MULTIGLANDULAR PARATHYROID GLAND DISEASE: AN INCIDENTAL DISCOVERY IN NORMOCALCEMIC PATIENTS DURING THYROID SURGERY

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Abstract

Context. Several enlarged parathyroid glands could be found during thyroid surgery in normocalcemic patients without evidence of primary or secondary hyperparathyroidism, indicating multiglandular parathyroid gland disease (MGD).

Objective. Clinical role of various levels of serum ionized calcium (Ca^{2+}) in patients diagnosed with incidental MGD during thyroid surgery remains controversial. The aim of the study was to evaluate the features of PHPT and the clinical role of serum Ca^{2+} in normocalcemic patients diagnosed with incidental MGD.

Study design. A prospective study of patients with normal preoperative Ca^{2+} to be operated on for thyroid diseases in 2010-2013 and diagnosed with MGD during thyroid surgery.

Methods. An analysis of clinical data from 3,561 patients to be surgically treated for thyroid diseases revealed 219 (6%) patients with MGD and normal serum Ca^{2+} . Further data analyses showed patients with MGD and high normal ($\geq 1.25 - 1.3$ mmol/L) serum Ca^{2+} ($n = 89$) and with moderate-low ($1.0 - 1.24$ mmol/L) serum Ca^{2+} ($n = 130$).

Results. Primary hyperparathyroidism was diagnosed intra- and post-operatively in 48 (54%) patients with high-normal serum Ca^{2+} and in 2 (2%) patients with moderate-low serum Ca^{2+} ($p < 0.0001$). Parathyroid hormone, serum Ca^{2+} as well as urine calcium excretion were elevated in 2 (2%) patients with moderate-low serum Ca^{2+} and in 18 (20%) patients with high-normal Ca^{2+} at follow-up ($p < 0.0001$).

Conclusion. Serum Ca^{2+} level within the normal range, but higher than 1.25 mmol/L (high-normal) is associated with primary hyperparathyroidism, which should be considered in patients with visually diagnosed MGD, but without clinical symptoms of hyperparathyroidism.

Key words: parathyroid enlargement, multiglandular parathyroid disease, normocalcemic, thyroid surgery.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the most common benign disorder of parathyroid gland associated with parathyroid adenoma (PTA) or hyperplasia, which has resulted in elevation of parathyroid hormone (PTH) and serum calcium levels (1, 2). PHPT could be also associated with the multiglandular disease (MGD), which is diagnosed in patients with 2 and more enlarged parathyroid glands. According to data from published series, MGD could be diagnosed as incidental discovery during thyroid surgery in up to 34% of patients to be operated on for benign and malignant thyroid lesions (3-9). Pathogenesis of MGD and other parathyroid diseases demonstrates various molecular abnormalities, playing role for diagnosis of multiple endocrine neoplasia (MEN) and other hereditary syndromes associated with parathyroid gland lesions (10, 11). Furthermore, MGD can be associated with sporadic PTA or hyperplasia of parathyroid gland and diagnosed in individuals with mild or normocalcemic PHPT (7, 9, 12). The latter could represent a clinical challenge since it may demonstrate asymptomatic course with slightly elevated serum calcium or related to MGD with secondary HPT associating with vitamin D deficiency (13). In such circumstance, intraoperative discovery of MGD is supported neither by symptoms nor by preoperative PTH measurement, which is not regularly performed in patients before thyroid surgery. Intraoperative PTH assay (IOPTH) is highly informative and can be applied during the surgery in case of MGD, however this diagnostic tool is not always available in many hospitals of middle-income countries, including Ukraine. Also, frozen section biopsy could be performed for macroscopically abnormal parathyroid glands during thyroidectomy or other types of thyroid surgery, which is a useful intraoperative diagnostic

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tool (12). Furthermore, preoperative serum ionized calcium (Ca^{2+}) could also be taken into consideration whether or not parathyroidectomy must be performed for macroscopically abnormal parathyroid gland in patients with asymptomatic PHPT and serum Ca^{2+} is usually included in preoperative blood evaluation. Although normocalcemic hyperparathyroidism shows normal ranges of serum Ca^{2+} we hypothesize that PHPT could be associated more often with borderline levels of serum Ca^{2+} . However, little is known about the association between MGD, hyperparathyroidism and serum Ca^{2+} levels. The aim of the study was to evaluate the features of PHPT and the clinical role of serum Ca^{2+} in normocalcemic patients diagnosed with incidental MGD during thyroid surgery.

PATIENTS AND METHODS

All surgically treated patients with thyroid pathology between January 2010 and December 2013 at the Ukrainian Scientific and Practical Center for Endocrine Surgery (Kyiv, Ukraine) were eligible for the study. All patients provided their written informed consent to participate in the study. The study was approved by the local ethical committee. Among 3,561 individuals who underwent thyroid surgery, 219 patients were diagnosed with MGD and normal preoperative serum Ca^{2+} level. Of these, 89 patients were identified with high-normal serum Ca^{2+} (range 1.25-1.3 mmol/L) and 130 patients had moderate-low serum Ca^{2+} (range 1.0-1.24 mmol/L). The possible history of radiation exposure could be considered, because most of patients from the study lived in 1986 within the area of radioactive contamination after Chernobyl accident in 1986. We excluded patients diagnosed with PHPT or renal secondary HPT, MEN1 or MEN2 syndromes before the operation.

Pre-operative investigation

An ultrasound (US) examination of thyroid was performed for all patients by using an ultrasonography system equipped with 3.5– 7.5 MHz transducers (Toshiba, Japan).

Blood testing was performed for all patients to evaluate serum free thyroxine (normal ranges 11.96 – 22.01 pmol/L), free triiodothyronine (normal ranges 3.1 – 3.73 pmol/L), thyroid stimulating hormone (normal ranges 0.27 – 4.2 mIU/L), serum Ca^{2+} (normal ranges 1.0 – 1.3 mmol/L), phosphorus (normal ranges 0.81–1.45 mmol/L), creatinine (normal ranges 62 – 106 $\mu\text{mol/L}$ for male and 44– 80 $\mu\text{mol/L}$ for female) by using Cobas

E 411 analyzer (Roche Diagnostics GmbH, Germany) and Sapphir-400 (Tokyo Boeki Ltd, Japan).

Surgical approach

During thyroid surgery a routine identification of parathyroid glands was performed followed by their mobilization from the side of thyroid resection, preserving blood supply of the parathyroid gland, identification and preservation of laryngeal nerves. The enlarged parathyroid gland was determined as a tan to red-brown color, well-circumscribed solitary mass larger than 6*4*2 mm (7, 14). The visual evaluation of the parathyroid gland is an appropriate approach to suspect pathological changes, which is also supported by current consensus report of the European Society of Endocrine Surgeons (9). In this study, if one of parathyroids was enlarged, the remaining glands were also revised. This policy is routinely applied in our institution by senior surgeons including the author of the current study (S.M.C.). However, systematic identification of parathyroid glands is not usually performed in case of macroscopically unchanged parathyroids, which is in line with other professionals in the field (15). Intraoperative frozen section biopsy was performed for the largest parathyroid gland by using cryostat Leica (Leica Biosystems, Germany). The biopsy of parathyroid gland was performed only in patients with high-normal levels of Ca^{2+} demonstrating 3 or 4 enlarged parathyroids. Biopsy was also performed in 6 patients with two enlarged parathyroids because of significant asymmetrical shape and size of the glands. A parathyroidectomy was performed if frozen section showed a hypercellular pattern and a proportion of the fat cells less than 20% of the specimen view field. Frozen section biopsy was not performed in patients with moderate-low serum Ca^{2+} levels due to the risk of hypoparathyroidism. The remained parathyroid glands were marked with non-absorbable colored suture or titanium clips to improve their identification in case of possible reoperation (Fig. 1). The diagnosis was confirmed by histopathological examination of sections routinely stained with hematoxylin and eosin according to WHO classification of endocrine tumors (1). IOPTH assay was not available.

Post-operative evaluation

Postoperatively, serum concentrations of vitamin D (normal range 30– 100ng/mL), Ca^{2+} , PTH (normal range 15– 65 pmol/L), calcitonin (normal range 2– 15pg/mL), urinary excretion of calcium (normal range 2.5 – 7.5 mmol/24h) were determined

in all patients with MGD. Furthermore, serum Ca^{2+} and PTH were evaluated 1-2 times a year during the follow-up.

After parathyroidectomy patients with vitamin D deficiency were administer cholecalciferol or ergocalciferol. Kidney function was evaluated by analyses of creatinine levels, and patients with signs of chronic kidney failure were undergone for treatment with active forms of vitamin D3 (calcitriol).

Statistical analyses

All statistical analyses were performed by using IBM SPSS v.22 (IBM Corporation, USA). The Mann-Whitney U Test and Fisher's (two-tailed) exact test were applied to evaluate differences in studied parameters. Results with p-values <0.05 were considered as statistically significant.

RESULTS

In total we identified 219 patients who were diagnosed with MGD during thyroid surgery within a four-year period, giving a proportion of 6% out of all surgically treated patients diagnosed with thyroid pathology. Thyroid surgery was performed to treat patients with multinodular goiter, thyroid carcinoma or Graves' disease. All patients were euthyroid at operation. MGD were diagnosed predominantly in female patients > 45 years in both study groups. Evaluation of US data revealed features of thyroid pathology, but showed no signs of parathyroid enlargement. Analyses of the clinical data and laboratory findings are summarized in Tables 1 and 2, respectively. A representative case of MGD is

illustrated in Figure 1. The mean follow-up time for patients was 24 months (range 12 – 54 months).

Surgical findings

During thyroid surgery 43 (48%) frozen section biopsies were performed in patients with high-normal serum Ca^{2+} . Of these, 35 patients underwent parathyroidectomy, considering possible PHPT due to visually eminent enlargement parathyroid glands and hypercellular pattern of their histopathology at frozen section. Histopathological examination of these 35 patients with possible PHPT demonstrated chief parathyroid cell hyperplasia in 29 (33%) patients (Fig. 2), oncocytic parathyroid hyperplasia in 5 (6%) patients, and PTA in 1 (1.1%) patient. Decreasing of PTH under the lower border of normal range was detected in 27 (30%) patients with high-normal Ca^{2+} after removing of single enlarged parathyroid gland (mean: 14.3 ± 3.8 pmol/L; range: 4.1-19.9 pmol/L) and 8 (9%) patients demonstrated normal range of PTH after the operation (46.5 ± 5.9 pmol/L). Furthermore, of 35 patients who underwent parathyroidectomy 9 patients had mild vitamin D deficiency. All these patients were administer Vitamin D supplementation. Overall, vitamin D deficiency was diagnosed in 23 (26%) of patients with high-normal Ca^{2+} and in 112 (86%) of group with moderate-low Ca^{2+} (Table 1).

Parathyroidectomy during thyroid surgery was not performed in 8 (9%) cases, because frozen section biopsy demonstrated a high proportion of fat cells and no evidence of hypercellularity (Fig. 2). In these 8 patients parathyroid glands were not considered as hyperfunctional and clinical or laboratory signs of PHPT did not show PHPT at follow-up.

Figure 1. Illustration of intraoperatively discovered parathyroid gland enlargement. (A) Yellowish enlarged parathyroid gland (marked by arrow) is dissected for frozen biopsy. (B) The remnant part of parathyroid gland is marked by non-absorbable suture with titanium clips.

Table 1. Summary of clinical data from patients with multiglandular parathyroid disease

Parameter	Patients (n = 219)		P-value
	Moderate-low Ca ²⁺ (n = 130)	High-normal Ca ²⁺ (n = 89)	
Preoperative diagnosis			
Thyroid carcinoma, n =	61 (47%)	49 (55%)	NS
Multinodular goiter, n =	55 (42%)	29 (33%)	NS
Graves' disease, n =	14 (11%)	11 (12%)	NS
Thyroid surgery			
Total thyroidectomy	109 (84%)	79 (89%)	NS
Hemithyroidectomy	21 (16%)	10 (11%)	NS
No. of enlarged parathyroid glands			
2	61 (47%)	52 (58%)	NS
3	39 (30%)	28 (32%)	NS
4	30 (23%)	9 (10%)	0.02
Frozen section biopsy			
Yes	-	43 (48%)	-
No	-	46 (52%)	-
Parathyroid surgery			
At time of thyroid surgery	0	35 (39%)	<0.0001
At follow-up	1 (0.8%)	18 (20%)	<0.0001
PHPT diagnosis			
Yes	2 (2%)*	48 (54%)	<0.0001
No	128 (98%)	41 (56%)	
Chronic renal failure			
Yes	9 (7%)	1 (1%)	0.051
No	121 (93%)	88 (99%)	
25-OH vitamin D deficiency			
Yes	112 (86%)	23 (26%)	<0.0001
No	18 (14%)	66 (74%)	

- = not applicable or not available; NS = not significant; * = diagnosed at follow-up; PHPT = primary hyperparathyroidism.

Figure 2. Microphotographs illustrating frozen section specimens of enlarged parathyroid gland (hematoxylin & eosin staining, x200). (A) A hypercellular pattern of chief cells is observed without evidence of parenchymal fat cells indicating hyperplasia of parathyroid gland. (B) Enlarged parathyroid gland without histopathological features of hyperplasia: chief and oxyphil parathyroid cells accompanied by parenchymal fat cells, indicating normal microscopical histopathology of frozen section sample.

Table 2. Analyses of laboratory findings of study cohort

Parameter	Patients (n = 219)		Normal range	P-value
	Moderate-normal Ca ²⁺ (n = 130)	High-normal Ca ²⁺ (n = 89)		
Serum Ca ²⁺ , mean (range) mmol/L	1.12 (0.99–1.24)	1.28 (1.25–1.31)	1.0–1.3	0.044
Urinary calcium*, mean (range), mmol/L/24h	2.7 (1.9–3.1)	4.9 (3.1–9.3)	2.5–7.5	NS
Phosphorus, mean (range) mmol/L	1.45 (1.11–1.94)	0.97 (0.7–1.14)	0.81–1.45	NS
PTH*, mean (range), pmol/L	89 (54–112)	74 (11–134)	15–65	NS
Vitamin D*, mean (range), ng/mL	19 (7–49)	31 (19–64)	30–100	0.04
Creatinine, mean (range), µmol/L	89 (63–127)	68 (46–89)	62–106	0.03

NS = not significant; * = evaluated postoperatively.

PHPT diagnosis at follow-up

At follow-up, a slightly decreasing PTH level (within normal range but at upper limit) was detected in 71 (80%) patients with high-normal serum Ca²⁺ after vitamin D administration. Significant decreasing of PTH level followed by its normalization was achieved in 121 (93%) patients with moderate-low serum Ca²⁺ after vitamin D administration >3 months. CRF was detected in 1 (1%) patient with high-normal serum Ca²⁺ and in 9 (7%) patients with moderate-low serum Ca²⁺, demonstrating borderline difference (p=0.051). PTH level, serum Ca²⁺ as well as urine calcium excretion were elevated in 2 (2%) patients with moderate-low serum Ca²⁺ and in 18 (20%) patients with high-normal Ca²⁺ (p<0.0001), indicating possible PHPT. Of these 18 individuals with high-normal serum Ca²⁺, frozen section biopsy of enlarged parathyroid gland was not performed in 13 patients, whereas in 5 patients one parathyroid gland was previously removed during the thyroid surgery (all of these 5 patients did not demonstrate decreasing of PTH below the lower border of its normal range after removing of one parathyroid gland (at the first operation during thyroid surgery).

Parathyroidectomy of one parathyroid gland was performed in 18 patients with high-normal serum Ca²⁺ and in 1 patient with moderate-low normal Ca²⁺. Final histopathological examination revealed PTA (n = 2) and parathyroid chief cell hyperplasia (n = 17). At reoperation previously marked by non-absorbable suture parathyroid glands were identified, and therefore minimal extent of tissue dissection was achieved. A palsy of recurrent laryngeal nerve was not detected, which was confirmed by both laryngoscopy and US of vocal cords. Parathyroid surgery was not performed for one patient with initially moderate-low serum Ca²⁺, who was diagnosed with PHPT postoperatively and received medication by vitamin D.

After initial operation during thyroid surgery a PHPT was diagnosed in 18 patients from high-normal

Ca²⁺ group (including 5 patients after removing of 1 parathyroid gland) and 1 patient from moderate-low Ca²⁺ group. All these patients (except one patient with mild PHPT, who refused to undergo surgery) were operated on PHPT with excision of one enlarged parathyroid gland (largest or marked at previous operation). Of these 18 patients, one enlarged parathyroid gland was removed in 5 patients, thus another parathyroid gland was excised at second operation. No signs of PHPT relapse were detected within the mean follow-up of 24 months.

Taken together, these findings indicate that PHPT was diagnosed totally in 48 (54%) patients with high-normal serum Ca²⁺ (30 patients who were operated initially during thyroid surgery as well as 18 patients with high-normal Ca²⁺ who were operated at follow-up) and in 2 (2%) patients with moderate-low serum Ca²⁺ (p<0.0001).

DISCUSSION

In this clinical study we investigated a cohort of patients with normal serum Ca²⁺ levels who were diagnosed with MGD during thyroid surgery.

Our findings demonstrate that MGD was diagnosed in 219 patients, constituting 6% out of all patients being operated on for benign and malignant thyroid lesions at our institution. Furthermore, our study shows that incidental identification of enlarged parathyroid glands is a relatively frequent discovery during thyroid surgery, which is in agreement with other studies demonstrating MGD in 0.2–4.5% of patients (3–8). It is worth mentioning that Boehm *et al.* suggested radiation exposure to play a certain role as a possible risk factor for the development of hyperparathyroidism as a late adverse effect after the accident at Chernobyl nuclear plant in 1986 (16). Although patients from the current study lived in 1986 within the radioactively contaminated, further investigations are needed to test

this hypothesis in such a cohort of adult patients as for instance Dinets *et al.* performed for thyroid carcinoma (17).

In line with other professionals in surgery centers, we did not perform routine PTH measurement before thyroid surgery in patients with normal serum Ca^{2+} (8, 18). Intraoperative discovery of MGD raises the question whether or not parathyroidectomy must be performed for macroscopically enlarged parathyroid gland without preoperatively established diagnosis of PHPT in patients with normal serum Ca^{2+} . Studies suggest to apply IOPTH measurement or frozen section biopsy (12, 19–22). However, both diagnostic methods demonstrate advantages and limitations. In current study frozen section biopsy was performed in patients having 2–4 enlarged parathyroid glands and high-normal serum Ca^{2+} to avoid postoperative hypoparathyroidism (19). Similar to other reports we demonstrated that frozen section biopsy is a highly informative tool for intraoperative diagnosis of parathyroid lesions (20, 21). In contrast, Nagar *et al.* performed mainly IOPTH and a few frozen sections in the study of minimally invasive parathyroidectomy for PHPT management (22). However, in that study PTH level was failed to drop by 50% in cases of MGD resulting in conversion to open neck exploration. The using of IOPTH remains controversial for detection of MGD as shown in studies of preoperatively suspected PHPT (20, 23). It is worth mentioning that in patients without preoperative information about PTH and with moderate-low or normal-high serum Ca^{2+} , IOPTH can be elevated or decreased due to parathyroid gland reaction to surgical manipulations, which could result in IOPTH misinterpretation (24). Furthermore, IOPTH assay is not available in some investigations including the current study (8). Final histopathology showed chief cell hyperplasia of parathyroid gland in majority of patients, which is consistent with Alhefdhi *et al.* and Cayo *et al.* (25, 26), whereas other studies found that PTA was the most common histopathological diagnosis of parathyroid gland removed (4, 7, 8, 14).

At follow-up a significant decrease of PTH level followed by its normalization was achieved in majority of patients with moderate-low serum Ca^{2+} after vitamin D administration >3 months, indicating a vitamin D insufficiency. These data are in agreement with Beyer *et al.* who showed a MGD in association with vitamin D insufficiency (27). The overall recurrence of PHPT in our cohort was 8% in the close follow-up. Similar observation has also been reported by Schneider *et al.* demonstrating PHPT recurrences during the

relatively short follow-up which could be considered as a specific feature of multiglandular disease (28). In the current study, we found that patients with MGD and high-normal serum Ca^{2+} had a significantly higher frequency of PHPT recurrence at follow-up as compared to patients with moderate-low levels of serum Ca^{2+} . This observation implies that high-normal levels of preoperative serum Ca^{2+} may be associated with a higher risk of PHPT relapse in patients who were not surgically treated for MGD. This hypothesis is also supported by low recurrence rate among the individuals who underwent parathyroidectomy during the thyroid surgery. The relatively low recurrence rate was achieved in patients after frozen section biopsy of macroscopically enlarged parathyroid gland followed by parathyroidectomy. We diagnosed the recurrence after the parathyroidectomy in 5 (14%) patients with high-normal serum Ca^{2+} which can be attributed to asynchronous hyperplasia development in MGD as suggested by Alhefdhi *et al.* (25). At reoperation parathyroid glands were identified, which also was confirmed by identification of non-absorbable suture with titanium clips to be applied during the previous thyroid surgery. Although all reoperations were performed by experienced endocrine surgeon (S.M.C.), we consider the intraoperative marking of parathyroid glands by non-absorbable suture as a useful tool for better identification of parathyroid glands at the next surgical interventions resulting in reduction of postoperative complications, e.g. recurrent nerve palsy.

The possible limitation of the study is within the confirmation of PHPT diagnosis, which is possible based only on preoperative laboratory data: elevated serum PTH and Ca^{2+} after compensation of vitamin D deficiency. We speculated that probably all patients with MGD may have an increased concentration of PTH before surgery (reflected primary or secondary hyperparathyroidism), but only patients treated properly with PHPT might demonstrate a significant decrease of PTH level after removing one of the largest parathyroid glands. In contrast, patients with secondary hyperparathyroidism (mostly due to vitamin D deficiency) are not expected to clinically react on parathyroidectomy of single gland, but these patients may respond to administration of vitamin D. Moreover, patients with PHPT in relation to MGD are expected to show only a temporary decrease of PTH.

In conclusion, we reported the results of a clinical study of patients with moderate-low and high-normal serum Ca^{2+} level in patients with MGD to be identified during the thyroid surgery. Our findings

imply that serum Ca^{2+} level within the normal range, but higher than 1.25 mmol/L (high-normal) is associated with a high risk of occult PHPT, which should be considered in patients with MGD, but without clinical symptoms of hyperparathyroidism.

Conflict of interest

The authors declare that they have no conflict of interest.

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