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CLINICAL VARIANTS AND ASPECTS OF SURGICAL TREATMENT OF PATIENTS WITH HYPERPARATHYROIDISM

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Abstract

Introduction. In clinical practice, it is important to apply a differentiated approach to selecting the treatment strategy for patients with hyperparathyroidism, depending on clinical manifestations and laboratory changes.
Aim. To analyse clinical variants and approaches of surgical treatment of patients with hyperparathyroidism.
Materials and methods. We conducted a retrospective analytical study of hyperparathyroidism cases in patients who underwent surgery at the Non-Profit Enterprise «Regional Clinical Hospital of the Ivano-Frankivsk Regional Council» during 2019-2024. Clinical and laboratory characteristics and surgical approaches were studied. For statistical processing, STATISTICA 12 (StatSoft Inc., USA), Microsoft Excel, and variance-statistical analysis were used. Numerical data are presented as arithmetic mean (M), standard deviation (SD), and number of observations (n). Differences were assessed using Student's t-test; statistical significance was set at $p < 0.05$.
Results. A total of 77 surgeries were analysed: 67 for primary and 10 for tertiary hyperparathyroidism. In 62 patients (95.40%) with primary hyperparathyroidism, a solid adenoma was found, mostly in the lower parathyroid glands (85.07%). Most adenomas were diagnosed incidentally during thyroid ultrasound, predominantly in women (83.6%). The hypercalcaemic variant of primary hyperparathyroidism was detected in 56 patients (83.58%), while normal calcium levels were found in 11 (16.42%). There was insufficient evidence to confirm the normocalcaemic variant based on diagnostic criteria. Patients with primary hyperparathyroidism underwent selective parathyroidectomy; those with tertiary – subtotal parathyroidectomy. In all cases, the diagnosis was confirmed histologically.
Conclusions. Most operated patients had the hypercalcaemic variant of primary hyperparathyroidism. Normocalcaemic variant cases require documented confirmation: stable normocalcaemia, elevated parathyroid hormone, and exclusion of causes of secondary hyperparathyroidism. Hyperparathyroidism treatment requires a personalized approach, considering type, variant, complications, and surgical indications.

Keywords: **hyperparathyroidism, hypercalcaemic hyperparathyroidism, normocalcaemic hyperparathyroidism, treatment approaches, retrospective study**

INTRODUCTION

The imperative of timely diagnosis and effective treatment of patients with hyperparathyroidism are justified by the high risk of severe, disabling complications resulting from disturbances in calcium-mineral metabolism.

Hyperparathyroidism (HPT) is an endocrine disorder caused by overproduction of parathyroid hormone (PTH) by parathyroid glands (PTGs). HPT is the third most common endocrine disorder, following diabetes mellitus and thyroid gland diseases. There are three types of hyperparathyroidism: primary, secondary, and tertiary.

Primary hyperparathyroidism (PHPT) is the most common type, with causes including a benign solid adenoma of the PTG (80.0%), multiple adenomas (5.0%), carcinoma (< 5.0%), or PTG hyperplasia (15.0%). In addition, PHPT can be diagnosed as part of multiple endocrine neoplasia syndromes (MEN-1, MEN-2). Secondary HPT (SHPT) is a compensatory hyperplasia

and hyperfunction of PTGs in response to prolonged hypocalcaemia and hyperphosphataemia of different origins. Tertiary HPT (THPT) is characterized by growth of adenomas or hyperplasia of the PTGs in the setting of long-standing SHPT.

Until the mid-20th century, the diagnosis of PHPT was based on the identification of manifest forms of the disease with severe clinical presentations. The improvement in PHPT diagnosis resulted from the inclusion of serum calcium level testing in routine patient examinations [1, 2], as well as from screening for HPT. These diagnostic measures have enabled the identification of asymptomatic and normocalcaemic variants of PHPT [3].

A benign parathyroid adenoma, the most common cause of PHPT, results from mutations in genes controlling cell division and parathyroid cell proliferation, such as CDC73 (cell division cycle 73) or the calcium-sensing receptor (CASR). Malignant parathyroid carcinomas are often linked to mutations in the CCND1 (Cyclin D1) gene [4]. Genetically determined PHPT forms account for about 10% of cases [5].

Pathogenesis of PHPT is due to hyperproduction of PTH, which leads to an increase in calcium reabsorption and a decrease in phosphate and bicarbonate reabsorption in the kidneys. It also enhances intestinal calcium absorption due to increased activity of vitamin D 1α-hydroxylase, a regulator of active vitamin D synthesis [6]. Excessive production of PTH results in a decreased bone mineral density, leading to the development of osteoporosis, as well as chronic hypercalcaemia with the formation of calcium deposits in parenchymal organs, and calcification of heart valves, blood vessels, and nerve fibres [7].

Based on clinical manifestations and associated disorders, PHPT can be classified into osseous, visceropathic (non-osseous), and mixed forms. PHPT is further divided into overt and latent types based on symptom severity. Additionally, hypercalcaemic and normocalcaemic variants are recognized. The mechanisms behind normocalcaemic PHPT and its consequences are still under investigation [8].

Unfortunately, there are no official data on the prevalence of HPT in Ukraine; however, it is known that the disease is underdiagnosed. In various countries around the world, the prevalence of HPT ranges from 200 to 1300 cases per 100.000 population [1]. Analytical studies focused on HPT remain highly relevant for improving the effectiveness of treatment for this disease.

AIM

To analyse the clinical variants and surgical treatment strategies in patients with hyperparathyroidism.

MATERIALS AND METHODS

A retrospective analytical study was carried out on cases of HPT in patients who underwent surgical treatment at the Municipal Non-Profit Enterprise «Regional Clinical Hospital of the Ivano-Frankivsk Regional Council» over a 5-year period (2019-2024). The study materials included inpatient medical records (Form 003/0, approved by the Order of the Ministry of Health of Ukraine No. 110, dated February 14, 2012). The research involved the analysis of HPT incidence in different districts of the region. The clinical and laboratory characteristics of patients and surgical treatment approaches were studied.

For statistical data processing software programs such as STATISTICA 12 (StatSoft Inc., USA), Microsoft Excel and variance-statistical analysis were used. Numerical data are presented as arithmetic mean (M), standard deviation (SD), and number of examined individuals (n). The differences between the data were assessed using Student's t-test and were considered statistically significant at $p < 0.05$.

This study is a fragment of the complex scientific research work of the Ivano- Frankivsk National Medical University: «Improving surgical strategies in diseases of the neuroendocrine system to enhance treatment outcomes and quality of life in patients» (2022-2027, state registration number 0122U001740).

RESULTS

A total of 77 cases of surgical intervention were analysed: 67 for primary hyperparathyroidism (PHPT) and 10 for tertiary hyperparathyroidism (THPT). The majority of cases were diagnosed in residents of Ivano-Frankivsk.

The most common cause of PHPT was found to be a solid adenoma of the PTG, present in 62 patients (95.40%). Two adenomas were found in 5 patients (4.60%). The majority of tumours were located in the lower PTGs – 57 cases (85.07%). A left lower PTG adenoma was found in 29 out of 32 patients, and a right lower PTG adenoma in 28 out of 30 patients. Ten individuals (6 women and 4 men) undergoing maintenance haemodialysis were diagnosed with THPT. The average duration of replacement therapy was 11.2 ± 1.15 years. The most common causes of chronic renal insufficiency were chronic glomerulonephritis and polycystic kidney disease (PKD).

PHPT was most frequently diagnosed in women – 56 cases (83.6%). There was no significant difference in age or BMI between men and women with PHPT ($p > 0.05$). Most adenomas were diagnosed incidentally during thyroid ultrasound. In total, 37 patients (55.20%) had thyroid gland disorders, most commonly nodular goitre (29 patients) and autoimmune thyroiditis (8 patients).

We studied the spectrum of comorbidities in patients with PHPT.

The most common diseases in patients with PHPT were hypertension (62,7%), urolithiasis (29,8%), and cholelithiasis (14,9%). In 13 patients, no disorders potentially caused by excess PTH production were identified (Figure 1).

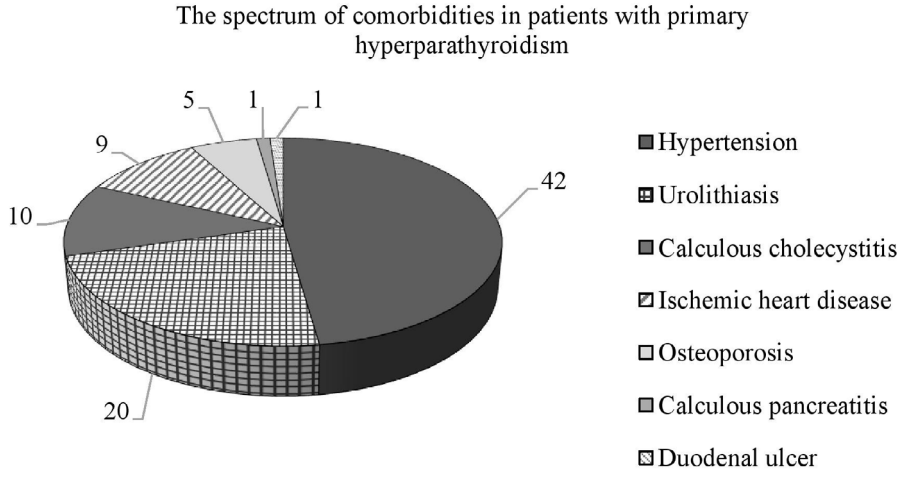

Figure 1. Spectrum of comorbidities in patients with primary hyperparathyroidism.

Diagnostic methods for PHPT included laboratory confirmation of PTH overproduction and hypercalcaemia (due to elevated ionized calcium), visualization of parathyroid adenoma using high-resolution ultrasound, and subtraction scintigraphy with technetium-99m-sestamibi and contrast-enhanced computed tomography. Possible causes of SHPT – whether related or unrelated to renal dysfunction, vitamin D deficiency, or the effects of certain medications – were ruled out during the inpatient diagnostic stage.

A comparative analysis of clinical and laboratory findings between patients with PHPT and THPT was performed (Table 1). Patients with THPT were found to be older than those with PHPT ($p < 0.05$). No significant difference was found in body mass index (BMI) between the two groups ($p > 0.05$) (Table 1).

Table 1

Clinical and Laboratory Findings in Patients with Primary and Tertiary Hyperparathyroidism (M±SD)

Indicators	Patients with PHPT (n= 67)	Patients with THPT (n= 10)
Age, years	52.74±8.21	70.10±13.96*
BMI, kg/m^2	26.12±3.20	24.38±2.18
Fasting blood glucose, mmol/L	5.03±0.85	4.86±0.86
Ionized calcium, mmol/L	1.51±0.24	1.73±0.17*
25(OH)D, ng/ml	42.38±8.55	26.33±6.91*
Serum creatinine, µmol/L	89.02±27.72	519.50±184.70*
Parathyroid hormone, pg/ml	159.47±65.51	1871.4±1003.04*

Note: 1. * – significant difference between comparison groups according to the Student's t-criterion ($p < 0.05$); 2. PHPT – primary hyperparathyroidism, THPT – tertiary hyperparathyroidism.

In the majority of patients with PHPT – 56 individuals (83.58%) – the classical hypercalcaemic form of PHPT was identified. Eleven patients (16.42%) were found to have PHPT with normal calcium levels, which may indicate a normocalcaemic variant of PHPT. In 8 out of 11 cases, disorders that can be pathogenetically associated with hypercalcaemia were identified: urolithiasis, cholelithiasis, duodenal ulcers, and osteoporosis. To confirm the presence of normocalcaemic PHPT in these patients, there was insufficient longitudinal

data on PTH and calcium levels (3-6 months prior to HPT diagnosis).

A comparative analysis of laboratory parameters between patients with hypercalcaemic PHPT and those with PHPT and normal calcium levels was conducted. Ionized calcium levels in individuals with hypercalcaemic PHPT were 1.56 ± 0.23 mmol/L and were significantly higher in comparison to patients with PHPT and normal calcium levels: 1.25 ± 0.08 mmol/L ($p < 0.05$). The levels of 25(OH)D, creatinine, and PTH did not differ significantly between the two groups ($p > 0.05$).

Patients with PHPT underwent selective parathyroidectomy involving the removal of one (62 individuals) and two (5 individuals) PTG adenomas. Patients with THPT underwent subtotal parathyroidectomy. In all cases, histological examination of the resected tissue confirmed the presence of PTG adenomas.

DISCUSSION

According to the results of the conducted analysis, it was determined that 67 patients with PHPT (87.01%) underwent selective parathyroidectomy. Parathyroidectomy is acknowledged as the gold standard treatment option for patients with PHPT presenting with classical manifestations of the disease [9]. The relevance of surgical treatment is emphasized in the recommendations of the International Expert Panel on the Management of PHPT (2022), according to which parathyroidectomy is indicated for patients with PHPT – including asymptomatic individuals – if any of the following indications are present: serum calcium level >1 mg/dL (0.25 mmol/L) above the upper limit of normal, skeletal system changes (fracture confirmed by radiography or reduced bone mineral density (T-score < –2.5)), renal function impairment (decrease in glomerular filtration rate < 60 mL/min, nephrocalcinosis, or nephrolithiasis), hypercalciuria (> 250 mg/day in women; > 300 mg/day in men), age < 50 years [8].

In addition to PHPT cases, 10 individuals with THPT (12.98%) underwent subtotal parathyroidectomy, involving the removal of the three most affected PTGs, along with resection of the fourth gland. Total parathyroidectomy, which involves the removal of all PTGs with or without autotransplantation, is less commonly performed in THPT. Surgical treatment of THPT is characterized by its radical nature: identification and visualization of all four PTGs with minimal PTG volume preserved to prevent persistent hypocalcaemia [10]. According to the analysed data, there were no cases of surgical treatment for SHPT in the last 5 years. Surgical treatment of SHPT (subtotal or total parathyroidectomy) is performed based on strict, well-defined indications [10].

Most PHPT cases were diagnosed incidentally during thyroid gland ultrasound examinations. This highlights both the expertise of ultrasound specialists and the insufficient use of other HPT screening methods. Patients were referred for PTH and ionized calcium level testing after parathyroid gland adenomas were discovered. Ionized calcium more accurately reflects the actual concentration of this electrolyte in the blood and has lower variability, as it is not influenced by plasma protein levels [11]. To accurately interpret total calcium, adjustments for albumin levels are necessary.

Classical hypercalcaemic PHPT was diagnosed in 56 individuals, while 11 patients had normal blood calcium levels. Among these, 8 patients had diseases potentially mediated by hypercalcaemia. However, based on the available data, we cannot confirm normocalcaemic PHPT in these 11 patients due to insufficient documentary evidence. Diagnosis of normocalcaemic PHPT requires evidence, particularly the confirmation of persistently normal total and ionized calcium levels on three separate occasions, along with elevated serum PTH over 3 to 6 months, after excluding SHPT causes. Some studies have shown intermittent hypercalcaemia in patients with normocalcaemic PHPT, suggesting that it may represent a mild form of classical hypercalcaemic PHPT [12].

The most recent recommendations for the diagnosis and treatment of normocalcaemic hyperparathyroidism were presented in 2021 as part of the European Society of Endocrinology's educational program on parathyroid disorders [13]. In our study, we found that most patients with normocalcaemia and HPT had diseases potentially associated with hypercalcaemia. Although our sample size is insufficient for statistical conclusions, our findings align with previous studies showing the impact of normocalcaemic PHPT on the risk of various disorders [14]. According to Gheorghe A. M. and colleagues, six studies revealed a significant prevalence of osteoporosis in patients with normocalcaemic hyperparathyroidism, with frequencies ranging from 41.7% to 100%. Additionally, improvements in bone mineral density were noted after parathyroidectomy [15]. Mathematical models for predicting fractures associated with osteoporosis have been developed by Ukrainian researchers [16].

It was found that 62.7% of patients with PHPT had hypertension. Studies have shown that parathyroid hormone activates mineralocorticoid receptors [17], suggesting that hypertension can also be a complication of normocalcaemic HPT.

For a long time, the issue of surgical treatment in patients with normocalcaemic PHPT remained controversial. In 2014, the International Workshop on the Management of HPT recommended surgical treatment for normocalcaemic PHPT in cases where certain comorbidities, such as osteoporosis or urolithiasis, were progressing, similar to patients with hypercalcaemia [8]. The recommendations of the American Association of Endocrine Surgeons are similar [18]. A recent expert consensus by the European

Society of Endocrinology (ESE, 2022) stated that surgical intervention should be considered when strong clinical indications and a clearly defined surgical target are present [13, 19]. Any surgical treatment for HPT requires precise anatomical techniques, visualization and identification of the recurrent laryngeal nerve and the external branch of the superior laryngeal nerve, as well as mandatory histological examination of the excised tissue. The conducted analysis highlights the importance of thorough patient assessment in line with current recommendations for diagnosis and treatment strategy selection.

CONCLUSIONS

The vast majority of operated patients were diagnosed with the hypercalcaemic variant of primary hyperparathyroidism. The characteristics of patients with the normocalcaemic variant of primary hyperparathyroidism require support by documented evidence in accordance with diagnostic criteria: prolonged and stable normocalcaemia, hypersecretion of parathyroid hormone, and exclusion of secondary hyperparathyroidism causes. The treatment of hyperparathyroidism requires a personalized approach, including the identification of the type, variant, complications, and indications for surgical intervention.

Perspectives for further research. In future research, we aim to assess the status of the skeletal system in patients with normocalcaemic hyperparathyroidism and to conduct a correlation analysis between parathyroid hormone levels and bone density parameters in individuals without persistent hypercalcaemia.

FUNDING AND CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this article. No external funding was provided for this study.

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COMPLIANCE WITH ETHICAL REQUIREMENTS

Ethical approval was obtained from the Bioethics Committee of the Ivano- Frankivsk National Medical University (protocol No. 150/25 dated February 27, 2025). The study was conducted in accordance with the recommendations of the Ethics Committees for Biomedical Research, Ukrainian Health Legislation and the Declaration of Helsinki (2000), European Community Directive 86/609 On Human Participation in Biomedical Research. All patients provided informed consent for the processing of the data used in the study.

AUTHOR CONTRIBUTIONS

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Резюме

КЛІНІЧНІ ВАРІАНТИ ТА АСПЕКТИ ХІРУРГІЧНОГО ЛІКУВАННЯ ПАЦІЄНТІВ З ГІПЕРПАРАТИРЕОЗОМ

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Вступ. В клінічній практиці важливо застосовувати диференційований підхід при виборі тактики лікування пацієнтів з гіперпаратиреозом, залежно від клінічних проявів та лабораторних змін.

Мета. Провести аналіз клінічних варіантів та підходів до хірургічного лікування пацієнтів з гіперпаратиреозом.

Матеріали та методи. Проведено ретроспективно-аналітичне дослідження випадків гіперпаратиреозу у пацієнтів, прооперованих у КНП «Обласна клінічна лікарня Івано-Франківської обласної ради» за 2019-2024рр. Вивчено клінічні і лабораторні характеристики пацієнтів та підходи до хірургічного лікування. Для статистичної обробки результатів використано комп'ютерні програми STATISTIKA-12 (StatSoft Inc., США), «Microsoft Excel» та варіаційно-статистичний аналіз. Числові дані наведено у вигляді середньої арифметичної величини M, стандартного відхилення SD, числа варіанта n. Відмінності між даними перевіряли за t-критерієм Стьюдента і вважали достовірними при $p<0,05$.

Результати. Проаналізовано 77 випадків оперативних втручань, з яких: 67 – з приводу первинного гіперпаратиреозу і 10 – з приводу третинного гіперпаратиреозу. У 62 пацієнтів (95,40%) з первинним гіперпаратиреозом виявлено солідну аденому, найчастіше у нижніх паращитовидних залозах (85,07%). Більшість аденом було діагностовано «як знахідку», при ультразвуковому дослідженні щитоподібної залози, найчастіше у жінок (83,6%). В 56 осіб (83,58%) з первинним гіперпаратиреозом виявлено гіперкальціємічний варіант хвороби, а в 11 пацієнтів (16,42%) рівень кальцію не перевищував показники норми. В медичних картах недостатньо доказів для підтвердження нормокальціємічного варіанту первинного гіперпаратиреозу. Пацієнтам з первинним гіперпаратиреозом проведено селективну паратиреоїдектомію, з третинним гіперпаратиреозом – субтотальну паратиреоїдектомію. В усіх випадках діагноз підтверджено післяопераційним гістологічним дослідженням.

Висновки. Абсолютну більшість серед прооперованих пацієнтів становили хворі з первинним гіперкальціємічним варіантом хвороби. Характеристики пацієнтів з нормокальціємічним варіантом первинного гіперпаратиреозу потребують підкріплення задокументованими доказами, відповідно до критеріїв діагнозу: тривало-стабільних нормокальціємії, гіперпродукції паратиреоїдного гормону та виключення причин вторинного гіперпаратиреозу. Лікування гіперпаратиреозу потребує персоналізованого підходу, який включає визначення типу, варіанта, ускладнень та показань до хірургічного втручання.

Ключові слова: **гіперпаратиреоз, гіперкальціємічний гіперпаратиреоз, нормокальціємічний гіперпаратиреоз, підходи до лікування, ретроспективне дослідження**

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