

Features of the clinical course of nephrolithiasis in patients with hyperparathyroidism

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Abstract

Aim. To assess the incidence of kidney stone disease and to identify its clinical course in patients with primary hyperparathyroidism.

Methods. 48 medical records of patients hospitalized with primary hyperparathyroidism were retrospectively analyzed. The average age of the patients was 57 [53; 61] years. The medical history, complaints upon admission, the clinical presentation, the results of laboratory test and instrumental examination were studied in evaluating the medical records. The patients were divided into the group with nephrolithiasis (n=33) and the group without nephrolithiasis (n=15). The differences between the two groups were tested for statistical significance by the Mann–Whitney U test.

Results. Among patients with primary hyperparathyroidism, nephrolithiasis was detected in 69% of patients, of which 90% were women in the postmenopausal period. The course of the kidney stone disease in these patients was characterized by frequent recurrence with a predominance of bilateral renal impairment (62%). The duration of nephrolithiasis before the diagnosis of primary hyperparathyroidism was 6 [1; 19] years, and this complication was often the first manifestation of the disease. According to the instrumental examination of kidney in patients with nephrolithiasis, small stones up to 5 mm in diameter were detected in 42% of cases, asymptomatic kidney stones — in 15% of cases. A severe complication of primary hyperparathyroidism — staghorn calculi were found in 2 (10%) patients. The patients in the group with nephrolithiasis showed higher serum calcium ($p=0.022$) and parathyroid hormone ($p=0.007$) levels compared with patients in the group without nephrolithiasis.

Conclusion. Nephrolithiasis is a common complication of primary hyperparathyroidism; the presence of nephrolithiasis is associated with more significant changes in calcium and phosphate metabolism and is also characterized by a frequent asymptomatic course, thus requiring attention of specialists to this type of complications in primary hyperparathyroidism.

Keywords: primary hyperparathyroidism, kidney stone disease, staghorn calculus, hypercalciuria.

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Background. Kidney stone disease (KSD) is one of the most common diseases. It remains an urgent problem for both urologists and general practitioners. KSD occurs in all regions of the world at a frequency between 5% and 10% [1]. The ratio of men to women with KSD varies from 1.8:1 to 3.8:1 [2]. In Russia, KSD in urological hospitals is more than 30%, and the number of patients with KSD is increasing every year [3].

KSD is a polyetiological disease caused by various exogenous and endogenous factors [4]. The first group of factors includes the nature of the diet, taking certain medications, living in endemic areas (which include the Arkhangelsk region), occupa-

tional hazards, and several others [4]. The group of endogenous causes includes genetic diseases (enzymatic and tubulopathies) in humans, morphofunctional changes in the urinary system, and some metabolic and endocrine diseases [4].

One of the most common types of endocrine system pathologies associated with nephrolithiasis is primary hyperparathyroidism (PHPT). PHPT is a disease caused by an adenoma of the parathyroid glands (PTH), leading to excessive secretion of parathyroid hormone (PTH) and an increase in blood calcium (Ca) [5]. For a long time, PHPT was considered a rare disabling disease associated with severe complications, such as staghorn nephroli-

thiasis and fibrocystic osteitis [6]. Currently, according to epidemiological studies, PHPT is the third most common endocrine disease in the world. Its frequency is about 1% and can reach 2% in postmenopausal women [7].

Hypercalciuria is the main factor of stone formation in PHPT. This pathology can increase the risk of stone formation by 3.7 times [8]. According to global data, at the end of the twentieth century the prevalence of KSD in patients with PHPT at the end of the twentieth century, reached between 40% and 60%. However, over the past two decades, it has sharply decreased from 10% to 20% because of the introduction of blood Ca levels in biochemical examinations in Western Europe and the United States and the detection of large numbers of mild, uncomplicated forms of PHPT (up to 80%) [9]. Nevertheless, in Russia, the incidence of complications in the form of nephrolithiasis in patients with PHPT remains high. It can reach 50% due to the lack of early diagnosis and study of blood Ca levels in routine practice [10].

Other kidney problems in patients with PHPT include decreased filtration and concentration and urinary tract infection. Renal failure is one of the most severe complications of PHPT and is associated with an increased risk of morbidity and mortality [11].

Surgical removal of the affected thyroid gland (parathyroidectomy) is an effective method. It contributes to the normalization of calcium-phosphorus metabolic indicators, a significant reduction in stone formation risk in PHPT, prevention of nephrolithiasis recurrence, improvement of kidney filtration and concentration functions, and improvement of the quality of life of patients [8].

Aim. This study aims to assess the incidence of KSD and identify the features of its clinical course in patients with PHPT.

Materials and methods. We performed a retrospective analysis of 48 case histories of patients (continuous samples) who received inpatient treatment with a final diagnosis of PHPT in the endocrinological and surgical departments of two large clinics in Arkhangelsk — First City Clinical Hospital named after E.E. Volosevich and Arkhangelsk Regional Clinical Hospital from 2005 to 2015.

The study inclusion criteria were age at least 18 years and a final diagnosis of PHPT in patients who received inpatient treatment for this disease from 2005 to 2015. The diagnosis of PHPT was made based on elevated blood Ca level in two tests combined with an elevated PTH level.

The exclusion criteria were secondary and tertiary hyperparathyroidism.

When evaluating the case histories, medical history, complaints upon admission, the clinical pic-

ture, physical examination results, laboratory tests, and instrumental examination were studied. The patient diagnosis of a manifest or mild form of PHPT and surgical treatment indications were established based on international recommendations for PHPT treatment (2014) [12].

The presence of nephrolithiasis was confirmed by anamnesis, ultrasound, or computed tomography of the kidneys. The filtration function of the kidneys was assessed by the level of creatinine with the calculation of the glomerular filtration rate (GFR) according to the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration).

Statistical analysis was performed using the statistical software package SPSS 22 (IBM SPSS Statistics, 2013). Quantitative signs are presented as the median [first and third quartiles], the distribution was taken as abnormal. Comparison of the two groups regarding quantitative characteristics was performed using the Mann–Whitney U-test for independent groups. The probability of random error less than 5% ($p < 0.05$) was chosen as the statistical significance criterion.

Results. Among hospitalized patients with PHPT from 2005 to 2015, the median and quartiles of age were 57 [53; 61] years ($n = 48$), the peak incidence was in the age groups 50–59 and 60–69 years (min 22 years, max 75 years). The overwhelming majority were women: 96% (46/48), and 76% of female patients (35/46) with PHPT were postmenopausal.

Depending on the clinical manifestations when assessing the case histories, the following forms of PHPT were identified: visceral form in 42% of cases (20/48), mixed form in 27% of cases (13/48), bone form in 19% of cases (9/48), and mild form in 12% of cases (6/48). There were no cases of the normocalcemic variant of PHPT [13].

The incidence of nephrolithiasis in hospitalized patients with PHPT was 69% (33/48) [13]. Among them female patients also predominated (93%, 31/33); 90% of them were postmenopausal (28/31). The median and quartiles of the duration of nephrolithiasis were 6 [1; 19] years (min 0 years, max 37 years). This complication was often the first manifestation of PHPT.

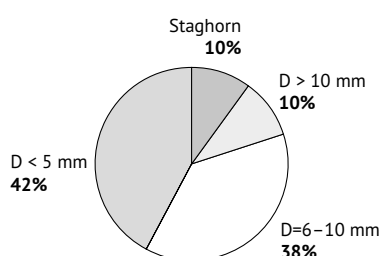
Among the group of patients with nephrolithiasis ($n = 33$), complaints of renal colic in their histories were registered in 42% of cases, for polydipsia in 21%, and polyuria in 27%. A history of fractures was present in 12% of cases, weight loss was noted in 24% of patients due to a more severe disease course [the mixed form in this group was 33% (11/33)].

In the group of patients without nephrolithiasis ($n = 15$), 13% had complaints of polydipsia, 20% of polyuria, and fractures were noted in 13%

Table 1. Comparative characteristics of laboratory parameters in patients with primary hyperparathyroidism by the presence or absence of nephrolithiasis, median [first and third quartiles]

Parameters	Patients with nephrolithiasis	Patients without nephrolithiasis	p
n	33	15	
Age, years	58 [54; 62]	56 [51; 61]	0.666
Total Ca, mol/l	2.88 [2.69; 3.21]	2.79 [2.54; 2.99]	0.022
Ca ⁺⁺ , mmol/l	1.44 [1.37; 1.72]	1.42 [1.25; 1.52]	0.240
PTH, pg/ml	283 [198; 897]	167 [132; 253]	0.007
Phosphorus, mmol/l	0.82 [0.61; 0.92]	0.85 [0.67; 1.03]	0.310
Creatinine, μ mol/l	83 [73; 106]	74 [62; 91]	0.411
CPK, ml/min/1.73 m ²	72 [57; 85]	81 [60; 95]	0.456

Note: PTH — parathyroid hormone, GFR — glomerular filtration rate.

**Fig. 1.** The size of renal calculi in patients with nephrolithiasis on the background of primary hyperparathyroidism according to imaging studies (n = 21); D – diameter

of cases. According to the case history data, fewer complaints were registered in this group because of a milder disease course 40% of patients had a mild form of PHPT (6/15).

According to the results of the findings of ultrasound or computed tomography of the kidneys in the examined patients with PHPT, in 42% of cases (9/21), small stones with a diameter of up to 5 mm were found (Fig. 1), which is typical for PHPT. In most cases, bilateral kidney damage was diagnosed (62%). As one of the rare severe complications of PHPT, staghorn nephrolithiasis was diagnosed in 10% of cases (2/21) [13]. Nephrocalcinosis was recorded in four patients. In all cases, it was combined with nephrolithiasis.

The asymptomatic course of nephrolithiasis was registered in 15% of cases (5/33), with the detection of renal stones up to 2 mm in size in the absence of KSD history. In all these cases, the clinical picture already had bone manifestations of PHPT in the form of osteoporosis. Nephrolithiasis was associated with a significantly higher level of total blood Ca and PTH (Table 1). Surgical treatment to remove calculi or lithotripsy among patients with KSD was performed in almost one-fifth of patients before the diagnosis of PHPT was established.

Quantitative data of patients were compared in the two groups (with and without PHPT) using the

Mann–Whitney test. The level of $p < 0.05$ was considered statistically significant in pairwise comparisons. An increase in calcium excretion in daily urine greater than 10 mmol/day was recorded in 42% of the examined patients (8/19), and in 63% of them, it was combined with KSD (5/8). The median and quartiles of Ca excretion in daily urine were 8.9 [5.4; 11.5] mmol/day (n = 19). Hypocalciuria was not recorded in any case.

Infection of the urinary system was diagnosed in 25% of patients with PHPT (12/48) in the form of a recurrent course of chronic pyelonephritis, 75% of whom had it combined with KSD. According to the results of urine tests, bacteriuria was detected in five (15%) patients with PHPT in the presence of nephrolithiasis.

The other most common complication of PHPT was bone damage. In the examined group of patients (n = 48), osteoporosis of one or more localizations was detected in 79% of cases (22/28) during X-ray densitometry or skeletal radiography. A history of fractures was noted in 13% of cases (6/48), of which multiple fractures accounted for 67% (4/6): in four cases, fractures of the femoral shaft occurred, in three cases, fractures of the distal third of the radius occurred, and in two cases, compression fractures of the lumbar spine occurred. In 44% of patients examined by X-ray (8/18), a severe complication in the form of fibrocystic osteitis (subperiosteal resorption and cystic bone cavities) was revealed [13].

Thus, in accordance with international recommendations (2014) [12], the indications for surgical removal of the affected thyroid gland in the general group of patients with PHPT (n = 48) were as follows: nephrolithiasis or nephrocalcinosis in 33 patients; decreased GFR < 60 ml/min/1.73 m² in 10 patients (among them six with nephrolithiasis); hypercalciuria > 10 mmol/day in eight patients (among them five with nephrolithiasis); osteoporosis or

low-energy fractures of the skeletal bones in 22 patients (among them 13 in combination with nephrolithiasis (mixed form)); blood calcium level is more than 0.25 mmol/l higher than the upper limit of the norm in 26 patients (among them 18 with nephrolithiasis); age less than 50 years in seven patients (among them four with nephrolithiasis).

According to case histories, parathyroidectomy was performed in 90% of patients with PHPT (43/48), including 37 patients with manifest forms and six patients with mild forms of PHPT. According to the histological report results, the following morphological forms of damage to the thyroid gland were found adenoma 98% (42/43) and hyperplasia 2% (1/43). There were no cases of cancer. In patients with manifest forms ($n = 42$), surgery was not performed in five cases because of referral to central medical research centers ($n = 4$) or patient refusal ($n = 1$).

Discussion. The incidence of nephrolithiasis registered in our study in patients with PHPT was identified over a 10-year period in the region (69%). This greatly exceeds the global prevalence of this complication due to PHPT in countries where routine screening of blood calcium levels is performed (10%-20%) [9]. The course of KSD among patients with PHPT was characterized by frequent recurrence with a predominance of bilateral renal damage and the identification of staghorn nephrolithiasis cases. This result indicates that PHPT in the Arkhangelsk region currently remains a rare but severe disease with a prevalence of complicated forms. Also, this disease has already become a common pathology worldwide with a predominantly asymptomatic course.

According to the literature, the incidence of KSD in the general population prevails in men and occurs less often in women (the ratio is about 3:1) [1]. However, in our group, the majority of patients with KSD due to PHPT were postmenopausal women who belonged to the main at-risk group for developing PHPT, according to the results of other researchers (the ratio of men and women in Western Europe and the United States is 1:3–1:5 [6], in Russia, it is 1:8 [14]).

Often, the diagnosis of PHPT by doctors of various specialties is associated with the presence of staghorn kidney stones. However, the course of nephrolithiasis in PHPT is most often characterized by detecting small kidney stones not exceeding 10 mm in diameter in 80% of cases [15], which coincides with our study results.

Thus, PHPT as an etiopathogenetic cause of stone formation can be present in KSD with calculi of any size. Therefore, additional laboratory tests are required to search for secondary causes

of nephrolithiasis. Also, among our patients, there were cases of asymptomatic course of KSD, which is not uncommon with PHPT according to other observations [15, 16].

A rather long period from the establishment of KSD to the diagnosis of PHPT may be associated with the difficulty of differential diagnosis of secondary nephrolithiasis due to PHPT and primary KSD and the low awareness of doctors about the complications of PHPT [8]. According to our data, one-fifth of patients have already undergone some type of surgery to remove kidney stones. However, as is known, surgical removal of calculi with PHPT does not bring a satisfactory effect because of frequent relapses due to persistent hypercalcemia and hypercalciuria. On the other hand, one year after removing the thyroid gland adenoma, 50% of patients with calculi of sizes up to 1.0 cm are likely to be completely free of kidney stones, indicating the importance of early diagnosis of PHPT in patients with KSD [1].

Long-term hypercalcemia with PHPT impairs renal function, and a decrease in filtration function is a common phenomenon in the later stages of PHPT. According to the latest consensus on the management of patients with PHPT (2014) [12], a decrease in renal filtration function below 60 ml/min/1.73 m² is considered an indication for surgical treatment of PHPT. The state of the renal filtration function can also be improved after surgical treatment of hyperparathyroidism, but the prognosis depends on the degree of the previous decrease in GFR [1]. Infection of the urinary system is quite common due to PHPT. For example, according to Russian data, urinary system infection frequency in patients with PHPT is 36% of cases, and due to nephrolithiasis, it can reach 50% [8].

CONCLUSIONS

1. Our study demonstrated a high incidence of nephrolithiasis and its challenging course in patients with primary hyperparathyroidism due to the late diagnosis of this disease in our region.

2. Specialists dealing with the problem of diagnosis and treatment of urolithiasis should be aware of such a disease as primary hyperparathyroidism, and its complications since timely surgical removal of the affected parathyroid gland can reduce the risk of stone formation and the development of renal failure.

3. If primary hyperparathyroidism is detected in patients without clinically apparent nephrolithiasis, additional imaging studies are recommended to exclude its asymptomatic course and examination to identify other pathology from the urinary system.

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