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KIDNEY TUBULAR ACIDOSIS: CAUSES, SYMPTOMS, DIAGNOSTICS, TREATMENT (LITERATURE DATA AND THE AUTHORS’ OWN OBSERVATIONS)*

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The article presents a literature review on the etiology, pathogenesis, clinical presentation, diagnosis and therapy of renal tubular acidosis in children, as well as our own 9-years-long observation of a child with this disease. Clinical manifestations from the initial symptoms starting at 3.5 years of age in the form of recurrent acetonemic states, episodias of dehydration with fever, and polyuria were analyzed. Further dynamics of symptoms was traced in the form of severe weakness in the legs, rapid fatigue, qait disturbance, inability to running, jumping, X-shaped deformity of the lower extremities. The literature data on the erroneous prescription of massage to a child with rickets is presented. Analysis of these mistakes was carried out and the positive dynamics was demonstrated in the clinical condition and development of the child in response to adequate treatment after a correctly made diagnosis. The differential diagnosis was carried out with Fanconi’s syndrome, proximal RTA, hyperparathyroidism, primary hyperoxaluria. Molecular genetic study permitted to exclude cystinosis. Such children require constant monitoring and treatment by specialists, primarily from the point of view of preventing the renal failure progression. Knowledge of the features of renal tubular acidosis course will significantly help the clinicians in making the diagnosis, prescribing consultations of narrow specialists, as well as choosing an adequate treatment tactics.

Key words: renal tubular acidosis type I, renal tubular acidosis type II, children.

Diagnosis of tubulopathy in childhood is a complicated task, whose solution is possible with knowledge of clinical polymorphism of the disease, the features of its onset and course, as well as a thorough diagnostic search. Difficulties in the early diagnosis of tubulopathy are associated both with a rare occurrence of individual forms, and with a significant similarity of clinical symptoms, which causes frequent diagnostic errors.

Renal tubular acidosis (RTA) is a clinical-laboratory symptom complex, resulting from a defect in the reabsorption of bicarbonates in the proximal tubules or impaired acidogenesis in the distal tubules, characterized by metabolic acidosis and a decrease in the ability of the kidneys to acidify urine. One of the main RTA signs is the bone skeleton changes resembling those of rickets [1, 2, 3]. There are 4 types of primary (hereditary) and secon-
The aim of the research is to familiarize a wide circle of pediatricians with a 9-year observation of a child with renal tubular acidosis (RTA) and therapeutic tactics that have overcome the lag in the child’s development and eliminated most of the symptoms.

Below is a case from our own clinical observation.

Girl E., b. 11.2010 (4 years 10 months) was admitted to the children’s neurological department of the Mariupol Territorial Medical Association “Child’s and Woman’s Health” on September 21, 2015 with complaints of weakness in the legs, rapid fatigability, gait impairment, inability to run, to jump.

Life history: early anamnesis without specific findings.

The patient started walking from the age of 10 months. The hereditary history is not burdened.

Present history: at the age of 3.5 years (May, 2014), the child was treated at the children’s infectious ward of City Hospital No. 4 in Mariupol due to food poisoning. After discharge from the hospital, polyuria, recurrent aconitonic conditions, and episodes of fever developed. In spring 2015, (at the age of 4.5 years), parents paid attention to a change in gait, weakness in legs, rapid fatigability, the girl stopped running and jumping. These complaints progressed. The significant levels of pain in the lower extremities occurred, their X-shaped deformation was formed. There was a loss in weight (at the age of 4 years the weight was 18 kg, at the age of 5 - 14 kg, the normal weight at the age of 5 being 20.0-20.5 kg), delayed growth (at 3 years of age the body height was 104 cm, at the age of 5 years - 104 cm, the required increase in growth being 5-6 cm per year).

Neurological status: muscular tone is sharply reduced in the limbs, more in the legs. The child lags behind in height and weight. There is a pronounced X-shaped deformation of the lower extremities, flat valgus feet. The lumbar lordosis is smoothed. The gait is paretic, waddling, the child cannot jump, run, walk up the stairs. An electromyogram (EMG) was taken at the department: diffuse neuronal level of disturbances. A study of the spinal muscular atrophy genes (SMN1, NAIP) was carried out at the regional medical and genetic center; no mutations were detected. Magnetic resonance imaging (MRI) of the brain and the spinal cord was performed: no damage to the brain and the spinal cord was detected.

The child was consulted by a professor at the Department of Pediatric Neurology of the Kharkov Medical Academy of Postgraduate Education, Dr. habil. in Medicine Evtushenko S.K. Diagnosis: Mitochondrial encephalopathy with lower paraparesis, with impaired walking function. Recommendations: EMG in dynamics, blood lactate study, for treatment - cerebrum compositum, co-enzyme compositum.

The child’s condition has significantly improved against the background of ongoing metabolic therapy. However, after massage courses in the regional children’s bone-tuberculosis sanatorium in Mariupol and at home, a significant health deterioration was noted. After the massage courses, the girl had difficulty in walking. Since March 2016 (5 years 3 months), the girl almost stopped walking unassisted. On 19.03.16 EMG showed that the myopathic pattern of disturbances prevailed. On 12.11.15 blood lactate increased to 8.10 mmol/L, by February 2016 it was normalized (on 24.02.16 it was 2.09 mmol/L, the normal value being 0.5-2.20 mmol/L). The girl was consulted at Kharkov Specialized Medical Genetic Center (HSMHC), where she was examined in May 2016: changes in ketosis metabolites and a de-
The study revealed hypocalcemia - 1.28 mmol/L (N - 2.25-2.75 mmol/L), hypophosphatemia - 0.75 mmol/L (N - 1.45-1.78 mmol/L), increased alkaline phosphatase (ALP) - 897 U/L (N - up to 297 U/L). Subcompensated acidosis was detected - pH - 7.29 (N - 7.36-7.42), a decrease in the bicarbonate blood anion up to 13.8 mmol/L (N -21-26 mmol/L) and a deficiency of buffer bases - "N-11.2 mmol/L *(N - 2 mol/L) were revealed. In daily urine, hypercalciumia was observed - 4.7 mmol/day (N - 0.5-3.8 mmol/day), alkaline reaction of urine - urine pH was 8.1 (N - 5.5-7.0). Consultations of specialty physicians were held. Neurologist: Myopathic syndrome against the background of the underlying disease. Orthopedist: Osteoporosis, epimetafysyeal dysplasia due to tubulopathy, tibia valga deformity. Geneticist: To exclude a congenital metabolic disease, blood and urine tests for the amino acid spectrum are recommended. Ultrasound study of the kidneys: the kidneys are enlarged: right - 9.6x4.0 cm, left - 10.6x4.3 cm. The renal parenchyma is indurated, the pyramids contours are indurated, thickened. Multiple calcifications up to 5 mm are visualized in the projection of the pyramids. Ultrasound images of other abdominal organs are without abnormalities. Ultrasound images of the thyroid and parathyroid glands are without structural changes. Plain abdominal radiography: Phenomena of nephrocalcinosis. Molecular genetic research (Institute of Molecular Biology and Genetics, Kyiv) dated 20.10.2015: No mutations in the genes of spinal muscular atrophy (SMN1, NAIP).

The following diagnosis was made: tubulopathy. Renal tubular acidosis type I. Chronic renal failure (tubular).


The conducted therapy included diet, soda-buffer, alpha-D3-Teva, calcium-D3 nycomed, magnerot, dimephosphon, osteogenon, physiotherapy exercises (exercise therapy), braces (removable joint-immobilizers).

Promotion. In October 2016, the girl sustained a fracture of her right femur during a game.

During the follow-up examinations at the nephrology department of Kyiv City Clinical Hospital No. 1 09.04. – 15.04.2017 and 13.12. – 18.12./2017, in the blood biochemical analysis indices of potassium, calcium, phosphorus, alkaline phosphatase, creatinine were normalized. The glomerular filtration rate was slightly decreased - 103 ml/min (N -133 ± 27 ml/min /m² of body surface), blood acidosis was detected - pH - 7.26; decrease in the bicarbonate blood anion to a lesser extent than before - to 19.0 mmol/L (N -21-26 mmol/L) and deficiency of buffer bases to "7.9 mmol/L (N - "4.2 mmol/L)". The daily fluctuations in the specific gravity (SG) in the urine analysis according to Zimnitsky are insufficient - 1011-1014; Ca in the daily urine was within normal limits - 2.8 mmol/day.

Ultrasound study of the kidney retains signs of nephrocalcinosis. The genetic study of 13.12.2017 at the "EUROLAB" laboratory by direct automatic sequencing of the nephropathic CTNS cystinosis gene coding sequence revealed no pathogenic and probably pathogenic variants. Recommendations are given: diet, long-term soda-buffer, alpha-D3-Teva, calcium-D3-nyomed. Courses of magnerot, avcantar (Lit), dimephosphon, osteogenon (then aleander), blemaren, smart omega for children were prescribed. Growth hormone (somatin) was prescribed: s/c 4 IU once a day, 5 days a week.

From 08.06 to 23.06.2017 the girl was treated in the traumatological department of Kyiv City Clinical Hospital No. 1.

Shortening of the left lower limb is detected. Misaligned pelvis on the right. Coxa valga on the left. Valgus deformity in both legs of a severe degree. Valgus deformity of the feet.

In June 2017, surgical correction of the valgus deformity in both legs was performed - medial epiphysiodesis of the femoral lower third, upper third of the tibia from 2 sides using titanium plates. In February 2018, screws were removed from the lower third of both femurs and the upper third of the tibia.
The child was examined at the Orphan Diseases Center of the Children's National Specialized Hospital "OKHMATDET" on 03.12.2018. (7 years 3 months):

1. Urinary screening: test for protein is negative; Feling test - negative; Sulkowitch test - (+); test for hyperaminoaciduria is negative; Benedict test is negative; test with dinitrophenylhydrazine (DNPH) - negative; Obermeyer test - negative; Legal test - negative; test for cystine - negative;

2. TLC of carbohydrates in the urine is within the norm; glucosaminoglycans (GAG) in the urine of CPC (cetylpyridinium chloride) - 45/213 from CPC/g of creatinine.

3. Tandem mass spectrometry (TMS) of amino acids and acylcarnitines in the blood: the level of the studied metabolites is within normal limits.

4. On 19.07.2017 HPLC of amino acids in the urine was performed: increased concentration of arginine, cystine, lysine was detected. HPLC of amino acids in the blood: generalized aminoacidemia.

On 18.12.2017, HPLC of amino acids in the urine showed the following: decrease in the concentration of glycine, threonine, alanine, tyrosine, phenylalanine. HPLC of amino acids in the blood revealed no amino acid concentration disorders in the blood.

Geneticist's consultation: Tubulopathy, progressing with skeleton disorders. This condition requires differential diagnosis with cystinosis, renal tubular metabolic acidosis, De Tony-Debre-Fanconi disease. There are no data testifying to the hereditary diseases of amino acid, acylcarnitines metabolism.

The last hospitalization in the nephrology department of Kiev City Clinical Hospital No. 1 from 04.11. to 08.11. 2019. Examination data: potassium, sodium, calcium, ionized calcium, phosphorus, chlorine, PTH, alkaline phosphatase, glucose, creatinine, 25-OH vit. D3 is normal. Blood acidosis persists - pH 7.26 (N - 7.36-7.42) with a slight decrease in the bicarbonate blood anion to 19.9 mmol/L (N -21-26 mmol/L); and the buffer bases deficiency - "- 7.6 mmol/L" (N - "± 2 mmol/L"), a decrease in glomerular filtration to 100 ml/min. (N - 133 ± 27 ml/min/m² of body surface), insufficient fluctuation in the urine SG according to Zimnitsky - 1008 - 1010.

Diagnosis on discharge: First degree chronic kidney disease. Renal tubular acidosis type I. Fanconi's syndrome. Chronic renal failure (tubular). Nephrocalcinosis. Osteoporosis. The state after the operation of correction of the both legs tibial valgus deformity, medial epiphysiodesis of the hip lower third, upper third of the lower leg from 2 sides using titanium plates.

Against the background of the therapy, a significant positive dynamics is noted. Normalized levels of calcium, phosphorus in the blood and urine are observed. The level of creatinine, blood urea is within normal limits. Changes in blood acid-base balance (ABB), a low level of glomerular filtration rate (GFR), insufficient fluctuation of the urine specific gravity in the sample according to Zimnitsky test are preserved. Signs of nephrocalcinosis according to renal ultrasound study do not increase. During the first 6 months of therapy, growth hormone (somatine) has increased by 12 cm, the girl gained 5 kg in weight. Today, the child is 9 years old, the height is 130 cm, the weight is 26 kg, the normal weight according to the centile tables is 25.5-32.0 kg, the normal height according to the centile tables is 128.5-136.5 cm.

The girl runs, jumps, dances, and is active. There is no weakness in the legs, fatigue, pain in the lower extremities. There are no complaints. The patient attends school. She continues to receive soda-buffer, growth hormone, alpha-D3-Teva (detrimax); receives courses of magnerot, ayzvantar (L-carnitine), dimephosphon, osteogenon (aleander), blemarin, smart omega for children. Calcium preparations are withdrawn, the dose of alpha-D3-Teva is reduced.

The above case report demonstrates a rare hereditary disease of type I renal-tubular acidosis. In our patient, the disease manifested itself at the age of 3.5 years, which was manifested by recurring acetonemic conditions, episodes of dehydration with fever, and polyuria. However, only 1.5 years after the disease manifestation, the complaints of sharp weakness in the legs, rapid fatigability, impaired gait, inability to run, jump, the X-shaped deformation of the lower extremities were the reason for a more thorough examination.
The prescription of massage was erroneous, and it led to deterioration in the child’s condition. According to the published data, the prescription of massage for rickets-like diseases is only indicated with normalization of phosphorus-calcium metabolism and disappearance of acidosis signs [2, 7]. Insufficient weight gain, growth retardation, pronounced later (after 3.5 years of life), ricketsy manifestations in the form of the bent lower extremities were ignored.

The neurological pathology was initially excluded at the children's neurological department of the Mariupol Territorial Medical Association “Child's and Woman's Health” due to the presence of severe muscular weakness and impaired walking. Spinal muscular atrophy, organic damage to the brain and the spinal cord were excluded. Considering changes in the bones (late rickets deformity of the lower extremities), muscles (severe muscular weakness), urinary system (polyuria, constant alkaline reaction of the urine, the presence of nephrocalcinosis), the child was suspected of tubulopathy, and therefore the child was referred to the children's nephrology department of Kyiv, where metabolic acidosis, metabolic disorders of phosphorus and calcium were detected. To identify distal RTA, the differential diagnosis was carried out with Fanconi syndrome (there was no glucosuria and aminoaciduria), with proximal RTA (there was no acidification of urine - pH <5.5 in the presence of nephrocalcinosis).

After molecular genetic studies, cystinosis was excluded. In our case, we also excluded hyperparathyroidism, primary hyperoxaluria, the child did not receive nephrotoxic drugs. Adequate RTA therapy gave positive results in the form of a complete leveling of the child's lagging in the weight, growth and development, and significantly improved the patient's quality of life. Such children require constant monitoring and treatment by specialists, especially in terms of preventing the renal failure progression. Each observation of a child with renal tubular disorders permits to expand the clinical concept of these diseases.

Fig. 2. Photo No. 4-6 – August, 2019 (8 years 9 months).

References