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Diagnostics and Differential Diagnostics of Urolithiasis and Renal Form of Primary Hyperparathyroidism in Children

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Annotation: It has been established that differential diagnostics of renal form of primary hyperparathyroidism (PHPT) is based on detection of phosphorus-calcium metabolism disorders, the most sensitive and effective is carrying out of loading tests. For the first time it is shown that renal failure in patients with RF PHPT aggravates the imbalance of hormones regulating calcium homeostasis, and indicates a marked impairment of the functional activity of the parathyroid glands (PGG). Kidney dyMFunction in children with USD had no significant effect on the level of calcium-regulating hormones. Diagnostic criteria and differential diagnostics of RF PHPT have been scientifically substantiated; as a result, a diagnostic algorithm of USD and RF PHPT has been created.

Keywords: children, urolithiasis, primary hyperparathyroidism (PHPT), renal form (RF), mixed form (MF), urinary stone disease (USD).

Introduction. Urinary stone disease (USD) of hyperparathyroidism genesis in children is rare and rather unstudied, and the diagnosis of PHPT is difficult and requires comprehensive investigation [2, 9,11]. The available data on PHPT in children are insufficient and do not allow to analyse the etiopathogenesis of this disease [1,4,5.9].

Many factors lead to renal dysfunction and stone formation, one of them is parathyroid hyperfunction . The reasons for the development of primary hyperparathyroidism (PHPT) are not known [3,10,12].

PHPT is a clinical syndrome with characteristic symptoms and signs due to increased production of parathyroid hormone (PTH) by the parathyroid glands(PTG). Hypercalciuria, in the renal form (RP) of PHPT, is due to the toxic effect of excess PTH on the epithelium of the convoluted renal tubules. Hypercalciuria reduces reabsorption of inorganic phosphorus in the renal tubules, resulting in hyperphosphaturia. Inorganic phosphorus is replenished from bone, where it is combined with calcium salts, are also excreted into the blood and then excreted by the kidneys [6, 8,13].

In case of late etiotropic diagnosis, when there are severe destructive changes in the hepatic tissue, unfortunately, full recovery may not occur [7,14]. Therefore, the recognition of PHPT should be early, before the development of severe complications.

Purpose of the study. to develop criteria for differential diagnosis of PHPT and USD in children based on the study of phosphorus-calcium metabolism with stress tests and calcium-regulating hormones.

Subjects and methods of research. As a result of the examination the diagnosis of PHPT was confirmed in 52 children (2.5%) (main group). The comparison group included 54 patients with urolithiasis without PHPT. The study was conducted in the Republican Specialised Scientific and Practical Medical Centre of Endocrinology and the clinic of the Tashkent Paediatric Medical Institute.

The age of children was from 3 to 15 years. They were followed up for 2-5 years.

Instrumental methods of examination (review and excretory urogram, ultrasound of kidneys and urinary tract) made it possible to characterise and determine the location of concrements in the kidneys and urinary tract in the examined children.

Results and their discussion. The obtained data indicate that the severity of clinical symptoms in children with RF PHPT is determined by the disorder of calcium-phosphorus metabolism (calcium and inorganic phosphorus in blood and daily urine) and imbalance of calcium-regulating hormones (PTH and vitamin D), as well as by the duration of the disease, functional state of the kidneys and the degree of their damage by the concrement, the combination of these factors leads to profound changes in organs and systems, worsening the course and prognosis of the underlying disease, manifested with varying intensity, and often has a hidden nature.

Symptoms and syndromes manifested with changes in the bone and joint system were more typical for children with MF PHPT.

Hypercalcaemia was observed in 13 (25,0%) of PHPT patients, hypophosphatemia in 12 (23,1%) children. In 34 (65,4%) children normocalcaemia was observed and in 5 (9,6%) patients the content of total calcium was below the norm. Also in 35 (67,3%) children there was normophosphatemia and in 5 (9,6%) children hyperphosphatemia. Increase of ionised calcium level in blood serum was observed in 43 (82,7%) children with RF PHPT.

We analysed the data of calcium loading test (intravenous injection of 10% calcium chloride solution at the rate of 12.4 mg/kg).

Artificial increase of calcium level in blood, decreases the function of thyroid gland (PTH secretion decreases), calcium absorption through intestinal walls stops, calcium reabsorption decreases. To normalise calcium levels, the thyroid gland produces calcitonin, so in children with USD, calcium concentrations are reduced to baseline levels

PTH increases calcium absorption through intestine, promotes calcium output from bone tissue and increases calcium reabsorption in distal renal tubules, as a result of what at RF PHPT calcium level at 120 minutes is significantly higher not only in relation to the initial level, but also in relation to the corresponding values in USD patients.

The further stage of our study was to investigate the effect of sodium on calcium homeostasis by intravenous injection of 5% sodium chloride solution (0.125 ml/kg/min for 45 minutes), which increases calcium excretion through the renal tubule apparatus.

When comparing the calcium content after the test in patients with RF PHPT and USD, there is a significant increase (2.5 times) of the index in daily urine, while in blood its level rose insignificantly ($p>0.05$).

Apparently, the increase of sodium level in loops of Henley and distal renal tubules stimulated its excretion, but decreased its reabsorption, what led to the increase of calcium level in daily urine in RF PHPT children. Thus, calcium and sodium chloride load tests are more specific diagnostic methods and increase the diagnostic efficiency of RF PHPT, in turn helping the differential diagnosis of PHPT from other hypercalcaemic and hypercalciuric conditions.

PTH increases osteolysis of osteocytes and resorption of osteoclasts. Biochemical sign of osteodystrophy, is an increase in the activity of GTP. In children with RF PHPT the activity of GTP increased by age, and had a significant difference in relation to the indicators of children of the comparison group. In MF PHPT, there was a significant increase in the activity of GTP and registered a significant difference in relation to the children of RF PHPT.

Thus, in children with USD renal failure had no effect on the activity of GTF. In RF PHPT with PH, the activity of GTF increased almost 2 times in relation to the indicators of the USD group and 1.4 times in comparison with those of RF PHPT patients without PH. GTP activity in children with MF PHPT without PU was 2.8 times higher than in children with USD and 1.9 times higher than in patients with RF PHPT. In the presence of PU, the activity of HCF in the MF PHPT group was 6.4 and 3.4 times higher than in the USD and RF PHPT groups, respectively.

Radiological signs of osteoporosis were detected with more significant mineral losses by bone tissue. In our study, radiological bone osteoporosis was noted in 7 (13.5%) children with RF PHPT. At

compensatory hypercalcaemia or at the initial stage of bone resorption there is compensatory calcium deposition in bones, however, despite the high level of calcium in serum, the process of bone demineralisation does not occur.

The speed of ultrasound waves travelling through the bone is related to the saturation of bone tissue with mineral substances. At RF and MF PHPT there is a decrease in the echo-wave permeability in all studied bones. There is also a difference in ultrasound conduction velocity depending on the form of PHPT. In children with MF PHPT the speed of ultrasound passage through the tibia is lower 1.43 times, through the ulna - 1.37 times, through the clavicle - 1.28 times and the mandible - 1.35 times compared to the indicators in patients with RF PHPT. In renal dysfunction, the ultrasound wave transmission through the bone decreased, in RF PHPT by 12.4%, 11.1%, 13.4% and 13% and in MF PHPT by 18.5%, 15.0%, 13.9%, 13.6% in the tibia, ulna, clavicle and mandible, respectively. In MF PHPT, a statistically significant decrease was observed in the tibia, who USD may be due to physical load on the tibia region increasing bone demineralisation.

It is known that in healthy children the process of ossification prevails over the process of bone resorption. This state is carried out due to the preservation of precise regulation of the mineral composition of bone tissue.

According to X-ray densitometric indices, bone mineral density (BMD) increases with age in USD patients. There is a significant decrease in BMD in children with RF ($p<0.05$) and MF PHPT ($p<0.01$) compared to the indicators of USD patients. There is also a decrease in mineral density of compact (3-7 years - by 6.1 mg/mm, 8-11 years - by 8.9 mg/mm and 12-15 years - by 4.1 mg/mm) and spongy (3-7 years - by 4.8 mg/mm, 8-11 years - by 10.9 mg/mm and 12-15 years - by 5.6 mg/mm) substance in all age groups in MF PHPT compared to RF PHPT.

In renal disfunction in children with USD, BMD decreased by 4.8 mg/mm ($p>0.05$) in KB and by 5.5 mg/mm in GW ($p<0.05$). Significant reduction in bone density at renal failere was observed in children with RF PHPT (9.2 mg/mm in KB and 7.9 mg/mm in GW), compared to those with MF PHPT (8.9 mg/mm in KB and 1.8 mg/mm in GW).

Thus, the studies of bone structure in children with PHPT indicate that the degree of bone demineralisation is not affected by USD or its complications, but is related to the disease itself and depends on its nosological form, with USD we found by correlation analysis.

We found a negative correlation between PTH level and ultrasound transmission rate in tibia ($r=-0.72$) and mandible ($r=- 0.72$), as well as between calcium activity coefficient and ultrasound wave transmission in these bones (respectively $r=-0.79$ and $r=-0.70$).

Conclusions: 1.Increased ionised calcium (82.7%), calcium activity coefficient (96.2%), loading tests with calcium and 5% sodium chloride (96.0%), increased PTH (88.5%), vitamin D (92.3%) and cAMP (88.5%), with calculation of calcitropic hormone index (100%), scintigraphy of the PTG (100%) can be considered as differential diagnostic criteria of RF PHPT.

2. The renal form of primary hyperparathyroidism in children is characterised by: increased alkaline phosphatase activity, decreased ultrasound bone velocity and decreased bone mass in 44.2% of cases. The inverse correlation between PTH level, calcium activity ratio and echosteometry parameters indicates the risk of hypercalcaemia and hypercalciuria underlying kidney stone formation.

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