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Original Article

How should normocalcemic primary hyperparathyroidism be managed? Comparison with classical hypercalcemic form

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Abstract

Aim: Normocalcemic primary hyperparathyroidism (N-PHPT) is a different variant of primary hyperparathyroidism characterized by normal serum calcium (Ca) concentrations and elevated parathormone (PTH) levels in the absence of secondary causes of hyperparathyroidism. However, the clinical course and therapeutic approaches of this entity have been not fully demonstrated. We aimed to determine the clinicopathological characteristics and surgical outcomes of patients with N-PHPT, comparing with patients who had hypercalcemic PHPT (H-PHPT).

Materials and Methods: A total of 185 patients who underwent parathyroidectomy for PHPT were included in the study. The patients were classified as N-PHPT and H-PHPT. The two groups were then compared between each other in terms of all demographic, clinical, and surgical features.

Results: One hundred and fifty-one (81.6%) patients had a diagnosis of H-PHPT while 34 (18.4%) patients were normocalcemic. Both groups were similar in age, preoperative vitamin D level, preoperative PTH level, and type of surgery ($p > 0.05$). Preoperative Ca level was significantly different between the groups ($p < 0.01$). Prevalence of urolithiasis and decreased bone density was similar between the groups ($p > 0.05$).

Conclusion: N-PHPT patients had similar demographic and clinical features in comparison to those with H-PHPT, indicating that the surgical decision in patients with N-PHPT should be similar with H-PHPT cases.

Keywords: Hypercalcemic; management; normocalcemic; primary hyperparathyroidism

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder associated with excessively secretion of parathyroid hormone (PTH) by one or more parathyroid glands. Although this disease is traditionally characterized by elevated serum levels of calcium (Ca) and PTH, a new and different clinical entity, named as normocalcemic primary hyperparathyroidism (N-PHPT), has been recognized over the last decade. In this distinct phenomenon of PHPT, exact diagnosis is based on normal serum Ca concentrations and elevated PTH levels in the absence of secondary causes of hyperparathyroidism such as chronic renal failure, vitamin D (vit D) insufficiency, and use of medications altering Ca homeostasis (thiazide, lithium, etc.) (1). Because N-PHPT is a relatively new entity and related-data is quite limited, discussions about the clinical course of this disorder and therapeutic approaches are still ongoing (2,3). Therefore, in recent years, studies have focused on the comparison of N-PHPT with the classical type of disease, in order to make a definitive definition of this entity and clarify its clinicopathological features (4-6).

In this study, we aimed to determine the clinicopathological characteristics and surgical outcomes of patients with N-PHPT, comparing with patients with classical PHPT.

MATERIALS and METHODS

Patients and Study Design

A total of 185 consecutive patients who underwent parathyroidectomy for PHPT at the endocrine surgery department of a single tertiary level referral center, between January 2016 and December 2018 were included in this retrospective study. Patients' age and gender, baseline biochemical parameters, and final pathology results were recorded. Being under 18 years old, using a drug that interfered with calcium (Ca) homeostasis (Ca or vitamin D supplements, bisphosphonates, diuretics, lithium, etc.), biochemical findings indicating renal insufficiency,

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and causes of secondary hyperparathyroidism were the exclusion criteria. Hypocalcemia was defined as serum corrected Ca level less than 8.0 ng/mL. Serum corrected Ca was measured as follows: measured Ca + 0.02 × (40 – serum albumin). Serum vit D level less than 30 ng/mL accepted as deficiency.

All patients were classified as normocalcemic PHPT and hypercalcemic PHPT. The two groups were then compared between each other in terms of all demographic, clinical, and surgical features. Insti¬tutional ethical committee of Ankara City Hospital approved the study on December 9, 2020 (Number of ethics committee approval: E1-20-1336). This study was conducted in accordance with the Declaration of Helsinki. Written informed consent form was obtained from patients at the time of the registry.

Statistical Analysis

The Statistical package for social science (SPSS 20.0 software, IL-Chicago-USA) standard version was used for data analysis. Descriptive analyses were presented as number/percentage for categorical variables, and mean±SD/percentages for continuous variables. Chi-square test, Mann Whitney U test, and Fisher's exact test were used to evaluate the differences between the two groups. P < 0.05 was accepted as significance level.

RESULTS

A total of 185 patients (ranging from 18 to 86) with a mean age of 54.1±11.4 years were included in this study. There were 27 (14.6%) males and 158 (85.4%) females.

Table 1. Baseline patient characteristics (n=185)

Characteristics	n (%)
Age (years)	54.1±11.4 (18-86)
Gender (F/M)	158 (85.4%)/27 (14.6%)
Preoperative Ca (ng/mL)	11.07±0.9 (9.1-16.4)
Preoperative P (ng/mL)	2.62±1.6 (1.4-24)
Preoperative PTH (ng/mL)	245.8±24.4 (150.3-1685.3)
Preoperative vit D (ng/mL)	16.9±2.6 (2.8-39)
Type of surgery	
Minimal invasive surgery	145 (78.4%)
Classical surgery (four gland exploration)	40 (21.6%)
Final pathology	
Single adenoma	161 (84.9%)
Double adenoma	10 (5.4%)
Hyperplasia	14 (7.7%)

Data are presented as mean±SD (min-max) for age, preoperative Ca, preoperative P, preoperative PTH and preoperative vit D

Table 2. Comparison of demographic, clinical, and operative data between the groups

Data	patients with H-PHPT (n=158)	patients with N-PHPT (n=34)	p
Age (years)	54.1±11.2	54.4±12.2	0.750
Gender			< 0.01
Female	124 (82.1%)	34 (100%)	
Male	27 (17.9%)	0	
Preoperative Ca (ng/mL)	11.3±0.8	10±0.4	< 0.01
Preoperative P (ng/mL)	2.6±1.8	2.6±0.6	0.147
Preoperative PTH (ng/mL)	246.9±23.8	241.1±29.2	0.556
Preoperative vit D (ng/mL)	17.6±18.4	13.5±10.4	0.205
Presence of urolithiasis	30 (20%)	5 (14.7%)	0.476
Preoperative T score	-2.3±1.2	-2.4±0.9	0.775
Postoperative Ca (ng/mL)	8.8±0.9	8.5±0.9	0.058
Type of surgery			0.648
Minimal invasive surgery	117 (77.5%)	28 (82.4%)	
Classical surgery*	34 (22.5%)	6 (17.6%)	
Final pathology			0.868
Single adenoma	132 (87.4%)	29 (85.3%)	
Double adenoma	9 (6%)	1 (2.9%)	
Hyperplasia	10 (6.6%)	4 (11.8%)	
Persistent disease	6	2	0.642
Recurrent disease	1	0	0.060

Data are presented as mean±SD for age, preoperative Ca, postoperative Ca, preoperative P, preoperative PTH, and preoperative vit D; n (%) for other variables. *four gland exploration

One hundred and fifty one (81.6%) patients had a diagnosis of H-PHPT while the remaining 34 (18.4%) patients were normocalcemic. The demographic and clinicopathological data were presented in Table 1.

Patients were classified into two groups: patients with H-PHPT and those with N-PHPT. Both groups were similar in terms of age, preoperative vit D level, preoperative PTH level, and type of surgery ($p > 0.05$). Preoperative mean Ca level was significantly different between the two groups ($p < 0.01$). Prevalence of preoperative urolithiasis and decreased bone density was similar between the groups ($p > 0.05$).

Statistically, type of surgery, postoperative Ca level, persistent hyperparathyroidism, and recurrent hyperparathyroidism were not different between normocalcemic and hypercalcemic patients ($p > 0.05$). The comparison of all demographic, clinical, and operative data between the two patient groups were presented in Table 2.

DISCUSSION

In recent years, more patients have been diagnosed with N-PHPT, thanks to the widespread availability of PTH assays and increased awareness of this clinical entity among physicians. However, there is still no consensus on the management of this new phenomenon despite the recent international scientific efforts (3). First of all, the exact prevelance of N-PHPT is not well known since data regarding this disorder were mainly obtained from small-scale studies consisted of symptomatic cases diagnosed during an evaluation for bone health or urinary stone (4,7). In few studies addressed the issue of N-PHPT, its prevalence has been reported in a wide range between 0.4 and 19% (8-10). The differences between those studies were mainly due to the different patient populations, different cut-off values of serum Ca and/or vit D, and different diagnostic criteria used for N-PHPT. To us, the relatively high prevalence of 18.4% in our patient cohort can be explained by the high volume and referral center of our hospital in the country. The other controversial issue is whether N-PHPT is an indolent disease or early phase of hypercalcemic PHPT. Some authors reported a disease model that N-PHPT is said to progress classical hypercalcemic form within several years whereas others showed that a significant proportion of patients with N-PHPT would no longer fit this diagnosis during their follow-up periods (8, 11). In the literature, both similarities and differences in laboratory findings and clinical characteristics were reported between the normocalcemic and hypercalcemic PHPT patients. Therefore, in this study, we focused on the determination of biochemical and clinical features of N-PHPT, comparing with hypercalcemic PHPT.

In the present study, mean age was similar between patients with N-PHPT and those with H-PHPT, in consistent with the previous reports (12-14). As known, PHPT is more frequent in women than men (13,14). Although there was no difference in gender between N-PHPT and H-PHPT in previous reports, all patients with N-PHPT were female in our cohort. This may be explained by the limited number of patients and the fact that study population was usually composed of postmenopausal women (1,10,13,14).

In the comparison of biochemical findings between the two groups, patients with N-PHPT had lower mean Ca level compared with hypercalcemic patients, as expected. Vit D and PTH levels, however, were similar between the groups. This biochemical profile was comparable with those reported in other previous works (10,14-16). According to the recent guidelines permanently normal calcium levels and consistently high PTH levels could define N-PHPT. It is clear that the normal calcium assessment needs to be verified several times and an increased PTH level needs to be confirmed in at least 2 consecutive measurements. Moreover, other causes of secondary hyperparathyroidism should also be excluded. Among these, drugs such as diuretics, anticonvulsants, denosumab, lithium, bisphosphonates and phosphorus, diseases (celiac, inflammatory bowel disease and bariatric surgery history) in which calcium absorption are negatively affected from gastrointestinal tract, deficiency of vitamin D, chronic kidney disease and hypercalciuria are the reasons that come to mind first (17). However, the exact threshold value for vit D that causes an increase in PTH is still controversial and 30 ng/mL is a more widely accepted cut-off value which is also supported by the Endocrine Society. It should also be kept in mind that some normocalcemic patients displaying high PTH levels will become hypercalcemic when vit D levels are higher than 30 ng/mL and the correct diagnosis may change to "classical" hypercalcemic PHPT (6). In our study, the most important factor limiting the accurate identification of N-PHPT was the deficiency of vit D seen in the majority of the patients. Therefore, the approach as endocrine surgeons should be appropriate D vit supplementation in normocalcemic patients prior to surgery and subsequent re-evaluation of the defining factors such as Ca and PTH levels.

On the other hand, the main question is the clinical course of patients with N-PHPT. In the literature, there are conflicting data about the differences in clinical presentations between the normocalcemic and hypercalcemic variants of PHPT. According to us, one of the important reasons of this situation is the inappropriate use of diagnostic criteria of N-PHPT, especially in terms of exclusion of secondary causes of hyperparathyroidism. Therefore, in order to make an appropriate patient cohort, we tried to exclude all patients who had secondary causes of hyperparathyroidism in our study.

As is well known, kidney stones and presence of decreased bone mineral density are among the primary clinical manifestations in patients with PHPT. According to our results, normocalcemic patients had similar prevelances of nephrolithiasis and decreased bone density with hypercalcemic ones, comparable with findings in other

works (7,10,12,18,19). In our opinion, these results demonstrate that N-PHPT is not an indolent disease state and such patients had similar demographic and clinical patterns in comparison to patients with classical type of PHPT. Today, management guidelines have not been well established for N-PHPT. An approach including annual clinical and biochemical assessment for asymptomatic patients and surgery for symptomatic subjects or who have complications have been recently recommended (10). We also suggest that our findings supported this approach.

Postoperative courses of both patient groups were also evaluated in the present study. The prevalence of persistent or recurrent disease was not different between the normocalcemic and hypercalcemic patients.

CONCLUSION

This study reveals that patients with N-PHPT have similar demographic and clinical characteristics compared to patients with H-PHPT, and highlights that the surgical decision in patients with N-PHPT should be similar to H-PHPT cases.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: Local ethics board approval (Ankara City Hospital) was obtained for this study on December 9, 2020 (Number of ethics committee approval: E1-20-1336).

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