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LOWE-BICKEL SYNDROME IN CHILDREN

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Abstract:

Lowe-Bickel syndrome is a rare hereditary disease that affects various organs and systems. Three main signs of the disease are identified: congenital cataract, profound intellectual disability, and kidney pathology leading to slowly progressive renal failure. The cause of Lowe syndrome is mutations in the OCRL gene, which encodes one of the enzymes involved in the metabolism of inositol phosphates. Mutations in this gene are also associated with Dent's syndrome, which has overlapping manifestations with Lowe syndrome but expressed to a lesser degree. The disease follows an X-linked pattern of inheritance, which is why it primarily affects males. This paper discusses the clinical features, treatment, and outcomes of the Lowe syndrome in children. We describe the observation of two boys from the same family with Lowe syndrome, whose kidney involvement was characterized by Fanconi syndrome.

Keywords: children, Lowe-Bickel syndrome.

Lowe syndromeis a rare X-linked recessive disease in humans that belongs to the group of ciliopathies. In 1952, U. Lowe, M. Terry, and E. Lachlan described this congenital disease characterized by neurological, renal, and ocular anomalies in detail [1,6]. In the global literature, the disease is known as "oculo-cerebro-renal syndrome," or Lowe syndrome (Lowe), Lowe-syndrom, OCRL [5]; less commonly as Lowe-Terry-McLachlan syndrome, Lowe-Bickel syndrome, eye-kidney-brain Fanconi syndrome, and very rarely as Ziyl syndrome. The cause of Lowe syndrome is a congenital deficiency of the enzyme phosphatidylinositol-4,5-bisphosphate 5-phosphatase, resulting from mutations in the OCRL gene [5]. This gene is mapped to the long arm of the X chromosome (Xq25-q26). Therefore, the disease manifests only in males, while females are merely carriers. It occurs with a frequency of 1 in 500,000 live births.[1,2,5].

CLINICAL PRESENTATION. The diagnosis of Lowe syndrome is not difficult. Clinical symptoms are associated with renal, neurological, and ocular disorders. Initial symptoms of the disease are often identified in infancy and preschool age, but they may not always be fully expressed, leading to a wide age range for the description of the syndrome, from 1 month to 19-22 years. Only boys are affected. Patients typically have fair skin, light eyes, blue sclerae, large ears, and a saddle-shaped nose. Muscle hypotonia is characteristic. Children experience significant delays in physical development (both in weight and height). Patients may exhibit episodes of hyperthermia, obesity or hypotrophy, anorexia, constipation, rickets-related skeletal deformities, and often fractures.A characteristic symptom of the disease is intellectual disability of varying severity. The diagnosis of oculo-cerebro-renal syndrome can be compatible with normal intelligence; however, such patients are distinguished by their inability to behave appropriately, stubbornness, and temper outbursts. This likely defines the characteristic behavioral phenotype of the patient.

Outbursts of anger, stubbornness, and behavioral stereotypes should not be considered solely as a consequence of visual impairment, motor difficulties, or intellectual disability, but rather as a specific effect of the OCRL gene on the central nervous system. In affected individuals, episodes of anger and increased hair rigidity are associated with uncompensated metabolic acidosis and have been observed to resolve with pharmacological compensation of the acidosis. Pathological examination reveals demyelination of nerve fibers, gliosis, and disruption of layering.

Ocular Changes. In 90-100% of cases, congenital cataract is diagnosed, either bilateral or unilateral, with glaucoma being the second most common finding. These conditions often occur in combination. External examination may reveal strabismus, horizontal nystagmus, micro- or exophthalmos, blue sclerae, and constricted pupils. Intraocular pressure may be elevated or normal. Ocular changes frequently lead to blindness.

Renal Changes. Tubulopathy manifests as generalized hyperaminoaciduria, moderate proteinuria, intermittent glucosuria with normal glycemia, phosphaturia, calciuria, hypophosphatemic rickets, and proximal hyperchloremic metabolic acidosis with hypokalemia. Renal symptoms are due to proximal tubulopathy and correspond to those seen in Fanconi syndrome.Proteinuria, present since infancy, is initially

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tubular. Subsequently, due to glomerular involvement, proteinuria increases, leading to the development of a full nephrotic syndrome. Renal tubular acidosis is caused by impaired bicarbonate reabsorption in the proximal tubules and, as the disease progresses, by impaired acidification of urine in the distal tubules.We observed a 7-year-old boy, Patient X, who was admitted with complaints from his mother regarding polyuria, polydipsia, and unexplained fever. From the medical history, the child was from a third pregnancy and birth that proceeded without apparent pathology, from a consanguineous marriage (the father and mother are first cousins). Until now, the child had experienced anemia of unclear etiology, for which he had been treated multiple times at his place of residence. These complaints had persisted for the past year without any examination or treatment. Upon examination, the boy appeared to have a proper physique but was undernourished. There were no abnormalities in skeletal musculature. Notable features included light skin, light-colored eyes, and blue sclerae. Constant horizontal nystagmus and divergent strabismus were observed, along with decreased vision. The mucous membranes were clean and pale. An ophthalmologist's consultation revealed tapetoretinal abiotrophy and optic nerve atrophy. Nystagmus and divergent strabismus were also noted. No abnormalities were found in the internal organs. Neurologically, the boy was withdrawn, reluctant to engage in contact, and provided monosyllabic responses. He was very attached to his mother. Intelligence was preserved. Blood analysis showed significant anemia: red blood cells - 3.0, hemoglobin - 82 g/L, hematocrit - 0.8, leukocytes - 7.7, neutrophils - 0, segmented neutrophils - 46, eosinophils - 3, lymphocytes - 47, monocytes - 4, ESR - 5 mm/hour. Urinalysis indicated traces of protein, leukocytes, and erythrocytes. In the Nechiporenko test: leukocytes - 3000, erythrocytes - 1000. In the Zimnitsky test, urine relative density was 1002-1004, with a day-to-night diuresis ratio of 1:1. The urine showed glucosuria, aminoaciduria, calciuria, and metabolic renal tubular acidosis.

Daily diuresis is 5 liters (corresponds to the amount of liquid drunk). In the blood serum, the content of urea is 6.2 mmol / l, creatinine is 0.05 mmol / l. Total protein is 74.5 g / l. Calcium is 2.0 mmol / l, potassium is 3.0 mmol / l, total cholesterol is 7.1, triglycerides are 1.3. HbSAg is negative. ASLO is 250, CRP is negative, blood sugar is 5.0 mmol / l. Body temperature is constantly 38.0-38.5 C.Renal ultrasound and MRI revealed left-sided hydronephrosis. Additional medical history revealed that the family's second child, 12, had been institutionalized at the age of 8 due to congenital glaucoma and horizontal nystagmus. A follow-up examination revealed severe anemia, refractory to antianemic medications.A more thorough examination also revealed renal pathology (secondary contraction of the kidney) and signs of renal failure. For this reason, the child has been receiving hemodialysis sessions twice a week for the past year. Neither boy showed any signs of significant mental retardation.

The family's first child also suffered from severe iron deficiency anemia for a long time and died of anemia of unknown etiology at the age of 12. Regular administration of indomethacin at a dose of 0.025 mg and hypothiazide at a dose of 0.025 mg helped normalize body temperature, reduce polydipsia, and reduce polyuria to 1.5 liters per day.The boy was discharged for outpatient treatment in satisfactory condition. However, a year later, the patient was readmitted in serious condition with signs of renal failure: serum urea 35.0 mmol/L, creatinine 0.4 mmol/L, severe anemia (Hb 60 g/L). Urine proteinuria (0.132% protein, isolated leukocytes and erythrocytes) and blood pressure 120/80.The vision changes have not progressed. The child is also currently on hemodialysis.

Thus, two male members of the same family share the same condition: Lowe syndrome. The prognosis for this disease is poor. Death is possible due to secondary infectious complications, acidemic coma, pulmonary edema, cerebral edema, and end-stage renal failure.

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