Caractérisation et singularités phénotypiques des patients opérés pour hyperparathyroïde primaire étude observationnelle sur 600 patients

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Partie I : **RESUME**

Introduction

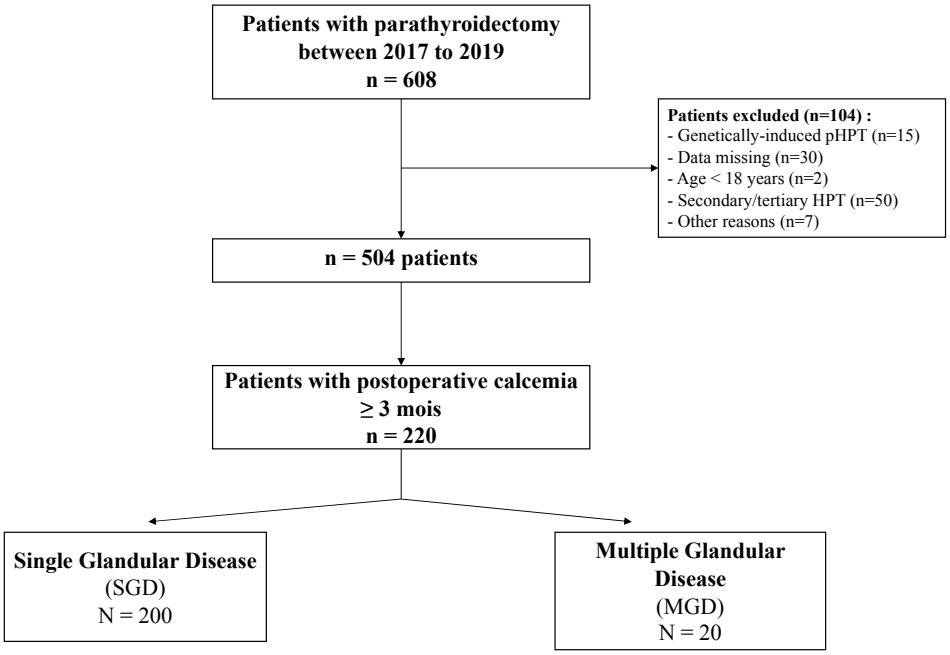
L'hyperparathyroïdie primaire (pHPT) est un trouble endocrinien caractérisé par une hypercalcémie (taux de calcium sérique élevé > 10,5 mg/dL ou 2,6 mmol/L) associée à un taux élevé ou anormalement normal de parathormone (PTH) (1). L'incidence de pHPT est d'environ 0,4 à 82 cas pour 100 000 (1, 2), elle augmente avec l'âge et est plus importante chez les femmes post-ménopausées (3). Depuis que la calcémie est dosée en routine, la présentation classique de la maladie est, à ce jour, le plus souvent asymptomatique, même si elle peut encore être à l'origine de complications telles que des lithiases rénales et/ou de l'ostéoporose (3, 4). Dans la littérature, il est rapporté que pHPT est causée par un adénome unique dans 80% des cas, définissant la maladie uniglandulaire (SGD), et, dans 10 à 15% des cas, par de multiples adénomes ou hyperplasies parathyroïdiens, définissant la maladie multiglandulaire (MGD) (5, 6, 7, 8). Dans des cas exceptionnels, pHPT peut être causée par un carcinome parathyroïdien (<1 %). Le seul traitement curatif de pHPT est la chirurgie parathyroïdienne (parathyroïdectomie) et, elle est recommandée lorsque les patients sont symptomatiques ou pour les patients asymptomatiques qui répondent à des critères détaillés dans les dernières recommandations datant du 4e International Workshop publiées en 2014 (9). Deux approches chirurgicales sont donc discutées : la parathyroïdectomie mini-invasive (MIP), lorsque la pHPT est consécutive à une maladie uniglandulaire et, d'autre part, l'exploration cervicale bilatérale lorsqu'une maladie multiglandulaire est suspectée comme en cas d'imagerie négative par exemple (10). Cette dernière intervention chirurgicale est cependant associée à un risque plus élevé d'hypocalcémie postopératoire, d'hématome cervical et de paralysie récurrente du nerf laryngé (11), faisant du diagnostic précis de SGD versus MGD avant la chirurgie un véritable défi pour la prise en charge bénéfique du patient. Les techniques d'imagerie (c'est-à-dire l'échographie cervicale et la scintigraphie au sestamibi) sont couramment utilisées en première intention pour distinguer la SGD et la MGD, bien que leurs valeurs prédictives positives respectives, allant de 80 à 90 %, suggèrent qu'un sous-ensemble de cas de pHPT demeure, finalement, d'étiologie indéterminée (12). D'autres options ont été testées pour préciser la cause de pHPT, comme la mesure des taux de PTH peropératoire, dont une diminution supérieure à 50 % au cours de l'intervention chirurgicale est vraisemblablement prédictive de la SGD (critères de Miami) (13, 14).

Dans cette étude, notre objectif était de décrire sur les plans clinique, biochimique et de l'imagerie, les causes de pHPT dans une grande série de patients opérés dans un centre de référence tertiaire, et d'identifier les facteurs cliniques prédictifs pertinents de MGD et SGD.

Matériels et méthodes

Une analyse rétrospective a été réalisée sur des patients opérés d'une parathyroïdectomie pour une pHPT dans notre centre entre 2017 et 2019. Les caractéristiques cliniques et biochimiques ont été comparées entre les patients présentant une pathologie uni- ou multi-glandulaire. Les facteurs de risque associés à la survenue d'une pathologie uni- ou multi-glandulaire ont été identifiés par régression logistique, en analyse univariée puis multivariée (OR, IC 95%).

Un recueil de données de 608 patients opérés d'une parathyroïdectomie a été réalisé. 504 patients ont été inclus, nous avons analysé les 220 patients qui présentaient une parathyroïdectomie pour une pHPT entre janvier 2017 et décembre 2019, et un suivi ≥ 3 mois. Parmi ces 220 patients, 200 avaient une maladie uniglandulaire et 20 avaient une maladie multiglandulaire.



Résultats

Nous n'avons observé aucune différence statistiquement significative entre les deux groupes concernant les paramètres cliniques et biochimiques. Les rapports d'imagerie diffèrent de manière significative, avec une échographie contributive dans 90 % des SGD contre 80 % dans les MGD (p = 0,006). En analyse multivariée, la maladie multiglandulaire est indépendamment associée à une échographie cervicale positive (lorsque > 1 glande anormale était identifiée) (OR 27,4, IC à 95 % : 2,99 à 250,3) et à la calcémie différentielle (OR 0,01, IC à 95 % : 0 à 0,44), définie comme la différence entre la calcémie en préopératoire et celle dosée à ≥ 3 mois.

Nos travaux suggèrent que l'échographie cervicale effectuée par un radiologue qualifié reste la meilleure procédure de diagnostic réalisée en préopératoire pour distinguer une maladie uniglandulaire d'une maladie multiglandulaire. Fait intéressant, nous avons trouvé une association entre la MGD et le degré de calcémie différentielle (OR 0,01, IC à 95 % : 0 à 0,44), cela signifie que plus la calcémie différentielle augmente, plus la probabilité d'avoir une pathologie multiglandulaire diminue indépendamment des autres variables. Ce résultat pourrait ouvrir la voie à des investigations complémentaires dans le suivi à moyen terme des patients opérés pour une pHPT. Cette hypothèse devra cependant être confirmée dans un premier temps dans une étude prospective.

En conclusion, la distinction entre la maladie uni- et multi-glandulaire dans l'hyperparathyroïdie primaire sporadique reste difficile. Selon nos résultats, l'association d'une analyse méticuleuse des glandes parathyroïdiennes par échographie et l'analyse de chirurgiens expérimentés demeure la procédure de référence pour garantir la meilleure approche diagnostique de cette maladie particulière. D'autres procédures d'imagerie comme la tomodensitométrie en 4D (CT-4D) et la TEP choline PET/CT, restent à comparer et à valider dans ces conditions pathologiques spécifiques.

Partie II : **ARTICLE**

Predictive factors of uni- or multiglandular disease in primary hyperparathyroidism: a cohort study

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Abstract

Background: Primary hyperparathyroidism (pHPT) is characterized by hypercalcemia associated with an elevated or inappropriately normal levels of parathormone (PTH). The only curative treatment is parathyroidectomy, making the characterization of the disease as uniglandular (SGD) or multiglandular (MGD), essential. Our aim was to describe at the clinical, biochemical and imaging levels, causes of pHPT in a large series of operated patients

Method: A retrospective analysis was performed on 608 patients with pHPT who underwent parathyroidectomy at our centre between 2017 and 2019. Preoperative clinical and biochemical parameters were compared in patients with SDG and MGD, and differential calcemia (= $Ca_{diagnosis}$ - $Ca_{last\ follow\text{-}up}$) was calculated. Risk factors associated with the occurrence of SGD/MGD were identified using univariate and then multivariate logistic regression (OR, 95% CI).

Results: Two hundred and twenty patients underwent parathyroidectomy with postoperative calcemia ≥ 3 months. 200 had SGD and 20 had MGD. We did not observe statistically significant difference between SDG and MGD groups regarding clinical and biochemical parameters. Imaging reports differed significantly with a contributive ultrasonography in 90% of SGD versus 80% in MGD (p = 0.006). In multivariable analysis, histological MGD was independently associated with positive cervical ultrasonography (when > 1 abnormal gland was identified) (OR 27.4, 95% CI: 2.99 to 250.3) and differential calcemia (OR 0.01, 95% CI: 0 to 0.44).

Conclusion: Meticulous analysis of the parathyroid glands by ultrasonography remain the gold-standard to predict multiglandular disease in pHPT, which is likely if differential calcemia remains low in the follow-up of the patient.

Introduction

Primary hyperparathyroidism (pHPT) is an endocrine disorder characterized by hypercalcemia (elevated serum calcium level >10.5 mg/dL or 2.6 mmol/l) associated with an elevated or inappropriately normal levels of parathormone (PTH) [1]. The incidence of pHPT is approximately between ~ 0,4 to 82 cases per 100,000 [2, 3], increases with age and is more important in post-menopausal women [4]. Since the serum calcium is routinely measured, the presentation of the disease is, nowadays, more often asymptomatic. However, these mild forms can result in complications such as kidney stones and/or osteoporosis [4, 5]. pHPT is caused by a single adenoma in 80% of cases, defining the single-gland disease (SGD), and, in 10 to 15% of cases, by multiple parathyroid adenomas or hyperplasia, both of these conditions defining multiglandular disease (MGD) [6–9]. In exceptional cases, pHPT is caused by a parathyroid carcinoma (<1 %). The only curative therapy for pHPT is parathyroidectomy and is recommended when patients are symptomatic or for asymptomatic patients who meet the guidelines of the fourth International Workshop [10]. Subsequently, two surgical approaches are discussed: the minimally invasive parathyroidectomy (MIP), when pHPT is consecutive to SGD, or bilateral neck surgery (BNS) when MGD is suspected, like in case of pHPT with negative imaging [11]. BNS is associated with a higher risk of postoperative hypocalcemia, neck hematoma and recurrent laryngeal nerve palsy [12], making the accurate diagnosis of SGD versus MGD, before surgery, a real challenge for the clinician. Imaging techniques using cervical ultrasonography (US) and sestamibi scintigraphy contribute to distinguish SGD from MGD, with respective sensitivity/specificity of 70-90% and 85-95%, respectively [13]. In contrast, few studies focused on the clinical and biochemical characteristics of patients with SGD and MGD, that could be helpful for further specifying the primary cause of pHPT.

In this study, our aim was to describe the clinical, biochemical and imaging data of operated pHPT and to seek for preoperative predictive factors of MGD and SGD.

Material and Methods

Study design and data collection

We performed a retrospective monocentric study at the University Hospital of Marseille and reviewed a cohort of 608 patients who underwent parathyroidectomy by 3 endocrine surgeons (FS, CG, CP), between 2017 and 2019. Diagnosis of pHPT was defined by an elevated serum calcium level (> 2.55mmol/l) and an inappropriately normal or elevated PTH level. All the cases were preoperatively discussed during an institutional board that gathered endocrinologist, endocrine surgeons, and nuclear medicine physicians.

Patients were included in the study if they had a complete biochemical evaluation including calcemia, albuminemia, phosphatemia, PTH, 24hrs-calciuria, vitamin D and creatininemia. Calcemia was measured by automated techniques, with a normal range of 2.2 - 2.55 mmol/l, adjusted for albumin by the following formula: Corrected calcemia (ca_{corr}) = calcemia measured - 0.025 x (albuminemia - 40). Phosphatemia, magnesemia, creatininemia, were also measured by automated techniques while calciuria was measured by colorimetric method. Were excluded from the study, patients with history of recurrent pHPT (i.e., hypercalcemia which presents after at least 6 months of normocalcemia following successful primary surgery for pHPT), secondary hyperparathyroidism, parathyroid carcinoma, genetically-induced pHPT (MEN syndrome, familial pHPT or multiple endocrine neoplasia syndrome, familial hypocalciuric hypercalcemia), use of lithium or bisphosphonates, and age < 18 years (Figure 1). Clinical criteria such as age, sex, body mass index (BMI), history of kidney lithiasis and/or bone fractures were collected. Once operated, patients had a new laboratory workup, that included calcemia, albuminemia, vitamin D and PTH, in their follow-up and treated with vitamin D3 (100,000 IU/3 months) in case of deficiency (vitamin D < 75 nmol/l).

Definitions of cure/persistent and single/multiple glandular disease

Cure was defined in our study by the ability the patient had to maintain calcemia ≤ 2.5 mmol/l long after surgery. As such, we focused our analysis on the population of patients with postoperative calcemia (Ca(po)) ≥ 3 months after surgery. In other patients (Ca(po) 7days-3months), cure was defined by the same cut-off of calcemia, however, we could not guarantee evidence that patient maintain normocalcemia on the long-term.

Persistent disease was defined when Ca(po) ≥ 2.6 mmol/l, at least 3 months after the surgery. Calcemia ranging 2.5-2.59 mmol/L were in the grey zone and required a careful analysis of the

pathological report to confirm SGD or MGD. Finally, we determined the differential calcemia (Ca(diff)) by subtracting the calcemia at the last follow up from the calcemia at diagnosis.
MGD was diagnosed if, 1) the surgeon observed and resected ≥1 abnormal glands which were histologically proven to be abnormals (hyperplasia or adenoma) and, 2) in patients with resection of a single gland but Ca(po) ≥ 2.6 mmol/L, 3 months after the surgery. On the contrary, patients were having SGD when one pathological gland was resected, confirmed as pathologically abnormal with cure of the disease at least 3 months after the surgery.
Our study was approved by the Ethics in Committee of Aix-Marseille University (Authorization PADS number PADS20-143).

Preoperative localization procedure and evaluation of pHPT complications

Almost all of our patients had cervical ultrasonography at our institution, performed by an expert radiologist (JVL). Sestamibi scintigraphy was performed either in our or in external centre. Because of its recent development, PET Choline has been used only in a small subset of patients with negative imaging (n = 44). Patients were systematically screened for pHPT complications. Bone fragility was assessed by bone mineral density (BMD) of the lumbar spine, the femoral neck and, in some patients, distal third of the radius using bone densitometry/dual-energy x-ray absorptiometry (DXA). The existence of nephrolithiasis was documented by medical history of renal colic and kidney ultrasonography.

Statistical analysis

Descriptive statistics including frequency and percentage for categorical variables and mean ± standard deviation for continuous variables were used to describe the sample of patients with pHPT. Baseline characteristics were compared between groups defined according to the presence of uni- or multi-glandular pathology using the Student's t test, or the Mann-Withney test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, when appropriate. Concordance of results between ultrasound and scintigraphy in the diagnosis of uni- or multiglandular pathology was assessed by Cohen's kappa coefficient with its associated 95% confidence interval (CI). The interpretation of the results was as follows: <0, no agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–0.99, almost perfect agreement (Landis and Koch). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of uni- and multiglandular diagnosis were then calculated for each diagnostic method with their associated 95% confidence intervals. Risk factors associated with the

occurrence of uni- or multiglandular pathology were identified using univariate and then multivariate logistic regression. Variables with a p-value no more than 0.2 in the univariate analysis were considered for inclusion in the multivariate analysis. Odds ratios (OR) with their associated 95% CI were reported. A p value <0.05 was considered statistically significant. All statistical analysis were performed using SPSS software, version 20.0 (SPSS, Inc., Chicago, Illinois).

Results

Characteristics of the population

A total of 608 patients underwent parathyroidectomy during the time of the study, of which, 504 (83%) met the inclusion criteria. The delay of the postoperative calcemia was ≥ 7 days in 485 patients (96%), ≥ 1 month in 424 patients (84%), ≥ 2 month in 249 patients (49%) and ≥ 3 months in 220 patients (36%), respectively. Cure rate, in these 4 respective subgroups of patients, was 92.7%, 92.2%, 91.1% and 90.9% (Figure 2). A total of 20 patients (4%) of our cohort had negative imaging (both US and scintigraphy). Amongst them, 12 (60%) had bilateral neck surgery and cure was obtained in 19 patients (95%).

In the subgroup of patients with Ca(po) ≥ 3 months after surgery, there were 33 men (15%) and 187 women (85%), with a mean age at diagnosis of 62.4 ± 13.4 years. Vitamin D level was normal in 130 patients (median value 99.5 nmol/L, IQR = 36) and below the normal range in the remaining cases (median value 54 nmol/L, IQR = 25). Based on our diagnosis criteria, 200 patients had SGD (90.9%), of which 92 (46%) had vitamin D deficiency at diagnosis and 20 had MGD (9.1%), of which 7 (35%) had vitamine D deficiency (Table 1). Amongst patients with calcemia ≥ 3 months ranging between 2.5-2.59 mmol/L, 4 were classified as having MGD and 21 as having SGD after a careful analysis of their clinical file. None of the patient developed hypoparathyroidism during the follow-up.

Differences between SGD and MGD

Characteristics for patients with SGD and MGD are summarized in Table 1. We did not observe statistically significant difference between SDG and MGD groups regarding clinical and biochemical parameters. In particular, calcemia at diagnosis (2.74 ± 0.19 mmol/L in the SGD vs. 2.7 ± 0.2 mmol/L in the MGD group, p = 0.34), PTH levels (129 ± 103 vs. 142 ± 174 pg/mL, p = 0.643) and calciuria (283 ± 124 vs. 337 ± 207 mg/24h, p = 0.539) did not differ between the two groups.

Imaging reports differed significantly with a contributive US in 90% of SGD versus 80% in MGD (p = 0.006). Out of 17 patients with normal US, fourteen (82.4%) had SGD at the final histological analysis. Sestamibi scintigraphy was performed for 162 patients (73.6%) in our institution, and in external centre in the remaining cases. This imaging procedure was negative in 6.5% patients with SGD as compared to 10% in patients with MGD (p = 0.049). Out of 15 patients with normal scintigraphy, 13 patients (86.6%) had confirmed SGD during and after the surgical procedure. Notably, the concordance between US and sestamibi scintigraphy was low

with kappa = 0.35 (95% CI: 0.14 to 0.52). As expected, the MIP surgical procedure had been predominantly performed in SGD (80.5%) versus MGD (30%), respectively ($p < 0.001$).

Univariate analysis shows that the risk of having MGD was significantly higher when US (OR 10.1, 2.05 - 50.3) or scintigraphy (OR 10.9, 1.41 - 84.6) detected multiple abnormal glands (Table 2). Notably, MGD was associated with a higher risk to develop renal colic (OR 2.92, 1.04 - 8.21), or lithiasis detected by US (OR 9.57, 1.79 - 51), although calciuria remained similar to the values observed in SGD.

In multivariable analysis (Table 3), MGD was independently associated with the presence of ≥ 1 pathological gland on the cervical ultrasonography (OR 27.4, 95% CI: 2.99 to 250.3) and a lower differential calcemia (OR 0.01, 95% CI: 0 to 0.44, Figure 3).

Discussion

Specifying the etiology of pHPT, preoperatively, is of upmost importance as it considerably influences the surgical procedure and impacts the risk of postoperative complications. The localization diagnosis currently depends on the realization of ultrasonography and scintigraphy, which, if both positive and concordant, usually resulted in high rate cure of the disease after surgery [15]. The situation considerably differs when imaging procedures are negative, with discrepant rate of surgical success reported in the literature, in these peculiar cases. For instance, the European database for endocrine surgery, which includes 5861 patients, showed that negative localization procedures increased the risk of persistent hypercalcemia after surgery (RR 2.54 (1·76, 3·66), $p < 0.001$) [14], but this result was not confirmed in a recent prospective study [15]. One of the reasons that could explain the different surgical outcomes observed, is the variability in the definition of cure, used in studies. In this present work, we arbitrarily defined cure of the disease when calcemia remained below 2.5 mmol/L at least 3 months after surgery. We acknowledge that our choice could interrogate, also because cure rate remained the same after 7 days and 3 months, however, in our experience, a subset of patients will experience a slow ascent of their calcemia in the first 3 months following surgery. Moreover, these patients are likely affected by multiglandular disease, which, to our opinion, would request a genetic analysis to rule out familial hypocalciuric hypercalcemia (FHH). Therefore, the existence of multiglandular disease cannot be definitely ruled out if calcemia is normalized soon after the surgical procedure. In that respect, predictive scores have been developed to guide the therapeutic strategy. One of them is the CaPTHUS score, which results from the combination of the results of ultrasound, scintigraphy, serum calcium (3 mmol/L [12 mg/dL]), levels of parathyroid hormone (2 times the upper limit of normal levels), and concordant sestamibi and neck ultrasound study results [16]. Each of these criteria was set as 1 point and a total score ≥ 3 was used as a cut-off point for predicting SGD with a positive predictive value of 100% but a low sensitivity (44%). A subsequent study using this score, found a positive predictive value of 91% to predict SGD [17]. Moreover, Kebebew et al., suggest that patients with a CaPTHUS score of 3 or higher can undergo a focused parathyroidectomy without the routine use of intraoperative PTH (ioPTH), another biochemical tool classically used by trained endocrine surgeons. Previous studies suggested that a ioPTH decrease greater than 50% during the surgical procedure was likely predictive of SGD (Miami criteria) [13, 14, 18].

Likewise, Mazeh et al. developed the Wisconsin Index (WIN) nomogram in order to predict the likelihood of additional hyperfunctioning glands during surgery [8]. WIN was calculated by

multiplying the preoperative serum calcium and PTH, and the WIN nomogram consist of the combination of WIN and parathyroid gland weight. This intraoperative tool may be used to guide the decision of whether to wait for ioPTH results or to proceed with further neck exploration, and stratified the patients into categories of high, medium, or low risk of MGD. Edafe et al. used both scores to discriminate SDG and MGD in their two endocrine surgical units, including 624 patients [20]. In their findings, the PPV of CaPTHUS ≥ 3 was 84.6% for predicting SGD, while for the WIN scores, there were no differences between patients with SGD and MGD (p=0.573). Subsequently, a study simultaneously applied the CaPTHUS and the Winconsin index to distinguish SGD and MGD [21]. The PPV of CaPTHUS for predicting SGD for a score ≥ 3 was 96,6%, and the area under the curve (AUC) value of this score was 0,74, while a score WIN > 2000, with a weight of the excised gland > 1g had a PPV for SGD of 92,5%. Although interesting, these predictive scores remain barely used in clinical practice, and the diagnosis of SGD- or MGD-related pHPT, still relies on the data of preoperative imaging, multidisciplinary discussion and surgeon's experience. For the sake of a practical approach, our aim was to look for predictors of SGD/MGD, however none of the clinical parameters we collected significantly differed between the two conditions. Furthermore, our study shows that cervical ultrasound (US), when performed by a skilled radiologist remains the best diagnostic procedure to preoperatively distinguish single glandular (one pathological gland observed) from multiglandular disease in pHPT, and that results was independent from other variables in our work. Attention must be paid to the fact that US has its own limitations, as it cannot identify some ectopic glands [22], can be hindered by thyroid pathology, and is dependent on operator experience.

At the biochemical level, we found no difference in the preoperative calcemia and/or PTH levels between patients with SGD and MGD, a result which is in line with another study [24], whereas others reported higher serum calcium and intact PTH levels in patients with SGD compared to MGD [16, 23]. Besides calcemia at diagnosis and during the follow-up, we attempted to determine value of differential calcemia by subtraction of these two parameters and interestingly found an association between MGD and the degree of differential calcemia (OR 0.01, 95% CI: 0 to 0.44). High differential calcemia at 3 months was associated with a low probability of having a multiglandular pathology independently of other variables. This finding could pave the way for evaluating this parameter in a prospective study, to validate or not, its add-value to settle on a second parathyroid surgery.

Our study has obvious several limitations due to its retrospective nature, a design that is ripe for missing data that could obscure associations between predictive factors and MGD.

Likewise, our decision to define remission of pHPT based on 3-months calcemia can be questioned, since persistent pHPT is usually defined as hypercalcemia within 6 months after primary surgery [25]. We justified this choice by the rate of cure in our study, that remains the same at 3 and 6 months (data not shown). This study also has many strengths, like having been carried out using data from an expert centre, in which standardized procedures, according to guidelines, are employed. We do believe that its design, from diagnosis to the final pathological analysis, make this work a "real-life" approach of pHPT in clinical practice. As such, we carefully set stringent inclusion and exclusion criteria to exclusively select patients with naive pHPT, over a recent period (from 2017 to 2019). The later also underlines that diagnostic approach and surgical techniques did not substantially change for all the patients included in our study. According to the literature, we found that roughly 90% of our pHPT patients carried parathyroid adenomas, like what is reported elsewhere, making our studying population representative of the pHPT patients in real life. Proportion of MGD-induced pHPT is higher in hereditary familial syndrome like multiple endocrine neoplasia type 1 (MEN1) syndrome, isolated familial primary hyperparathyroidism (IFPHT) or familial hypercalcemic hypocalciuric syndrome (FHH) [26]. In patient candidate to genetic testing, we paid attention to exclude the ones that carried mutations (a total of 15 patients in our database) and/or who had familial history of pHPT at the first degree relative. As such as our patients criteria better fit with the presumed sporadic presentation of the disease.

In conclusion, distinction of SGD and MGD in sporadic pHPT remains challenging, with no clinical markers of one disease over the other. According to our results, combination of meticulous analysis of the parathyroid glands by ultrasonography and experienced surgeons, remain the gold-standard procedure to guarantee the best diagnosis approach of this peculiar disease. Other imaging procedures like four-dimensional computed tomography (CT-4D) and Choline PET/CT, remain to be compared and validated in these specific pathological conditions [27, 28]**.**

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Legends

Figure 1. Flow chart of the study

Figure 2. Cure rate of pHPT depending on the delay of postoperative calcemia. Cure is defined by calcemia ≤ 2.5 mmol/L. SGD are represented in grey clear, MGD in grey dark.

Table 1. Characteristics of patients with single- and multiglandular disease

Table 2. Conditional logistic regression for testing the association of MGD with clinical, biochemical and imaging parameters.

Table 3. Multivariate logistic regression for testing the association of MGD with clinical, biochemical and imaging parameters. Note. p-value below 0.20 (or 0.05) are shown in bold

Figure 3. Differential calcemia (mmol/L) as defined by substration of calcemia at last follow-up from calcemia at diagnosis in patients with SGD and MGD. ** $p < 0.01$

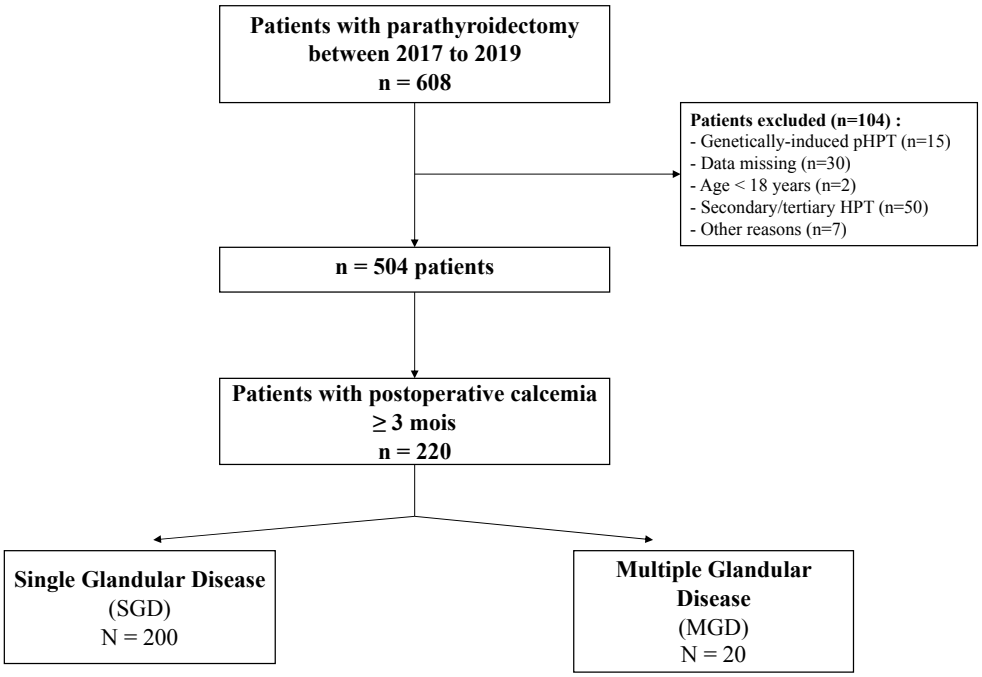
Patients with parathyroidectomy between 2017 to 2019
n = 608
Patients excluded (n=104) :
- Genetically-induced pHPT (n=15)
- Data missing (n=30)
- Age < 18 years (n=2)
- Secondary/tertiary HPT (n=50)
- Other reasons (n=7)
n = 504 patients
Patients with postoperative calcemia ≥ 3 mois
n = 220
Single Glandular Disease
(SGD)
N = 200
Multiple Glandular Disease
(MGD)
N = 20

Figure 1.

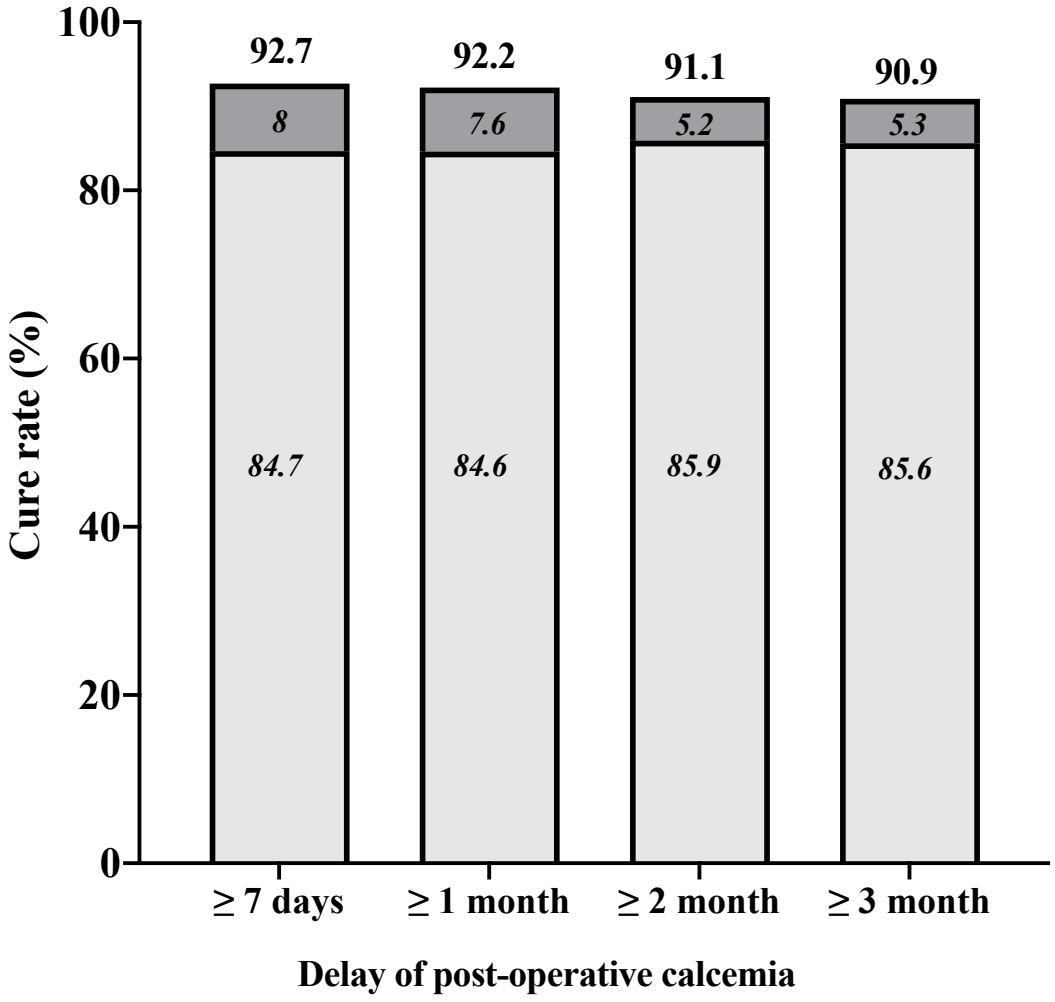
100
80
60
40
20
0
Cure rate (%)
92.7
92.2
91.1
90.9
8
7.6
5.2
5.3
84.7
84.6
85.9
85.6
≥ 7 days
≥ 1 month
≥ 2 month
≥ 3 month
Delay of post-operative calcemia

Figure 2.

Characteristics	**SGD (n= 200)**	**MGD (n=20)**	***p***
Sex, n (%)			0.745
Female	169 (84.5)	18 (90)	
Male	31 (15.5)	2 (10)	
Age, y			0.106
Mean ± SD	62.7 ± 13,4	58.9 ± 13	
Median (range)	64.2 (19-90)	58.9 (31-86)	
IMC, kg/m²			0.141
Mean ± SD	25.7 ± 5	27.6 ± 6.5	
Median (range)	24.5 (16-43)	26.6 (18-43)	
Calcemia, mmol/L (N: 2.2-2.55)			0.340
Mean ± SD	2.74 ± 0,19	2.70 ± 0,20	
Median (range)	2.71 (2.38-3.70)	2.68 (2.43-3.24)	
PTH level, pg/mL (N: 15-65)			0.643
Mean ± SD	129 ± 103	142 ± 174	
Median (range)	104 (35-1197)	98 (36-867)	
Phosphate, mmol/L (N: 0.81-1.45)			0.874
Mean ± SD	0.94 ± 0,20	0.74 ± 0.16	
Median (range)	0.94 (0.38-2.00)	0.75 (0.47-1.08)	
Calciuria, mg/24h			0.539
Mean ± SD	283 ± 124	337 ± 205	
Median (range)	277 (39-732)	313 (94-742)	
Complications, n (%)			0.740
Yes	127 (63.5)	15 (75)	
No	28 (14)	2 (10)	
No data	45 (22.5)	3 (15)	
Sestamibi scintigraphy, n (%)			**0.049**
Positive	133 (66.5)	14 (70)	
Negative	13 (6,5)	2 (10)	
Not performed	54 (27)	4 (20)	
Cervical ultrasonography, n (%)			**0.006**
Positive	180 (90)	16 (80)	
Negative	14 (7)	3 (15)	
Not performed	6 (3)	1 (5)	
Surgical approach			**< 0.001**
Bilateral/Unilateral neck exploration, n (%)	39 (19.5)	14 (70)	
Minimally invasive parathyroidectomy, n (%)	161 (80.5)	6 (30)	

Table 1.

Characteristics	Univariate logistic regression		
	OR	95% CI	P value
Weight	1.026	0.99-1.06	0.091
BMI	1.07	0.98-1.15	0.112
Sex	0.61	0.13-2.74	0.515
Hypercalcemia at LFU	2.70	0.89-8.14	0.078
25(OH)D	1.00	0.99-1.02	0.616
PTH	1.00	0.99-1.01	0.626
Calciuria mg/24h	1.00	0.99-1.01	0.118
Tscore Lumbar spine	0.97	0.62-1.54	0.914
Tscore Femoral neck	1.06	0.58-1 .94	0.840
Tscore Radius	1.58	0.80-3 .13	0.186
Renal colic	2.92	1.04-8.21	0.042
Kidney stones	9.57	1.79-51.0	0.008
Ultrasound			0.009
1 gland	2.90	0.74-11.4	0.13
> 1 gland	10.1	2.05-50.3	0.005
Scintigraphy			0.067
1 gland	1.68	0.33-8.33	0.53
> 1 gland	10.9	1.41-84.6	0.02
Differential Ca	0.02	0.01-0.41	0.011

Table 2.

Characteristics	Multivariate logistic regression		
	OR	95% CI	P value
BMI	1.08	0.95-1.23	0.223
Hypercalcemia at LFU	0.22	0.02-2.10	0.187
Calciuria mg/24h	1.005	0.99-1.01	0.074
Renal colic	3.11	0.68-14.18	0.143
Ultrasound			**0.014**
1 gland	2.75	0.32-23.8	0.358
> 1 gland	27.4	2.99-250.3	**0.003**
Scintigraphy			0.321
1 gland	0.65	0.07-6.07	0.703
> 1 gland	8.28	0.42-163.79	0.165
Differential Ca	0.001	0.00-0.44	**0.027**

Table 3.

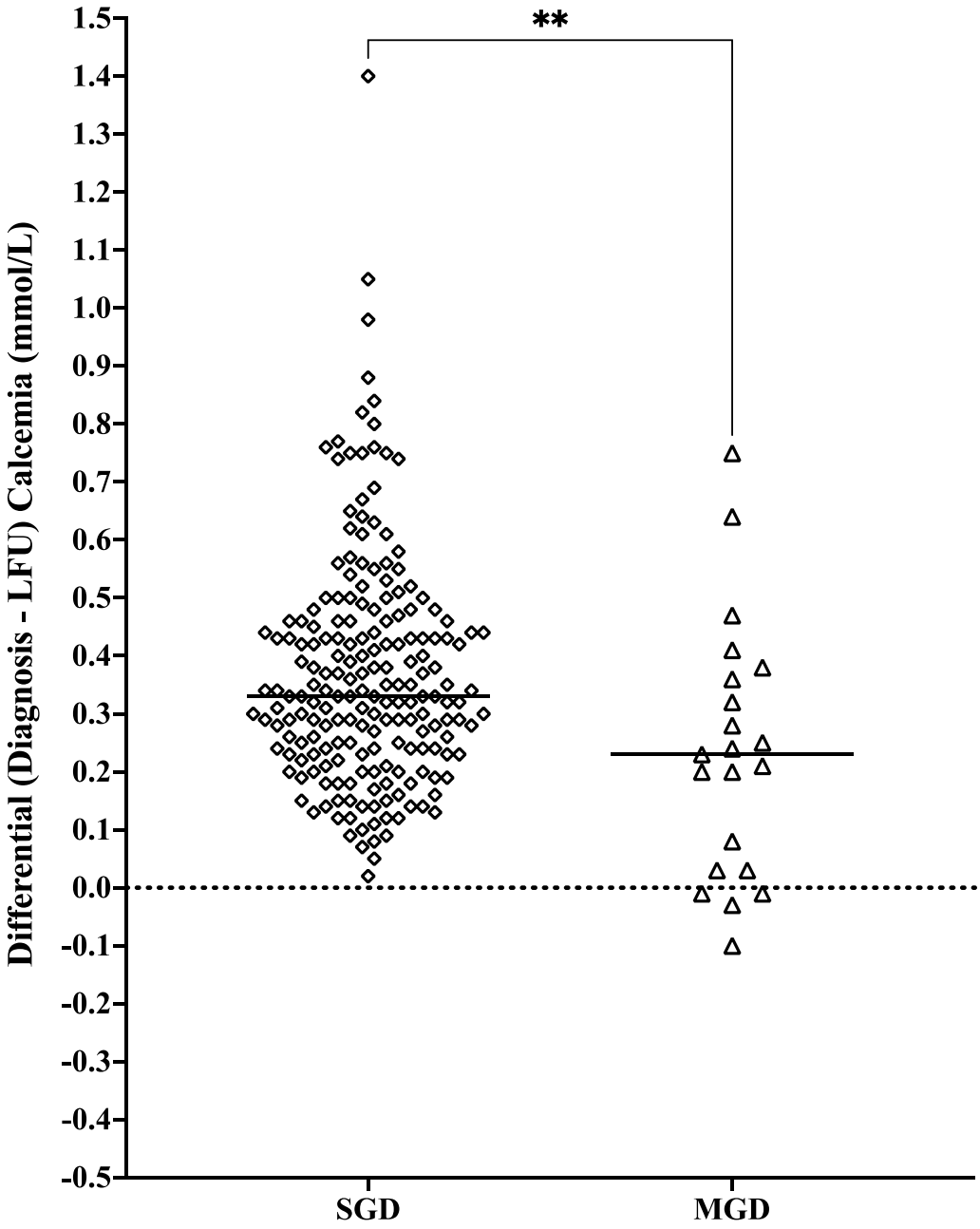
**
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
Differential (Diagnosis - LFU) Calcemia (mmol/L)
SGD
MGD

Figure 3.

SERMENT D'HIPPOCRATE

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

ORDRE NATIONAL DES MÉDECINS
Conseil National de l'Ordre