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ORIGINAL ARTICLE

Mild sporadic primary hyperparathyroidism: high rate of multiglandular disease is associated with lower surgical cure rate

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Abstract

Background Mild primary hyperparathyroidism (serum calcium ≤ 2.85 mmol/L) is the most representative form of pHPT nowadays. The aim of this study was to evaluate its subtypes and the multiglandular disease (MGD) rate as it may lower the sensitivity of preoperative parathyroid scintigraphy and the surgical cure rate.

Methods We retrospectively included patients with mild pHPT who underwent parathyroid dual-tracer scintigraphy with ^{99m}Tc-MIBI SPECT/CT and surgery between January 2013 and December 2015. Cure was defined as normalization of serum calcium (or PTH in the normocalcemic form) at 6 months. MGD was defined by either two abnormal resected glands or persistent disease after resection of at least one abnormal gland.

Results We included 121 patients. Median preoperative serum calcium was 2.68 mmol/L and median PTH was 83.4 pg/mL. A total of 141 glands were resected (95 adenomas, 33 hyperplasias). The subtypes were 57% classic, 32.2% normohormonal, and 10.7% normocalcemic. MGD occurred in 23.5% of patients divided as 13%, 30%, and 64% respectively ($p = 0.0011$). The surgical cure rate was 85.2%.

The normocalcemic form had lower cure rate than the normohormonal (45% vs 84%, $p = 0.018$) and classic forms (45% vs 93%, $p = 0.0006$). MIBI scintigraphy identified at least one abnormal lesion, later confirmed by the pathologist in 90/98 patients, making the sensitivity per patient 91.8% (95% CI 84.1–96.2%).

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Conclusions MGD is strongly associated with mild pHPT, especially the normocalcemic form where it accounts for 64% of cases. Bilateral neck exploration should be performed in this population to improve the cure rate, even if the scintigraphy shows a single focus.

Keywords Mild primary hyperparathyroidism · Multiglandular disease · Parathyroidectomy · MIBI scintigraphy · Neck ultrasound · Normocalcemic form · Sestamibi scan

Introduction

Mild sporadic primary hyperparathyroidism (pHPT) is increasingly being diagnosed due to routine measurement of serum calcium. It is the third most frequent endocrine disease after diabetes and thyroid disorders [1]. The most common presentation is a single adenoma, the resection of which leads to the cure of patients. The multiglandular disease (MGD) is more difficult to cure because of the need to resect two or more pathologic glands, requiring bilateral neck exploration (BNE) or unilateral neck exploration (UNE), as guided by preoperative imaging and/or intraoperative parathormone (PTH) assay. The incidence of MGD widely variates between 9 and 34% [2], depending on whether a BNE has been performed. The regular rate is around 20% [3].

The mild form of pHPT is characterized by asymptomatic or mildly symptomatic patients, for whom the surgical indications have been discussed during the Fourth International Workshop [4, 5]. The resulting guidelines recommend surgery for as follows: patients younger than 50 years, serum calcium higher than the upper normal limit by at least 0.25 mmol/L, a reduction in bone mineral density, the occurrence of a fragility fracture, a kidney stone, or a glomerular filtration rate lower than 60 mL/min/1.73 m^2.

The choice of treatment may be surgery versus active monitoring. In the monitoring group, serum calcium may be measured every semester, the creatinine annually, and the bone densitometry (DEXA) every 2 years. However, surgery is the only way to cure these patients and is therefore a good alternative to active monitoring [6–8].

The aim of this study was to evaluate, in this particular population of mild sporadic primary hyperparathyroidism, the frequency of multiglandular disease, the cure rate, and the diagnostic performance of preoperative imaging modalities (cervical ultrasonography and MIBI scintigraphy).

Methods

Patient selection

This retrospective study was carried on patients with mild sporadic pHPT managed between January 2013 and December 2015 in Nantes University Hospital (Department of Digestive and Endocrine Surgery). Patients were identified using the International Classification of Disease, 10th Revision, with a diagnosis associated with hospitalization coded as primary hyperparathyroidism (E21.0). Those with a serum calcium ≤ 2.85 mmol/L were included, then exclusions were done for those with recurrent hyperparathyroidism, MEN (multiple endocrine neoplasia) 1 or 2, secondary hyperparathyroidism, and glomerular filtration rate < 60 mL/min/1.73 m^2 (using the Modification of Diet in Renal Disease equation, MDRD). Finally, we included only those who underwent parathyroid double-phase scintigraphy with dual-tracer ^{99m}Technecium (Tc)/^{99m}Tc-MIBI (methoxyisobutylisonitrile) scintigraphy with single-photon emission computed tomography (SPECT)/computed tomography (CT) before surgery, performed exclusively in our Nuclear Medicine Department. Every patient signed an informed consent.

Biochemistry

Serum markers were collected preoperatively and at 3 months and at 6 months after surgery: calcium, PTH, phosphate, 25-hydroxyvitamin D3 (25-OH D3), creatinine, and urinary calcium. Levels of total serum calcium (normal range 2.20–2.55 mmol/L or 8.80–10.2 mg/dL) were measured by a routine laboratory analyzer. PTH was measured by an assay for intact PTH, reference ranging from 10 to 70 pg/mL (1.06–7.42 pmol/L). The estimated glomerular filtration rate (eGFR) was determined using the MDRD equation.

Imaging procedure

All patients underwent a parathyroid double-phase and dual-tracer ^{99m}Tc/^{99m}Tc-MIBI pinhole scans with ^{99m}Tc-MIBI SPECT/CT, following intravenous injections of 37 MBq ^{99m}Tc and 740 MBq ^{99m}Tc-MIBI. Focused uptake of ^{99m}Tc-MIBI without an uptake of ^{99m}Tc was considered compatible with a hyperfunctioning parathyroid gland. The uptake of ^{99m}Tc-MIBI in SPECT with or without a hypodense rounded formation on CT scan was also considered as a positive result. All the scans were performed in our radiology department in order to provide homogeneity in the results.

Additionally, most of the patients underwent a neck ultrasound (US) imaging done either in our center or elsewhere, and the results were available for comparison.

Outcomes

Cure was defined as normalization of serum calcium (≤ 2.55 mmol/L) at 6 months after surgery (or at 3 months if no data were available at 6 months) for patients with both elevated calcium level and PTH (classic form) or with hypercalcemia but normal PTH level (normohormonal form). For patients with normocalcemic hyperparathyroidism, we also needed a normal PTH level at 6 months (or at 3 months if no data were available at 6 months) after surgery (≤ 70 pg/mL) to confirm the cure. Single gland disease (SGD) was defined by a single abnormal resected gland leading to postoperative cure. Multiglandular disease (MGD) was defined by two abnormal resected glands confirmed by histopathology, or persistent disease after resection of at least one abnormal gland.

Statistical analyses

For categorical variables, patients' characteristics are described using group size (%), with associated Fisher's exact test for bivariable analyses. For quantitative parameters, we calculated the mean (± standard deviation, SD) or median (25th percentile, 75th percentile) in case of skewed distribution, and used Student's *t* test or Wilcoxon rank-sum test respectively for unpaired series in case of group comparisons.

For the assessment of the diagnostic performance of imaging procedures, we considered that for all patients at least one pathological gland was to be found. Diagnostic imaging was a success when at least one pathological gland, confirmed by the pathologist, was identified. Sensitivity was defined as the number of success divided by the number of patients. Results are first given in the whole population, then only for cured patients.

p values < 0.05 were deemed statistically significant. Analyses were performed using R® software (version 3.5.0; R Foundation for Statistical Computing).

Results

Patients and serum characteristics

Data were analyzed from 121 patients with mild sporadic pHPT out of 413 consecutive patients (29.3%) who underwent parathyroid surgery for pHPT: 109 women (90.1%) and 12 men (9.9%), with a mean age of 62.8 years (range 16–90). Seventy-one patients (62.3%) had a micro- or macro-nodular thyroid on ultrasound, 17 (14.0%) had hypothyroidism including 16 (94%) treated with L-thyroxin (Table 1).

Before surgery, median serum calcium level was 2.68 mmol/L (range 2.39–2.85 mmol/L) and median PTH level was 83 pg/mL (range 41–351 pg/mL).

The population was divided into 69 patients (57%) with a classic form, 39 patients (32.2%) with a normohormonal form, and 13 patients (10.7%) with a normocalcemic form.

Lesion characteristics

A total of 141 glands were resected, including 95 adenomas and 33 hyperplastic glands. There was no parathyroid carcinoma among the resected glands. The mean weight and mean greatest diameter of the resected glands were 0.53 g and 1.6 cm in adenomas and 0.18 g and 1.18 cm in hyperplastic glands, respectively.

There were 27 out of 115 patients (23.5%) with known cure status with multiple glands: 17 uncured (9 with one adenoma, 5 with 1 hyperplastic gland, 2 with two hyperplastic glands, 1 with a pathological lesion of unknown status) and 10 cured (3 with one adenoma and one hyperplastic gland, 7 with two hyperplastic glands).

In the specific case of normocalcemic form, 11 of 13 patients had known cured status 3 and 6 months after surgery. Lesion characteristics were as follows: 8 with one adenoma, 2 with one hyperplastic gland, 1 with one adenoma and one hyperplastic gland, 1 with two hyperplastic glands, 1 with a pathological lesion of unknown status.

There were more MGD in the normocalcemic form (7 out of 11, 64%) than in the classical form (9 out of 67, 13%, $p = 0.0009$) or in the normohormonal form although not significantly for the latter (11 out of 37, 30%, $p = 0.074$).

Surgical procedures and cure rate

Minimally invasive surgery (focused approach) was performed in 45 patients (37.2%), unilateral neck approach in 23 patients (19%), and bilateral neck exploration (BNE) in 53 patients (43.8%). BNE was planned preoperatively: due to either (a) preoperative imaging results which were suspicious of multiglandular disease in 13 patients or (b) surgeon's preference in 40 patients. Twenty-eight patients (23.1%) underwent thyroid surgery during the same procedure. Concerning postoperative morbidity, 26 patients (25%) had a transient moderate postoperative hypocalcemia (2.0–2.2 mmol/L), all of which resolved at 3 months after surgery. A single patient had a recurrent laryngeal nerve (RLN) paralysis preoperatively, and it persisted postoperatively. No other postoperative RLN paralysis was observed.

Among the 121 patients, 6 had missing data at 3 and at 6 months after surgery, which did not permit us to assess their recovery status. Ninety-eight patients out of 115 were cured after surgical treatment, leading to a cure rate of 85.2%.

Table 1 Characteristics of the population with mild sporadic hyperparathyroidism, presented by biological form ($n = 121$)

	Classic	Normocalcemic	Normohormonal	Whole population	Data available
Clinical data before procedure					
Age	64.4 (56.7–73.6)	56.3 (47.8–62.8)	66.2 (56.3–72.5)	63.3 (56.1–72)	121
Women	63 (91.3%)	12 (92.3%)	34 (87.2%)	109 (90.1%)	121
Vitamin D deficiency (< 20 ng/mL)	26 (40.6%)	3 (27.3%)	8 (24.2%)	37 (34.3%)	108
Associated thyroid disorder					
Hypothyroidism	10 (14.5%)	2 (15.4%)	5 (12.8%)	17 (14%)	121
Hyperthyroidism	0	1 (7.7%)	1 (2.6%)	2 (1.7%)	121
Nodule	39 (60.9%)	7 (53.8%)	25 (67.6%)	71 (62.3%)	114
Surgical procedure					121
Focused/minimally invasive	29 (42%)	4 (30.8%)	12 (30.8%)	45 (37.2%)	
Unilateral neck exploration (UNE)	13 (18.8%)	2 (15.4%)	8 (20.5%)	23 (19%)	
Bilateral neck exploration (BNE)	27 (39.1%)	7 (53.8%)	19 (48.7%)	53 (43.8%)	
Biological analyses					
Preoperative					
Serum calcium (mmol/L)	2.69 (2.63–2.75)	2.50 (2.46–2.52)	2.69 (2.64–2.74)	2.68 (2.62–2.74)	121
PTH (pg/mL)	94.5 (84–119.8)	92.4 (81–111.6)	55.9 (52.9–62.2)	83.4 (62.9–101.6)	121
Phosphate (mmol/L)	0.78 (0.65–0.90)	0.78 (0.66–0.92)	0.78 (0.71–0.93)	0.78 (0.68–0.91)	112
25(OH)D3 (ng/mL)	22.4 (13.1–32.2)	28 (20.5–42.5)	23.9 (20–32)	24.0 (15.4–32.9)	108
eGFR (MDRD, mL/min/1.73 m^2)	83.5 (67.2–93.5)	90 (82–109)	88 (78–105)	87 (71.5–103.5)	111
Urinary calcium (mmol/24 h)	7.6 (4.2–9.7)	7.9 (6.8–10.4)	7.8 (5.7–10.5)	7.7 (4.8–10.3)	88
PTH levels during intraoperative time (pg/mL)					
Induction	93 (76–119)	97 (84–112)	64.5 (53.8–74.5)	83.5 (67.0–103.8)	110
Dissection	95 (73–136)	111 (75–155)	67.5 (49.2–86)	84.5 (62.8–123.0)	106
10 min after dissection*	33.5 (25.8–63.8)	36 (25.2–56)	24 (17.5–48.5)	32.0 (20.5–51.5)	87
20 min after dissection*	33.5 (21.5–53)	22 (22–32)	21 (16–34)	28.0 (20.0–42.0)	46
Postoperative					
3 months serum calcium (mmol/L)	2.39 (2.33–2.47)	2.37 (2.32–2.46)	2.42 (2.37–2.52)	2.40 (2.34–2.49)	116
6 months serum calcium (mmol/L)	2.37 (2.32–2.42)	2.33 (2.26–2.51)	2.40 (2.33–2.51)	2.38 (2.3–2.43)	45
3 months PTH (pg/mL)	48.6 (36.8–61.8)	61 (52.2–79.1)	41.8 (31.8–59.6)	48.6 (36.3–62)	101
6 months PTH (pg/mL)	47.0 (31.2–63.2)	93.0 (92.8–108.5)	33.0 (30.4–41)	45.5 (31.1–66)	22
Phosphate (mmol/L)	0.95 (0.84–1.04)	0.90 (0.68–1.00)	0.98 (0.83–1.13)	0.95 (0.84–1.06)	95
25(OH)D3 (ng/mL)	32.1 (22.7–34.9)	28 (21.5–37.3)	30.1 (22.8–36.5)	31.2 (22.4–36)	83

Data are presented using size (%) or interquartile range (25th–75th percentile)

eGFR (MDRD) estimated glomerular filtration rate (Modification of Diet in Renal Disease), *PTH* parathyroid hormone

*PTH levels after dissection are given for patient with only one gland removed

Imaging results

The scintigraphy showed abnormal foci which were secondarily confirmed by the pathologist in 113 out of 121 patients (sensitivity per patient 93.4%, 95% confidence interval (CI) 87.0%–96.9%). When considering only the cured patients, this rate was 90 out of 98 patients (sensitivity per patient 91.8%, 95% CI 84.1–96.2%).

For the 114 patients who underwent US, only 70 abnormal single foci were secondarily confirmed by the pathologist (sensitivity per patient 61.4%, 95% CI 51.8–70.2%). When considering only the cured patients, this rate was 61 out of 98 patients (sensitivity per patient 64.9%, 95% CI 54.3–74.2%).

Thirteen normocalcemic patients underwent the MIBI scan; 10 had a single focus (true positive), 1 had a false positive focus, 1 had 2 foci: a true positive and a false positive, and 1 had 2 true positive foci.

Factors associated with the cure

Neither bloodwork variables, nor gender ($p = 0.67$), nor co-existing thyroid disorders ($p = 1$) were significantly

Table 2 Comparison of laboratory tests, patients' characteristics, and surgical data according to cured status (n = 115)

	Uncured $N = 17$	Cured $N = 98$	p value
Clinical data before procedure			
Age	56.3 (47.8–70.1)	64.9 (57.9–72.3)	0.074
Women	15 (88.2%)	89 (90.8%)	0.67
Vitamin D deficiency (< 20 ng/mL)	7 (46.7%)	28 (32.2%)	0.38
Associated thyroid disorder			
Hypothyroidism	1 (5.9%)	15 (15.3%)	0.46
Hyperthyroidism	1 (5.9%)	1 (1%)	0.27
Nodule	8 (53.3%)	61 (64.9%)	0.40
Surgical procedure			1
Focused	6 (35.3%)	37 (37.8%)	
Unilateral neck exploration	3 (17.6%)	18 (18.4%)	
Bilateral neck exploration	8 (47.1%)	43 (43.9%)	
MGD	17 (100%)	10 (10%)	< 0.0001
Biological analyses			
Preoperative			
Serum calcium (mmol/L)	2.69 (2.54–2.75)	2.68 (2.63–2.74)	0.63
Protein-corrected serum calcium (mmol/L)	2.63 (2.47–2.73)	2.66 (2.62–2.73)	0.28
PTH (pg/mL)	91.7 (61.7–115.9)	83.7 (64.2–101.5)	0.51
Phosphate (mmol/L)	0.78 (0.66–0.96)	0.78 (0.69–0.90)	0.96
25(OH)D3 (ng/mL)	22.1 (9.9–26.8)	24.0 (16.2–33.0)	0.15
eGFR (MDRD), mL/min/1.73 m^2	81 (62–106)	87 (74–99)	0.58
Urinary calcium (mmol/24 h)	5.7 (4.1–12.1)	7.8 (4.9–10.0)	0.90
PTH levels during intraoperative time (pg/mL)			
Induction	89 (66–108)	83 (68–105)	0.80
Dissection	111 (62.5–147)	83 (65–120)	0.35
10 min after dissection*	35 (16.5–60.5)	32 (21–49)	0.99
20 min after dissection*	37.5 (20.8–57.2)	26 (20–39)	0.77
PTH decreased ≥ 50% at 10 min after dissection*	7 (64)	50 (76%)	0.46
Postoperative			
3 months serum calcium (mmol/L)	2.61 (2.56–2.68)	2.39 (2.33–2.45)	< 0.0001
6 months serum calcium (mmol/L)	2.59 (2.35–2.61)	2.37 (2.3–2.42)	0.013
3 months PTH (pg/mL)	71.4 (58.7–76.7)	46.2 (35–57)	0.002
6 months PTH (pg/mL)	63 (46.4–83)	36 (31–54)	0.18
Phosphate (mmol/L)	0.91 (0.78–1.03)	0.96 (0.84–1.08)	0.23
25(OH)D3 (ng/mL)	34.2 (23.4–37)	30.3 (21–34.9)	0.23

Values are expressed using median (25th–75th percentiles). p values are given using Wilcoxon rank-sum test for unpaired series

eGFR (MDRD) estimated glomerular filtration rate (Modification of Diet in Renal Disease), *PTH* parathyroid hormone, *MGD* multiglandular disease

*PTH levels after dissection are only given for patient with only one gland removed

associated with cure (Table 2). Among the 77 patients with only one resected gland and available measurements, intraoperative PTH (ioPTH) did not decrease more significantly in the cured group than in the uncured group at 10 min after removal of the first gland (median decrease of 53.5 vs. 38.0 pg/mL, $p = 0.74$). IoPTH decreased by more than 50% in 57 patients (74%), with a cure rate of 88% in this group. In the 20 patients with an ioPTH drop of less than 50%, the cure rate was lower (80%) but not significantly ($p = 0.46$).

Concerning the different biological forms, the normocalcemic form was significantly less often cured than the classical form (45% vs. 93%, $p = 0.00061$) and the normohormonal form (cure rate 84%, $p = 0.18$). Patients with MGD were significantly less often cured than patients with SGD (10/27 (37%) vs 88/88 (100%), $p < 0.0001$).

Discussion

The present study confirms that patients with mild pHPT have a high rate of MGD (23.5%) and that MGD leads to a significantly decreased cure rate (37% compared to 100% in SGD). The cure rate depends on the type of mild pHPT (normocalcemic, normohormonal, or classic form).

Mild primary hyperparathyroidism is an increasingly common disease, with huge medico-economic issues that need to be considered closely. We observed that the rate of MGD depends on the subtype of pHPT: 64% in normocalcemic patients, 30% in normohormonal patients, and 13% in the classic form ($p = 0.0011$). Interestingly, the high rate of MGD in normocalcemic patients has already been described by Lim et al. [9], but these authors did not observe any difference between normohormonal (10% had MGD) and classic mild pHPT (9% had MGD). In our study, we selected only mild and apparently sporadic pHPT, excluding pathologies known to be associated with MGD such as MEN or renal failure. To define the "cured" status, we used the serum calcium normalization for normohormonal pHPT, and normalization of PTH in the normocalcemic form. Most studies used only normal serum calcium, therefore reporting much better cure rates [10], even those reporting MGD specifically [11] despite that the normocalcemic form is more represented in MGD than in SGD (26% versus 4.5% in our series).

The cure rate in mild pHPT was altered with only 85.2% of patients regaining normal serum calcium 6 months (or at 3 months if data were not available at 6 months) after surgery, associated with the normalization of PTH for the normocalcemic form. This result is lower than what is usually described in classic pHPT. Special attention must be paid to the normocalcemic form, as it seems to be particularly associated with a high rate of MGD (64% of cases) as well as hyperplastic glands (31.2%) and surgical failure (55%). Lim et al. [9] strongly recommended BNE in patients with normocalcemic pHPT. Given this study's results of MGD rate in mild pHPT patients, we decided to perform systematic BNE in all patients with mild pHPT regardless of PTH or calcium levels. This is supported by the postoperative morbidity: 23.8% moderate hypocalcaemia, which were all transient. The only mild pHPT patients who would receive a unilateral procedure are those who had undergone previous thyroid or parathyroid surgery. Especially for patients who had undergone a total thyroidectomy, the quality of residual parathyroid glands remains uncertain. In this situation, a BNE may expose patients to a definitive hypoparathyroidism.

Many authors reported that a negative MIBI scintigraphy predicts MGD [2]. Conversely, in our series, the sensitivity of MIBI scintigraphy is the same with mild pHPT than in those with classic pHPT (calcium level > 2.85 mmol/L) [12]. The sensitivity per patient reached 88.6% in our study versus 86% in a meta-analysis of patients explored for pHPT [13]. Correlations between calcium level, PTH level, parathyroid weight, and sensitivity of MIBI scintigraphy have been described [14–16]. The 88.6% sensitivity rate may appear high in patients with mild pHPT. The use of a combination of planar double tracer scintigraphy and SPECT/CT scan may explain the quality of these results [13, 17]. Furthermore, we can suggest that a positive imaging result cannot limit surgical exploration, as many MDG are not diagnosed.

In the present study, we could only evaluate persistent disease, but not recurrent disease, as we only had a 3-month and a 6-month blood test after surgery. In our experience, surgeons could not make use of the results of ioPTH routinely due to the delay between drawing the blood samples and obtaining the results (more than 45 min). Analyzing the data afterwards showed that a drop of ioPTH by at least 50% predicted success of parathyroidectomy in 88% of patients, while cure was obtained in 80% of patients with a drop of ioPTH less than 50%. Therefore, ioPTH may not be a great predictive tool in mild pHPT despite that it was shown in other studies with a cure of 97.5% of patients with MGD [11].

The normocalcemic form requires exclusion of secondary causes leading to an increased level of PTH [18]. One of the most important causes is vitamin D deficiency (level < 20 ng/mL [19]). This was the case in 34.3% of our patients (37/108), including 27% of the normocalcemic form (3/11) for which the diagnosis of primary HPT could be uncertain [20]. Pre- and postoperative vitamin D deficiencies were not systematically supplemented at the time of the study. The use of bisphosphonates, thiazide diuretics, or lithium and the presence of liver failure, metabolic or malabsorption diseases have been evaluated in our population to exclude secondary HPT, which may also influence the rate of MGD in each group. However, the high rate of MGD we observed in normocalcemic patients is not likely due to mild HPT secondary to vitamin D deficiency. Even though many of our patients had vitamin D deficiency, calcium level was near the upper limit, which is hardly compatible with secondary HPT.

In the future, 18F-fluorocholine-positron emission tomography/computed tomography (PET/CT), which demonstrated encouraging results, could become a useful tool in mild pHPT patients, especially those with negative or non-concordant preoperative imaging [20, 21]. Nevertheless, even though neck ultrasound has a low sensitivity, it is needed in order to describe the thyroid gland and eventually diagnose a thyroid nodule, which could be treated in the same surgical procedure if needed.

The principal limitations of this study reside in its retrospective nature, a limited 3- or 6-month postoperative follow-up, the inclusion of patients with vitamin D deficiency, and insufficient supplementation before surgery.

Conclusion

We conclude that patients with mild pHPT do have a high rate of MGD, mainly in normocalcemic forms. The data suggest a routine BNE as a surgical management for all mild pHPT patients, but further studies are needed to evaluate the benefit/risk balance of this strategy.

Authors' contributions Dr. Emmanuelle Trébouet contributed to the study conception and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, and critical revision of the manuscript.

Dr. Sahar Bannani contributed to the study conception and design, analysis and interpretation of the data, drafting of manuscript, and critical revision of the manuscript.

Dr. Matthieu Wargny contributed to the acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, and critical revision of the manuscript.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional, the national research committee and with the 1964 Helsinki Declaration and its later amendments.

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