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CLINICAL MANIFESTATIONS AND HORMONAL DISORDERS IN CHILDREN WITH PRIMARY HYPERPARATHYREOIDISM COMPLICATED UROLITHIASIS

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ABSTRACT

Hyperparathyroidism (HPT) in children is manifested by nephrolithiasis, nephrocalcinosis, and in 80-100% of cases, recurrence of kidney stones is observed. The aim of this work was to study the effects of calcium and calcium regulatory hormones on the clinical course of urolithiasis of hyperparathyroid genesis in children. From 2010 to 2019, 52 children with urolithiasis were diagnosed with primary hyperparathyroidism based on clinical and biochemical studies. Clinical symptoms and syndromes of the disease depended on the level of calcium and calcium-regulating hormones, and differed from the course of the disease in children with urolithiasis (control). In children of the second age group, the disease was difficult, with pronounced changes in organs and systems, exacerbating the course of the underlying disease. The developed renal failure and sclerotic changes in the renal tissue contributed to the disappearance of the difference in laboratory parameters between age groups.

KEYWORDS: Urology, kidney, urolithiasis, primary hyperparathyroidism, parathyroid hormone, calcitonin.

The relevance of the study

Urolithiasis is a common pathology that affects people of any age. In recent years, the incidence of urolithiasis in the youngest children's age group has increased from 17.8 to 19.8, in the adolescent - from 68.9 to 81.7, and in the adult - from 405.2 to 460.3 patients per 100,000 population.[1,2] Cases of repeated stone formation in the kidneys are 18-56%,[3,4] with hyperparathyroid etiology of urolithiasis, it reaches 80-100%.

The solution to the problem of diagnosing primary hyperparathyroidism (PHPT) in children determines the treatment of urolithiasis and prevents the development of complications of kidney stones. The slow development of the disease with a hidden course of the process, the polymorphism of nosological forms, the absence of specific laboratory tests is the cause of the belated and erroneous diagnosis of PHPT.[6,7]

Adenoma or hyperplastic parathyroid glands function autonomously, producing an excess of parathyroid hormone, which leads to primary hyperparathyroidism of.[8,9,10] Parathyroid hormone increases the concentration of calcium in the blood, acting on the bones, intestines and kidneys.

The effect of ionized calcium and calcium-regulating hormones on the clinical course of urolithiasis of hyperparathyroid etiology in children has not been studied enough, which determines the diagnosis and treatment tactics.

Objective: to study the effect of calcium and calcium-regulating hormones on the clinical course of urolithiasis, resulting from primary hyperparathyroidism in children.

MATERIAL AND RESEARCH METHODS

From 2010 to 2019, 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 Analyses apparatus, KONE Instruments (Finland). The concentration of parathyroid hormone, calcitonin, cyclic 3,5-adenosine monophosphate (cAMP) and vitamin D3 in blood serum was determined by immunoradiometric methods using CIS Bio international kits (France). Statistical analysis of the results was carried out according to the Fisher-Student method.

Bilateral nephrolithiasis in the examined children was noted in 41 (78.8%) children, unilateral - in 11 (21.1%) children. Before hospitalization in our clinic, 12 (23%) sick children were operated on for kidneys and urinary tracts 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, in 24 (46.1%) children - by renal failure. The analysis of the

results was carried out by age (children 3-7 years old and 8-15 years old) and by the functional state of the kidneys.

RESULTS AND DISCUSSION

The clinical symptoms and syndromes and their manifestations in children with urolithiasis resulting from primary hyperparathyroidism differed significantly from the clinical course of children with urolithiasis (control) (Table 1).

Adynamia and lack of exercise (general weakness) were observed in 47 (90%) children with urolithiasis, which arose as a result of primary hyperparathyroidism in the control group of children, these symptoms were manifested in 8 (29.6%) children. Pain in the extremities (in the forearm, thigh, and lower leg) was observed in 30 (58%) children. The pains were of varying intensity, and was a consequence of the effect of excess calcium on neuromuscular excitability, they were inconstant in nature, which depended on the concentration of calcium in the blood serum. Physical activity exacerbated muscle pain and hypotension, which worsened the general condition of children.

Table 1: Clinical characteristics of children with urolithiasis resulting from primary hyperparathyroidism.

№	Symptoms and Syndromes	First age group			Second age group		
		1	2	3	1	2	3
		п-12	п-10	п-12	п-16	п-14	п-15
1.	General weakness	10(83,3)	10(100)	4(33,3)	14(87,5)	13(92,80)	4(26,6)
2.	Pain in limbs	5(41,6)	6(60)	-	8(50)	11(78,5	-
3.	Gait impairment	3(25)	6(60)	1(8,3)	4(25)	6(42,8)	-
4.	Pathological changes in the teeth	4(33,3)	6(60)	-	4(25)	5(35,7)	-
5.	Curvature of the bones of the skull, spine and limbs	3(25)	4(40)	1(8,3)	5(31,2)	9(64,2)	1(6,7)
6.	Bone fractures	-	3(30)	-	-	4(28,5)	-
7.	Neurological signs	3(25)	5(50)	-	7(43,7)	10(71,4)	-
8.	Skin changes	-	2(20)	-	2(12,5)	5(35,7)	-
9.	Heart manifestations	6(50)	8(80)	3(25)	8(50)	10(71,4)	4(26,6)
10.	Gastrointestinal changes	3(25)	3(30)	-	3(19)	4(28,5)	1(6,7)
11.	Polydipsia, polyuria	10(83,3)	10(100)	-	12(75)	14(100)	2(13,3)
12.	Dysuria	8(66,6)	7(75)	2(16,6)	5(31,2)	6(42,8)	3(20)
13.	Urinary incontinence	5(41,6)	4(40)	3(25)	4(25)	7(50)	3(20)
14.	Fever	6(50)	4(40)	4(33,3)	9(56,2)	8(57,1)	6(40)
15.	Anemia	4(33,3)	8(80)	2(16,6)	9(56,2)	12(85,7)	3(20)
16.	Dysproteinemia	4(33,3)	6(60)	2(16,6)	7(43,7)	9(64,2)	2(13,3)
17.	Coagulopathy	5(41,6)	7(70)	1(8,3)	9(56,2)	10(71,4)	2(13,2)
18.	Leukocyturia	11(91,6)	9(90)	9(75)	16(100)	14(100)	12(80)
19.	Erythrocyturia	3(25)	-	5(41,6)	7(43,7)	5(35,7)	5(33,3)
20.	Frequent allocation of small stones	10(83,3)	10(100)	2(16,6)	14(87,5)	14(100)	3(20)
21	Hypertension	-	3(30)	-	2(12,5)	3(21,4)	-

1. Renal form of primary hyperparathyroidism.
2. Renal form of primary hyperparathyroidism complicated by renal insufficiency.
3. Children with urolithiasis (control group).

The clinical manifestations of osteoarticular disorders were gait disorders (19/37%), curvature of the bones of the skull, limbs and spine (21/40%), fractures of the tubular bones (7/13%), and pathological changes in the teeth (19/37%). These symptoms were more pronounced in older children, which is possibly related to the duration of the disease. In the control group of children, these symptoms did not appear.

Excess calcium and parathyroid hormone cause muscle hypotension, reduce bone mass, remove mineral substances from bone tissue, which led to the lag of children with urolithiasis, which arose as a result of primary hyperparathyroidism, in physical development (40 / 76.9%).

In the initial period of the disease, all children with urolithiasis resulting from primary hyperparathyroidism noted neuromuscular weakness, fatigue, headaches, memory loss, they were associated with the content of parathyroid hormone and calcium in the blood serum. With severe hypercalcemia (25/48%), neurological symptoms manifested intensely with pain at the points of Valle, weakness, fatigue. Headaches were of a constant nature and of varying intensity, there was an erased depression, drowsiness, mental disorders, memory impairment, neurosis, paresthesia, hyposthesia.

Skin changes - peeling of the epidermis with eczema-like ulcers in the neck, axillary and on the 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 muffled tones, and on the ECG, a shortening of the S - T interval was observed, which was not observed in children of the control group.

Hypercalcemia strongly 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). It was clinically manifested (13/25%) by poor appetite, nausea, vomiting, a feeling of heaviness and pain in the epigastric region. With fibrogastroduodenoscopy in these children, edema and foci of hyperemia of the mucosa of the pyloroduodenal stomach were found in 3 (5.7%) children with superficial ulcerations.

Calcium osmotically active substance, affecting proximal nephrons, increased osmotic diuresis, reduced water reabsorption, which was manifested by polydipsia and polyuria. In a state of hypercalcemia and hyperparatirinaemia, a spasm of afferent arterioles occurs, renal blood circulation is impaired, and the filtration capacity of the renal tubules is reduced, in addition, the thyroid gland secretes the parathyroid hypertensive factor, which was characterized by the development of hypertension (130–150 / 100–110 mm mercury) in 8, 3%) of children. Anemia, dysproteinemia, and coagulopathy (calcium ions play a key role in the process of blood coagulation) were observed more often in the examined children compared with children in the control group.

Clinical symptoms in children of the second age group manifested themselves more intensely, which is probably due to the duration of the effect on the child's body of excess calcium and calcium regulating hormones and the degree and duration of kidney damage with calculus.

Parathyroid hormone and 1,25- dihydroxycholecalciferol provides the main control over the serum calcium content. The content of ionized calcium in blood serum in healthy children and in children with urolithiasis of non-hyperparathyroid etiology (control) were the same ($p > 0.05$) (Table 2). In children with urolithiasis resulting from primary hyperparathyroidism, 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, a further increase in the level of ionized calcium in blood serum was not observed, although its level was higher than that of the control group ($p < 0.01$).

Table 2: Indicators of calcium regulatory hormones in children with urolithiasis resulting from primary hyperparathyroidism.

№	Surveyed groups of children	Indicators				
		Parathyroid hormone pg / ml	Calcitonin pg / ml	Vitamin D3 pg / ml	cAMP rM	Ca^{++}
1.	Healthy children	61,2±2,6 69,1±2,2*	10,0±1,7 16,1±1,9*	12,3±1,8 15,8±2,2	7,9±0,95 10,1±1,2	0,91±0,06 0,9±0,04
2.	Patients with urolithiasis (control group)	64,0±2,2 70,0±2,1*	11,1±1,3 17,2±2,4*	10,1±2,0 12,4±1,8	8,0±0,9 10,8±1,3	1,01±0,06 0,94±0,06
3.	Patients with renal form oh PHPT	89,0±2,6** 82,8±2,51**	17,6±2,74** 27,21±4,1**	17,0±1,2** 27,8±4,1**	11,7±1,04** 15,2±1,12**	1,24±0,03** 1,37±0,03**
4.	Patients with renal form of PHPT complicated by renal failure	115,6±2,8 122,3±2,91	27±3,36** 22,54±2,26**	22,3±2,05** 25,24±2,05**	19,8±0,94** 21,8±1,99**	1,27±0,05** 1,31±0,09**

Note: * - the reliability of the indicator by age.
** - the reliability of the indicator in relation to the control groups

The action of parathyroid hormone is aimed at maintaining calcium in the body and increasing its concentration in body fluids. The content of parathyroid hormone 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 with the indicator for children of the first age group. The content of parathyroid hormone in children of the control group (children with urolithiasis) in the second age group was also higher compared to that in children of the first age group ($p < 0.05$).

Parathyroid hormone metabolism occurs in the kidneys. Excessive secretion of parathyroid hormone by adenomatous or hyperplastic parathyroid glands showed a statistically significant, inversely proportional relationship between the functional state of the kidneys and the content of parathyroid hormone, which indicates the dependence of the functional state of the kidneys on the concentration of parathyroid hormone in the blood serum, which plays the main role in parathyroid metabolism. The content of parathyroid hormone increased 1.45 and 1.25 (respectively by age) times ($p < 0.001$ and $p < 0.01$) in children in whom primary hyperparathyroidism was the etiological factor of urolithiasis. 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 urolithiasis resulting from primary hyperparathyroidism complicated by renal

failure, a significant difference was observed compared with children without complications (p <0.01).

The main stimulants of calcitonin secretion (CT) are an increase in serum calcium and gastrointestinal hormone gastrin. Calcitonin plays some unknown role in the digestion and absorption of food, regulating the secretion of gastrin. The content of CT in the blood serum in both second age control groups was 1.6 times greater (p <0.05) than in the first. In urolithiasis, resulting from primary hyperparathyroidism, the mechanism of action of calcitonin in children is not well understood. Its content in both age groups in comparison with indicators of children in the control group increased by 1.7 times. If renal failure joined, its content continued to grow in the first age group and increased 2.5 times (p <0.001), and in the second age group - 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 parathyroid hormone. The role of vitamin D in regulating the secretion of parathyroid hormone is still not clear. Vitamin D may have an indirect, long-term inhibitory effect on the synthesis and secretion of parathyroid hormone, altering the absorption of calcium and phosphorus in the intestine. 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 resulting from primary hyperparathyroidism was higher in both age groups compared to children in the control group (p <0.001), and in children in the second age group it was 1.6 times higher (p <0 , 01) compared with the indicator of children of the first age group. If the disease in children with urolithiasis resulting from primary hyperparathyroidism was complicated by renal failure, the vitamin D content in the first age group increased by 1.31 times (p <0.01) compared with children without renal impairment. But compared with the indicator of children in the control group, it was 1.3 times more (p <0.001).

The mechanism of action of parathyroid hormone is based on the binding of specific plasma membrane receptors, and this interaction activates adenylate cyclase, which includes two secondary mediators - cAMP and calcium ions. At the same time, the concentration of cAMP rises in the kidney tissue, blood, and urine; as a result, the synthesis of intracellular proteins that specifically transfers calcium increases.

In healthy children and in children of the control group, the content of cAMP in the blood serum in both age groups were close to each other. The content of cAMP in children with urolithiasis that arose as a result of primary hyperparathyroidism in both age groups increased (p <0.05), compared with that in children in the control group. And in their second age group, the content of cAMP was 1.34 times higher than that of children in the first age group (p <0.02). A complication of kidney failure contributed to an increase in cAMP 2.5 and 2.1 times (respectively by age) compared with children in the control group (p <0.001), but the difference between age groups was not observed (p> 0.05).

CONCLUSION

The clinical manifestations of urolithiasis resulting from primary hyperparathyroidism in children depends on the content of calcium and calcium-regulating hormones, which can adversely affect the course of the disease, contributing to the development of complications. Clinical symptoms in children of the second age group manifested themselves more intensely, due to the prolonged effect of excess calcium and calcium regulating hormones on the growing organism, on the degree and duration of kidney damage with calculus. In children with urolithiasis, which arose as a result of primary hyperparathyroidism, the genesis of calcium and calcium-regulating hormones in all groups increased. Renal failure and the development of sclerotic changes in the kidney tissue under the influence of calcium and hormones helped to stop the increase in the level of calcitonin, vitamin D and ionized calcium in blood serum in children of the second age group, as well as to reduce the difference in indicators between age groups.

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