic brain damage, and deficiency of amino acids. In this Sm it is often possible to detect hypoplasia of the corpus callosum, subarachnoid cysts and hydrocephalus [7].

(3) Kidneys. The main syndrome that characterizes renal disease is Fanconi Sm determined by proximal tubular dysfunction, i. e., generalized proximal tubulopathy [4] and slow progressive renal insufficiency which lead to renal failure to the second or third decade of life [2]. Renal tubular dysfunction may not be present at birth but it may appear in the first weeks to months of life. The severity of kidney disease can vary significantly between patients and tends to worsen with age. Most patients will develop chronic renal insufficiency in the second decade of life, and in the final stage of the disease will require dialysis. Kidney transplantation may be a chance for these patients [1, 2, 4]. Common symptoms of Fanconi Sm include (1) low molecular weight proteinuria, present in all patients what can be used for perinatal diagnosis; (2) generalized hyperaminoaciduria which is occurs in less than 80% of patients with classic Lowe Sm, but only in 1/2 of patients with Dent-2 disease; (3) increased levels of lysosomic enzyme in urine which is suggests impaired absorption of proteins and can cause of tissue damage;

(4) hyperchloremic proximal renal tubular acidosis type II, i. e., decreasing in ammonia production, which differentiates Lowe Sm from other forms of Fanconi Sm; (5) phosphaturia, i. e., loss of renal phosphate, which leads to the development of hypophosphatemic rickets, osteomalacia and pathological fractures; (6) hypercalciuria, which leads to nephrocalcinosis and nephrolithiasis; (7) glucosuria; (8) hypokalemia, commonly related to secondary hyperaldosteronism; (9) defective renal accumulation of 99^{m}-Technetium-dimercaptosuccinic acid (^{99m}Tc-DMSA), which allow to detect of proximal tubular lesions and focal scars [2, 7, 10]. Have been established also other syndromes, namely, bilateral urethrohydronephrosis, obstructive nephropathy, pyelonephritis, and incomplete nephrotic syndrome [7]. Progressive slow renal insufficiency is a hallmark of Lowe Sm that occurs as a result of impaired glomerular filtration rate (GFR) [1, 2, 7]. Progressive renal tubular lesions lead to decreased renal function, glomerulosclerosis and, consequently, to tubulointerstitial fibrosis [2].

(4) *Complications* of Lowe Sm are described below. *Muscle* and *skeletal abnormalities* are common manifestations. Muscle hypotonia leads to joint hypermobility, while limiting of movements contributes to the development of contractures and osteopenia [1, 2]. *Osteopenia* is present in almost all patients with Lowe Sm and may worsen as a result of untreated acidosis and loss of renal phosphate [19]. Other complications of the disease are *rickets* and *pathological fractures*. Over the course of life, half of patients develop *scoliosis* with progression after puberty. Other symptoms described include *cryptorchidism*, which should be treated with hormones or, if necessary, surgically [1, 2, 14, 17]. Are noted also *tenosinovitis*, *arthritis* and *arthropathy* [20], more often reported in patients over 20 years of age [17]. The following clinical manifestations are also described, namely, *palmar* and *plantar fibrosis*, *focal nodules*, *edema of the joints*, *ankles* and *interphalangeal* and *metacarpal* joints, subsequently with flexion *contractures* and, ultimately, bone *fractures* [2]. A characteristic symptom is *severe retardation of growth* in the postnatal period [2], so these children have an average height below the third percentile until the age of 3 years, and further delay in the development of puberty [21]. *Oral* and *dental* manifestations include enamel hypoplasia, dysplastic dentin and delayed teething, associated with eruptive cysts [22]. *Benign cystic lesions* in the skin and large epidermal *cysts* located on the scalp, possibly related to increased extracellular concentrations of lysosome enzymes [23] have been reported in several patients.

For **confirmation of the diagnosis** of Lowe Sm is important the presence of clinical signs (Table 1), confirmed by molecular-genetic analysis. Cardinal symptoms are (1) ocular signs, i. e., congenital bilateral cataract present at birth; (2) symptoms of NS disorders, i. e., hypotonia and neonatal areflexia, delaying in psychomotor development and stereotypical behavior in adolescence and (3) kidney involvement, i. e., Fanconi Sm, which may occur in the first months of life and varying in severity between individuals.

Molecular-genetic analysis can confirm diagnosis. The *OCRL* gene is mapped on Xq25-26 and comprises 24 exons 52 kb in length. The encoding region includes exons 1 to 23. More than 200 mutation have been described in the *OCRL* gene, but in some patients suspected for Lowe Sm (10 – 20%) no mutations were found. In classical Lowe syndrome mutations are more common in exons 8 – 23 [24]. There is a genotype-phenotype correlation in Lowe Sm (classic phenotype) / Dent-2 disease (milder phenotype), which correlates with the clinical severity of the disease. Recently was reported a patient with p.Asp523Asn mutation who presented with cerebral and renal manifestations of Lowe Sm, while cataracts were first observed at the age of 10 [25]. Mutations de novo are reported in 30% of affected men. Thus, in female carriers there are mutations of *OCRL* gene what fact confirms the need for genetic counseling of pregnant women suspected of such a problem, in particular, in families with a known cases of *OCRL* gene mutations [2]. Studies confirms that carrier mothers in 25% have the possibility to give birth to an affected boy, in 25% – a carrier daughter, in 25% – an unaffected boy and in 25% – a non-carrier girl. Mothers of boys with Lowe Sm should undergo prenatal testing for possible germinal mosaicism. If necessary, the prenatal diagnosis, i. e., prenatal screening, is recommended using amniocentesis and evaluation of PIP_2 activity in cell culture of amniocytes [11]. Another marker that can be determined in maternal serum and amniotic fluid is alpha-fetoprotein [2, 26], or detecting of fetal cataract using ultrasonography [27]. Prenatal diagnosis should be ensured for all affected families, determining enzyme activity in amniotic fluid at 9 – 11 weeks of pregnancy and direct molecular testing for *OCRL1* gene mutations at 15 – 20 weeks of pregnancy.

Differential diagnosis of Lowe Sm is possible from the age of newborn with congenital infections, especially rubella, peroxisomal disorders, i. e., Zellweger-related disorders, mitochondrial diseases, congenital myotonic dystrophies or congenital myopathy (muscular – ocular – cerebral pathology), Nance-Horan Sm, Smith-Lemli-Opitz Sm; all of the above syndromes may be associated with ocular problems and hypotonia from birth. To review all these diagnoses it is important to exclude renal involvement [1]. Congenital rubella in fetuses exposed from the mother who contracted the virus during pregnancy is characterized by abnormalities of the heart, NS, eyes and ears. Zellweger-related disorders are characterized by hypotonia, feeding difficulties and abnormal facial characteristics, as well as impaired vision and hearing, seizures and liver dysfunction. Nance-Horan Sm, i. e., cataract-dental Sm, is characterized by tooth abnormalities and congenital cataract. Smith-Lemli-Opitz Sm is characterized by growth retardation before and after birth, microcephaly, developmental disability,

multiple anomalies, including facial dysmorphism, occasional congenital cataract, heart anomalies, defects of fingers, i. e., polydactyly, and malformations of genital organs, i. e., genital hypoplasia in men.

Therapy of the patients with Lowe Sm is directly related to the clinical and investigational data present from birth (Table 2).

Table 2. Basic clinical and investigational data suggestive for Lowe Sm

Affected organ	Symptoms
Eyes	Single- or bilateral congenital cataract, congenital glaucoma, bilateral buphthalmos, nystagmus, divergent stabismus, increased intraocular pressure, corneal opacity, chorioretinal foci, decreased retinal photosensitivity, lack of photoreaction, exophthalmos, blindness. Prenatal USG – degeneration of the primary fibers in posterior lens. Visit of ophthalmologist and ophthalmoscopy are indicated. Surgery.
Central nervous system (CNS)	Progressive retardation in psychomotor development, hydrocephalus, generalized hypotonia, flaccid tetraplegia, psychological developmental disorders. Brain MRI: ventriculomegaly, lesions in periventricular and deep white matter, hypogenesis of the corpus callosum, cerebral atrophy, cerebellar hypoplasia, pachygyria, polymicrogyria, aberrant neuronal migration, subependimal cysts, localized in the white matter and periventricular. Increasing serum levels of LDH, CK and aminotransferases.
Kidneys	Hypophosphatemic rickets, metabolic acidosis with phosphaturia and hypokalemia type II, glucosuria, hyperaminoaciduria. Obstructive nephropathy, pyelonephritis, uterohydronephrosis, incomplete nephrotic syndrome, renal failure. Serum and urinary ion levels Ca, Ca+, alkaline phosphatase, K, Na, Cl, P, Mg, creatinine and BUN, P and Ca excretion, calciuria, are evaluated. Renal USG is indicated to evaluate the size of kidneys bilaterally.

Molecular-genetic analysis is essential for the confirmation of Lowe Sm [28, 29]. The authors of one study conducted a genotype-phenotype analysis of mutations resulting in congenital glaucoma, i. e., the ocular phenotype of Lowe Sm. The authors presented two models of mutation analysis in 2 patients with Lowe Sm, i. e., sequence of *OCRL1* gene using DNA from keratinocytes. In the first patient, a new mutation located in exon 8 (c.739-742delAAAG, p. Lys192Lys fsX8) was found, revealing the change in the translation size of the OCRL protein from 901 to 200 amino acids. In the second patient, the sequencing revealed mutation at the tail of exon 14 of the *OCRL* (c. 1595-1631del, p. Tyr477Leu fsX), which caused a change in protein length to 506 amino acids [8].

Treatment of patients with Lowe Sm is complex. Hypotonia can lead to feeding problems, for which the application of nasogastric tube and standard procedures for gastroesophageal reflux are necessary. To ensure optimal vision correction, cataract should be removed early. Glaucoma required medication or surgery. Fanconi tubular dysfunction is treated with oral supplements of sodium bicarbonate, potassium, or citrate. Dosages must be calculated individually. Often, it is necessary to correct metabolic acidosis and hypophosphatemic rickets with calciuria and phosphaturia using calcium formulations, active metabolites and formulations of Vitamin D [2]. In infants and children of smaller age group oral supplements should be adjusted promptly. Infant rickets should be treated using oral supplements of phosphate, calcitriol and vitamin D, avoiding excessive amounts of vitamin D as it may increase renal calcium excretion. Treatment should be geared towards maintaining serum calcium and parathormon levels [1]. The diet is designed to ensure restriction of sodium chloride and galactose, but without restrictions in fluid intake [7]. Sometimes intravenous infusions may be needed [1, 7]. Surgical treatment for cataract removal should be early, to ensure prophylaxis of amblyopia and, rarely, goniotomy for glaucoma. Sometimes cataract relapses are possible [2, 16]. The ophthalmological examination should be performed frequently to detect glaucoma on early stage. Glasses are recommended in older children who have acquired visual abilities to improve visual function and psycho-social skills [1, 2, 7, 17]. Symptomatic therapy aims to stimulate metabolic processes in the CNS, to normalize indicators of physical development, to improve the status of the cardiovascular and muscular systems. Courses of Nootropil, Encefabol, Pantogam, B-group vitamins and antioxidants [7] are recommended. Renal tubular acidosis should be recognized and treated promptly in the child. Correction is required according to the bicarbonate/citrate scheme, i. e., sodium and/or potassium citrate and sodium bicarbonate in variable doses and combinations, calcium formulations, phosphate complex, active vitamin D metabolites, prescribed under the control of calcium levels and phosphates in serum and urine [7]. Similarly, serum bicarbonate levels should be kept below 20 mEq/l, doses may vary between 1 – 8 mEqKg/day, being divided into at least three separate doses. Potassium citrate helps prevent nephrocalcinosis, while it tends to reduce renal calcium excretion. Sodium intake should be adjusted according to the degree of salt loss by renal way. Additional fluids are given to patients with polyuria. Peritoneal dialysis or considering kidney transplant are indicated in chronic renal insufficiency [1]. Areflexia is a particular condition that does not require treatment. Seizures require treatment with specific drugs. Behavioral problems and obsessive-compulsive disorder can be treated with drugs such as neuroleptics,

antidepressants, stimulants and benzodiazepines, which are only partially effective. Promising results with Clomipramin, Paroxetine and Risperidone [1, 2, 17] have been reported. To improve growth is indicated growth hormone therapy [30]. Rickets should be treated correctly to maintain joint mobility, aiming of prophylaxis of osteopenia, pathological fractures and contractures. To prevent scoliosis are required standardized therapies, including wearing a corset and, if necessary, surgery [1]. To correct orthodontic complications, orthodontic therapy is required [31]. Hormone treatment is indicated in cryptorchidism, and surgery is rarely necessary [1]. There are no data in the literature on the treatment of nephrocalcinosis in Lowe Sm. Thiazide diuretics can be used to reduce calcium excretion in patients with Dent-1 [32]. Using of diuretics in renal potassium losses should be harnessed contrary to the risk of hypokalemia and hypovolemia. Potassium citrate may be useful as it corrects both hypokalemia and metabolic acidosis and has been shown to delay nephrocalcinosis in an animal model with Dent-1 disease [33]. Rehabilitation therapy is necessary for the treatment of hypotonia and its complications. Appropriate psychological, pedagogical and occupational programmes foster learning capacity and preventing behavioral crises during adolescence [1, 2, 17]. Early intervention programs are recommended that include physical therapy, occupational therapy, speech and language therapy, special education services and services for vision impaired people, which should start from childhood. Patients with Lowe Sm need to be monitored for life by a team of medical professionals, including nephrologist, ophthalmologist, pediatric neurologist, pediatrician, nephrologist, geneticist, orthopedic, dentist, dermatologist, imagist, nutritionist, endocrinologist, child development specialist, etc.

Prognosis and quality of life.

Patients may died in the first years of life as a result of kidney disease, hypotonia or increased susceptibility to infectious diseases. The most common causes of death are: respiratory diseases, seizures and sudden death. Most often, death occurs between the end of the second decade and the beginning of the fourth decade of life. The most remote cause of death is renal tubulopathy, progressively evolving into renal failure [1]. The risk of death in children who do not receive treatment is caused by cerebral and pulmonary edema, infectious complications, and progression to terminal uremia [7]. The quality of life depends on the duration of mental and renal manifestations, being related to blindness, mental retardation, severe rickets and muscular hypotonia, which limit mobility of the child [1, 2, 7, 17, 33].

In this study we presented a clinical observation on a boy of small age who was diagnosed with Lowe Sm. He presented congenital cataracts, severe muscular hypotonia, delay in neuropsychic and physical development. Renal failure develops on the very early stage of disease manifested with peripheral edema, metabolic acidosis and proteinuria, phosphaturia, hypercalciuria, hypokalemia, which is suggestive for the disorder of renal tubular reabsorption of phosphates and the increase of the FeP index. These clinical and laboratory findings were suggestive of Lowe syndrome. Sequencing revealed a mutation c.741G>T in exon 9 of the *OCRL1* gene, resulting in an amino acid substitution p.(Trp247Cys). Such mutations are described in the literature and represent a known pathogenic variant [34]. The patient was treated according to the treatment guide. The disease evolved progressively with renal failure, neurological complications and pulmonary edema, against the background of respiratory infection, which caused death at a young age.

Conclusions.

In this study presented a clinical case of Lowe syndrome in a boy of small age who had an unfavorable prognosis with single-gene X-linked recessive pathology, who has been diagnosed mutation in exon 9 of the *OCRL1* gene c.741G>T p.(Trp247Cys), which caused a multiorganic pathology involving the eyes, nervous system and kidneys. Congenital generalized proximal tubulopathy or Fanconi Sm progressed to the development of renal failure, cerebral edema, pulmonary edema and seizures, on whose background the child died. By presenting this case we demonstrated the existence of a variant of Lowe Sm which was characterized by a severe form of oculocerebrorenal syndrome. Over the years, much progress has been made in understanding the functions and role of the *OCRL-1* gene in cellular metabolism and understanding manifestations from many organs and systems. Possibly, the factors that determine the severity of the disease are related to the specifics of the mutation, age, concomitant diseases and complications. Clinical breakthroughs and identification of mutations in the *OCRL* gene can help genetic counseling and improve patient therapy.

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