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CLINICAL AND LABORATORY DIAGNOSIS OF HORMONAL DISORDERS IN CHILDREN WITH PRIMARY HYPERPARATHYROIDISM COMPLICATED BY UROLITHIASIS

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ABSTRACT

Background: Urolithiasis, a prevalent pathology affecting individuals of all age groups, has witnessed an alarming increase in incidence among children. Notably, primary hyperparathyroidism (PHPT) has emerged as a significant etiological factor, necessitating a deeper understanding of its impact on clinical manifestations and biochemical parameters in pediatric patients.

Methods: A retrospective study spanning 2009 to 2020 involved 52 children diagnosed with urolithiasis and PHPT. Clinical and biochemical analyses were conducted using specialized assays, including ionized calcium, parathyroid hormone (PTH), calcitonin, cyclic 3,5-adenosine monophosphate (cAMP), and vitamin D3. Statistical analysis employed the Fisher–Student method.

Results: Children with urolithiasis of PHPT origin exhibited distinct clinical symptoms, including adynamia, pain, and osteoarticular manifestations, differing significantly from the control group. Biochemically, elevated levels of ionized calcium, PTH, calcitonin, vitamin D3, and cAMP were observed,

emphasizing hormonal dysregulation. Renal complications and sclerotic changes influenced the trajectory of biochemical markers, particularly in the second age group.

Conclusion: The clinical course of urolithiasis in children with PHPT is intricately linked to elevated levels of calcium and calcium-regulating hormones. Age-specific variations highlight the prolonged impact on growing organisms. Renal complications contribute to dynamic alterations in biochemical markers, necessitating a nuanced approach to diagnosis and intervention. This study underscores the need for early recognition and comprehensive management of urolithiasis in pediatric PHPT, paving the way for future research to refine diagnostic strategies and optimize therapeutic interventions.

KEYWORDS: Urolithiasis, primary hyperparathyroidism, pediatric patients, biochemical markers, clinical manifestations

INTRODUCTION

Urolithiasis (UCD) is a common pathology that affects people of any age. In recent years, the incidence of urolithiasis in the younger children's age group has increased from 17.8 to 19.8, in adolescence - from 68.9 to 81.7, and in adults - from 405.2 to 460.3 patients per 100,000 population [1][2]. Cases of repeated formations of stones (relapse) in the kidneys are 18-56% [3,8], and with hyperparathyroidism (HPT) etiology of urolithiasis it reaches 80-100%.

Solving the problem of diagnosing primary hyperparathyroidism (PHPT) in children determines the treatment tactics for urolithiasis and prevents the development of complications of kidney stones [4]. The slow development of the disease with a hidden course of the process, polymorphism of nosological forms, and the lack of specific laboratory tests are the reasons for the delayed and erroneous diagnosis of PHPT [5,10].

Adenoma or hyperplastic parathyroid glands function autonomously, producing excessive amounts of PTH, which leads to primary hyperparathyroidism [6,7,9]. PTH increases calcium concentration in the blood, affecting the bones, intestines, and kidneys[11].

The influence of ionized calcium and calcium-regulating hormones on the clinical course of urolithiasis of hyperparathyroid etiology in children needs to be studied more, which determines diagnosis and treatment tactics.
Objective: To study the effect of calcium and calcium-regulating hormones on the clinical course of urolithiasis of hyperparathyroidism in children.

MATERIALS AND METHODS

In the period from 2009 to 2020, 52 children with urolithiasis were diagnosed with primary hyperparathyroidism based on clinical and biochemical studies. The content of ionized calcium was determined using a Microlyte 6 Lon Selective Analyzes apparatus, KONE Instruments. (Finland). The concentrations of parathyroid hormone (PTH), calcitonin, cyclic 3,5-adenosine monophosphate (cAMP), and vitamin D3 in blood serum were determined by immunoradiometric methods using CIS Bio international kits (France). Statistical analysis of the obtained results was carried out using the Fisher–Student method.
Bilateral nephrolithiasis in the examined children was observed in 41 (78.8%) children and unilateral - in 11 (21.1%) children. Before hospitalization in our clinic, 12 (23%) sick children were operated on the kidneys and urinary tract once, 9 (17.3%) patients - twice, and 10 (19.2%) children - three times. In 50 (96.15%) children, the disease was complicated by calculous pyelonephritis, and in 24 (46.1%) children - by renal failure. The results obtained were analyzed by age (children 3 - 7 years old and 8 - 15 years old) and by the functional state of the kidneys.

RESULTS AND DISCUSSION

Clinical symptoms, syndromes, and their manifestations in children with urolithiasis of PHPT genesis significantly differed from the clinical course of children with urolithiasis (control). Adynamia and physical inactivity (general weakness) were observed in 47(90%) children with ICD of PHPT origin; in the control group, these symptoms appeared in 8(29.6%) children. Pain in the extremities (forearm, thigh, and lower leg) was observed in 30 (58%) children. The pain was of varying intensity and was a consequence of the influence of excess calcium on neuromuscular excitability; it was variable, which depended on the concentration of calcium in the blood serum. Physical activity increased pain and muscle hypotension, which worsened the general condition of the children.
Clinical manifestations of osteoarticular diseases were gait disturbances (19/37%/), curvature of the bones of the skull, limbs and spine (21/40%/), fractures of tubular bones (7/13%/), pathological changes in the teeth (19/37 %/). These symptoms

were more pronounced in older children, which may be due to the duration of the disease. The control group of children did not show these symptoms.

Excess calcium and PTH cause muscle hypotonia, reduce bone mass, and remove minerals from bone tissue, which leads to a lag in the physical development of children with ICD of HPT origin (40 (76.9%)).

In the initial period of the disease, all children with ICD of PHPT origin had neuromuscular weakness, fatigue, headaches, and memory loss; they were related to the content of PTH and calcium in the blood serum. With severe hypercalcemia (in 25 (48%) children), neurological symptoms manifested themselves intensely with pain in Vallee points, weakness, and fatigue. Headaches were constant and varied in intensity; mild depression, drowsiness, mental disorders, memory impairment, neuroses, paresthesia, and hypoesthesia were noted.

Skin changes - peeling of the epidermis with eczema-like ulcers in the neck, axillary area, and inner thighs were observed in 9 (17%) children. The toxic effect of excess calcium led to an expansion of the border of the heart to the left with muted tones, and the ECG showed a shortening of the S-T interval, which was not observed in children of the control group.

Hypercalcemia intensely stimulated the secretion of acid and pepsin in the stomach, parathyroid hormone, affecting the antrum of the stomach, contributed to the excessive production of gastrin, which led to (hyperacid) gastritis and gastroduodenitis (pyloroduodenitis). Clinically, this was manifested in 13 (25%) children by poor appetite, nausea, vomiting, a feeling of heaviness and pain in the epigastric region. During fibrogastroduodenoscopy, edema, and foci of hyperemia of the mucous membrane of the pylori duodenal part of the stomach with superficial ulcerations were found in 3 (5.7%) children.

Calcium, an osmotically active substance, influencing proximal nephrons, increased osmotic diuresis and decreased water reabsorption, manifested by polydipsia and polyuria.

In a state of hypercalcemia and hyperparathyrinemia, spasm of the afferent arterioles occurs, renal circulation is disrupted, and the filtration capacity of the renal tubules is reduced, in addition, the parathyroid glands secrete parathyroid hypertensive factor (PHF), which was characterized by the development of hypertension (130 – 150 / 100 – 110 mmHg) in 8 (15.3%) children. Anemia, dysproteinemia and coagulopathy (calcium ions play a key role in the blood clotting) were observed more often in the examined children than in the control group.

Clinical symptoms in children of the second age group manifested themselves more intensely, which may be due to the duration of the influence of

excess calcium and calcium-regulating hormones on the child's body and the degree and duration of kidney damage from the calculus.

PTH and 1,25-dihydroxycholicalciferol provide primary control of serum calcium. The contents of ionized calcium in the blood serum in healthy children and children with urolithiasis of non-hyperparathyroid etiology (control) were the same ($p>0.05$) 2). In children with urolithiasis of PHPT origin, the content of ionized calcium increased sharply in both age groups ($p<0.01$); in the second age group, the content of ionized calcium was higher ($p<0.05$) compared to the first. In case of impaired renal function, no further increase in the ionized calcium level in the blood serum was observed, although its level was higher than that of the control group ($p < 0.01$).

PTH is aimed at preserving calcium in the body and increasing its concentration in body fluids. The PTH content is closely related to the content of ionized calcium in the blood; in healthy children in the second age group it was higher ($p < 0.05$) compared to the indicator in children of the first age group. The content of PTH in children of the control group (children with urolithiasis) in the second age group was also higher compared to that of children in the first age group ($p < 0.05$).

Metabolism of PTH occurs in the kidneys. Excessive secretion of PTH by adenomatous or hyperplastic parathyroid glands showed a statistically significant, inversely proportional relationship between the functional state of the kidneys and the content of PTH, which indicates the dependence of the functional state of the kidneys on the concentration of PTH in the blood serum, which plays a major role in the metabolism of PTH. The PTH content increased by 1.45 and 1.25 (by age, respectively) times ($p < 0.001$ and $p < 0.01$) in children in whom the etiological factor of urolithiasis was primary hyperparathyroidism. If the process was complicated by renal failure, this indicator increased by 1.8 times in both age groups ($p <0.001$). In children with ICD, PHPT of origin complicated by renal failure, compared with the indicators of children without complications, a significant difference was observed ($p < 0.01$).

The main stimulators of calcitonin (CT) secretion are an increase in the level of calcium in the blood serum and the hormone of the gastrointestinal tract - gastrin. KT plays some unknown role in food digestion and absorption by regulating gastrin secretion. The content of CT in the blood serum in both second age control groups was 1.6 times higher ($p < 0.05$) than in the first. In case of ICD PHPT genesis, the mechanism of action of CT in children has not been sufficiently studied. Its content in both age groups increased by 1.7 times compared to the indicators of children in the control group. If renal failure occurred, its content continued to increase in the

first age group and increased by 2.5 times ($p < 0.001$), and in the second age group - by 1.4 times ($p < 0.01$).

The exchange of calcium and phosphorus in the body occurs under the direct influence (control) of vitamin D. The main effect of vitamin D is to increase the intestinal absorption of calcium, which occurs under the direct control of PTH. Vitamin D directly affects the renal tubules, increasing calcium reabsorption. The vitamin D content in healthy children and in children with urolithiasis (control) were the same ($p > 0.05$).

The vitamin D content in children with urolithiasis of PHPT origin in both age groups was higher than in children in the control group ($p < 0.001$), and in children of the second age group it was 1.6 times higher ($p < 0.01$) compared with the indicator for children of the first age group. If the disease in children with ICD PHPT genesis was complicated by renal failure, then the vitamin D content in the first age group increased 1.31 times ($p < 0.01$) compared with the indicator for children without renal dysfunction. But compared to the indicator for children in the control group, it was 1.3 times higher ($p < 0.001$).

The mechanism of action of PTH is based on the binding reaction of specific receptors of the plasma membrane, and this interaction activates adenylate cyclase, which includes two second messengers - cAMP and calcium ions. At the same time, the concentration of cAMP increases in the kidney tissue, blood, and urine, as a result of which the synthesis of intracellular proteins that specifically transport calcium increases.

In healthy children and in children of the control group, the content of cAMP in the blood serum in both age groups was close to each other. The content of cAMP in children with ICD PHPT genesis in both age groups increased ($p < 0.05$), compared with the indicator for children in the control group. And in the second age group, the cAMP content was 1.34 times higher than in children of the first age group ($p < 0.02$). The complication of the disease, renal failure, contributed to an increase in the cAMP index by 2.5 and 2.1 times (by age, respectively) compared with the index in children.

CONCLUSION

Clinical manifestations of ICD PHPT genesis in children depend on the content of calcium and calcium-regulating hormones, which negatively affected the course of the disease, contributing to the development of complications. Clinical symptoms in children of the second age group manifested themselves more intensely, which is due to the long-term influence of excess calcium and calcium-regulating hormones on the growing organism, and the degree and duration of kidney damage from the calculus. In children with ICD PHPT genesis, the content of calcium and calcium-

regulating hormones increased in all groups. Renal failure and developed sclerotic changes in the renal tissue under the influence of calcium and hormones contributed to stopping the increase in the level of CT, vitamin D and ionized calcium in the blood serum in children of the second age group, as well as reducing the difference in indicators between age groups.

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