



Primary Hyperparathyroidism in Young Adult Patients

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ABSTRACT

Background. Primary hyperparathyroidism (PHPT) affects 2% of Americans over 55 years of age, and is less common in younger patients. Pediatric PHPT patients have higher rates of multigland disease (MGD). We studied young adult patients to determine whether they have similarly elevated rates of MGD and would benefit from routine bilateral neck exploration.

Methods. Retrospective chart review was performed on patients who underwent parathyroidectomy for PHPT (2000–2019). Cohorts were defined by age: Group A (18–40 years) and Group B (> 40 years). Univariate and multivariate logistic regression analyses were performed.

Results. Of 3889 patients with PHPT, 9.1% ($n = 352$) were included in Group A. On multivariate analysis, multiple endocrine neoplasia (odds ratio [OR] 6.3, 95% confidence interval [CI] 3.1–12.7), male sex (OR 1.3, 95% CI 1.0–1.5), family history of PHPT (OR 2.7, 95% CI 1.6–4.8), prior parathyroidectomy (OR 2.2, 95% CI 1.6–3.0), and non-localizing imaging (OR 1.8, 95% CI 1.5–2.1) were associated with MGD; younger age was not an independent risk factor. In patients with sporadic PHPT ($n = 3833$), family history was most strongly associated with MGD (OR 4.0, 95% CI 2.2–7.3).

Conclusions. In our population of patients with sporadic PHPT, a positive family history of PHPT was strongly associated with MGD; additional associations were found with prior parathyroidectomy, non-localizing imaging, and male sex. Younger age was not an independent risk factor.

Age alone in the absence of a family history should not raise suspicion for MGD nor determine the need for bilateral neck exploration.

BACKGROUND

Primary hyperparathyroidism (PHPT) affects approximately 2% of Americans over the age of 55 years,¹ and is less common in younger patients. Until 1982, just 86 cases of pediatric PHPT had been reported in the literature.^{2–4} High rates of multigland disease (MGD) have been reported in pediatric patients with PHPT diagnosed outside the neonatal period, with published incidences of hyperplasia ranging from 16 to 23% in larger pediatric series.^{2,4} Young adults also have a low prevalence of PHPT; one large institutional series found that approximately 3% of parathyroidectomies performed at a tertiary care center were performed on patients aged 28 years or younger.⁵ Greater proportions of MGD have also been identified in adolescent and young adult patients, 18.5–27% of whom have hyperplasia on surgical pathology.^{5,6} Notably, the majority of studies in young patients do not differentiate between sporadic PHPT and inherited PHPT, and include patients with multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A), and familial isolated hyperparathyroidism (FIHP). Systemic reviews show that up to half of cases of hyperplasia in patients under the age of 20 years are due to PHPT associated with inherited syndromes.⁷

Since patients with MGD are not eligible for minimally invasive parathyroidectomy (MIP), patients with MEN or other risk factors for MGD are best managed by bilateral neck exploration and subtotal parathyroidectomy. Classically, inherited endocrinopathies present at an early age, and current guidelines recommend genetic screening for MEN in patients presenting with PHPT at 40 years of age

or younger.⁸ Some authors suggest that younger age alone is a risk factor for MGD and advocate performing bilateral neck exploration routinely in young patients.⁹ We sought to establish whether young adult patients (18–40 years of age) with PHPT have heightened suspicion for MGD and would benefit from routine bilateral neck exploration and/or subtotal parathyroidectomy.

METHODS

Study Population

Consecutive patients who underwent parathyroidectomy for PHPT at our tertiary medical center over a 12-year period (January 2000–April 2013) were identified from our prospectively maintained endocrine surgery database. Children (< 18 years of age), and patients with secondary or tertiary hyperparathyroidism were excluded.

Variables

Data abstracted on retrospective chart review included patient demographics and past medical history (sex, age, positive family history of PHPT, history of prior parathyroidectomy, history of MEN1 or MEN2A), biochemical testing (preoperative serum calcium level, preoperative 24-h urinary calcium level, preoperative serum parathyroid hormone [PTH] level), preoperative signs (nephrolithiasis and loss of bone mineralization as determined by DXA scan), and symptoms (non-specific symptoms included known symptoms of hypercalcemia: bone pain, constipation, abdominal pain, and neurocognitive symptoms), preoperative localization by imaging (technetium-99 sestamibi scan, ultrasound, computed tomography [CT] scan, or magnetic resonance imaging [MRI]), operative approach (MIP or bilateral neck exploration), intraoperative findings (gland location, intraoperative PTH monitoring [IOPHT]), and surgical pathology (gland size, gland mass, final histopathologic diagnosis).

Definitions

Sporadic PHPT was defined as PHPT in the absence of a diagnosis of MEN1 or MEN2A; MIP was defined as directed unilateral exploration via a 2–3 cm incision; bilateral neck exploration was defined as bilateral cervical exploration with the goal of identification of all four parathyroid glands; MGD was defined as more than one parathyroid gland being abnormal, and included both double adenoma and four-gland hyperplasia; and cure was defined as eucalcemia on 6-month postoperative follow-up.

Statistical Analysis

For cohort analysis, patients were divided into Group A (18–40 years of age) and Group B (> 40 years of age), based on the age criteria for current MEN screening recommendations. Statistical analysis was performed using STATA/IC 12.1 software (StataCorp LLC, College Station, TX, USA). Group comparisons were made using the Chi-square test, Student's *t*-test, Fisher's exact test, or Wilcoxon rank-sum test, as appropriate. Data were reported as mean with standard deviation (SD) for normally distributed continuous variables, median with interquartile range (IQR) for non-normally distributed continuous variables, or percentages for dichotomous categorical variables. Subgroup analysis was performed on patients with sporadic PHPT. The primary outcome was MGD on final surgical pathology, while the secondary outcome was cure. A *p*-value ≤ 0.05 was considered significant. Factors reaching nominal significance ($p \leq 0.20$) in univariable logistic regression analysis were incorporated into a multivariable logistic regression model to identify factors independently associated with MGD.

Institutional Review Board approval for this study was obtained from the University of Pennsylvania (protocol #819382).

RESULTS

Characteristics of All Patients with Primary Hyperparathyroidism (PHPT)

Of 5152 consecutive parathyroidectomies performed, 3889 patients with PHPT were included in the study (Table 1), with a mean age of 59.0 years (SD 13.0). The population had marked female predominance (77.1% female vs. 22.9% male), with a female to male ratio of 3.4:1. The median preoperative serum calcium level was 10.8 mg/dL (IQR 10.4–11.2) and the median PTH was 86.5 pg/mL (IQR 53.8–124). The majority of patients (67.1%) reported non-specific symptoms of hypercalcemia; 53.7% were found to have loss of bone mineral density by DXA scan, and 16.9% experienced nephrolithiasis. 760 (19.7%) patients in this larger cohort were found to have MGD on final pathology. Median follow-up time after surgery was 6 months (IQR 2–20).

Characteristics of PHPT Patients, by Age Group

To evaluate the profile of young adult patients with PHPT, the study population was divided into Group A (18–40 years of age) and Group B (> 40 years of age). Group A consisted of 352 patients (9.1%), while Group B included 3537 patients (90.9%). The mean age for Group A was 32.4 years (SD 5.9), and 61.7 years (SD 10.2) for

TABLE 1 Cohort characteristics of patients undergoing parathyroidectomy for primary hyperparathyroidism, by age group

	Total population (<i>n</i> = 3889)	Group A: age 18–40 years (<i>n</i> = 352)	Group B: age > 40 years (<i>n</i> = 3537)	<i>p</i> -value
<i>Preoperative findings</i>				
Sex				
Female	3000 (77.1)	224 (63.6)	2776 (78.5)	< 0.001
Male	889 (22.9)	128 (36.4)	761 (21.5)	< 0.001
Age, years [mean (SD)]	59.0 (13.0)	32.4 (5.9)	61.7 (10.2)	–
Family history of HPT	72 (1.9)	25 (7.1)	47 (1.3)	< 0.001
MEN	53 (1.4)	29 (8.2)	24 (0.7)	< 0.001
Prior parathyroidectomy	210 (5.4)	32 (9.1)	178 (5.0)	0.001
Serum Ca, mg/dL [median (IQR)]	10.8 (10.4–11.2)	10.8 (10.4–11.3)	10.8 (10.4–11.2)	< 0.001
24-h urinary Ca, mg [median (IQR)]	285 (186–406)	320 (232–420)	280 (181–404)	0.006
Serum PTH, pg/mL [median (IQR)]	86.5 (53.8–124)	85 (57.7–121.6)	87 (53–124)	0.006
Signs and symptoms				
Nephrolithiasis	656 (16.9)	78 (22.2)	578 (16.3)	0.020
Abnormal DXA scan	2087 (53.7)	69 (19.6)	2018 (57.1)	< 0.001
DXA scan performed	2771 (71.3)	120 (34.1)	2651 (75.0)	< 0.001
Non-specific symptoms	2609 (67.1)	197 (56.0)	2412 (68.2)	< 0.001
Localization by imaging				
Localized	2292 (59.0)	180 (51.3)	2112 (59.7)	0.002
Localized by ultrasound	1359 (34.9)	108 (30.7)	1251 (35.4)	0.079
Localized by sestamibi	2324 (59.8)	211 (59.9)	2113 (59.7)	0.941
<i>Intraoperative findings</i>				
Operative approach				
MIP	996 (25.6)	74 (21.1)	922 (26.1)	0.044
BLNE	2889 (74.4)	276 (78.9)	2613 (73.9)	0.044
Ectopic gland	402 (10.4)	43 (12.3)	359 (10.2)	0.213
<i>Postoperative findings</i>				
Pathology				
Single adenoma	2988 (77.7)	253 (73.8)	2735 (77.9)	< 0.001
Double adenoma	348 (9.0)	21 (6.1)	327 (9.3)	< 0.001
Hyperplasia	412 (10.7)	49 (14.3)	363 (10.3)	< 0.001
Inconclusive	104 (2.7)	20 (5.8)	84 (2.4)	< 0.001
Dominant gland				
Median size (IQR), cm	1.5 (1.1–2.0)	1.4 (1.0–1.8)	1.5 (1.1–2.0)	0.078
Median mass (IQR), mg	367.9 (180–790)	300 (141–741)	373 (185–793.4)	0.658
Cure	3519 (96.6)	300 (94.3)	3219 (96.8)	0.075

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *HPT* hyperparathyroidism, *MEN* multiple endocrine neoplasia, *IQR* interquartile range, *MIP* minimally invasive parathyroidectomy, *BLNE* bilateral neck exploration

Group B. On cohort comparison of patient characteristics, Group A had a greater proportion of male patients (36.4 vs. 21.5%, $p < 0.001$) compared with Group B; the female to male ratio was 1.8:1 in Group A versus 3.6:1 in Group B. Younger patients were more likely to have a positive family history of PHPT (7.1 vs. 1.3%, $p < 0.001$), as well as higher rates of MEN (8.2 vs. 0.7%, $p < 0.001$). Younger patients were also more likely to have undergone a prior parathyroidectomy (9.1 vs. 5.0%, $p = 0.001$).

Analysis of preoperative signs and symptoms demonstrated higher rates of nephrolithiasis in Group A (22.2 vs. 16.3%, $p = 0.020$), and Group A also had lower rates of non-specific symptoms (56.0 vs. 68.2%, $p < 0.001$). Rates of bone demineralization were lower in younger patients (19.6 vs. 57.1%, $p < 0.001$) consistent with increasing prevalence of osteoporosis with aging. Patients in Group A were less likely to have had a DXA scan performed (34.1 vs. 75.0%, $p < 0.001$) prior to surgical evaluation.

Comparison of biochemical data between groups was significant for higher median 24-h urinary calcium level (320 vs. 280 mg, $p = 0.006$) in younger patients; there was no difference in median serum calcium (10.8 vs. 10.8 mg/dL, $p < 0.001$) or serum PTH levels (85 vs. 87 pg/mL, $p = 0.006$) between the cohorts. Younger patients had lower rates of successful preoperative localization of affected gland(s) by imaging (51.3 vs. 59.7%, $p = 0.002$), which was notable for ultrasound (30.7 vs. 35.4%, $p = 0.079$) but not for sestamibi scan (59.9 vs. 59.7%, $p = 0.941$). Intraoperative findings were not significant for a greater incidence of ectopic gland location in Group A (12.3 vs. 10.2%, $p = 0.213$). However, young patients were more likely to undergo bilateral neck exploration (78.9 vs. 73.9%, $p = 0.044$). On final surgical pathology, patients in Group A had lower rates of single adenoma (73.8 vs. 77.9%, $p < 0.001$), and higher rates of hyperplasia (14.3 vs. 10.3%, $p < 0.001$). Rates of MGD were similar between both groups (20.4 vs. 19.6%, $p < 0.001$). The dominant excised gland was smaller in young patients by both median size (1.4 vs. 1.5 cm, $p = 0.078$) and mass (300 vs. 373 mg, $p = 0.682$). Negative exploration rates were low (5.8 and 2.4%) and cure rates were high (94.3 and 96.8%), in younger and older patients, respectively.

Characteristics of Multiple Endocrine Neoplasia Patients

We analyzed our population to determine the prevalence of familial endocrinopathies. We identified 53 patients with confirmed diagnoses of MEN (MEN1, $n = 48$; MEN2A, $n = 5$) (Table 2). As has been previously described in the literature, these patients were characterized by a young age at presentation (MEN1: median 39.5 years and mean 42.9 years; MEN2A: median 34 years and mean 33.4 years). The majority (76.6%) of patients with MEN1 had hyperplasia on surgical pathology, while the majority of patients with MEN2A were found to have single adenomas (75.0%). Cure rates were 90.2% in MEN1 patients and 100% in MEN2A patients.

Characteristics of Patients with Sporadic PHPT

To determine whether the differences between younger and older patients was due to the disproportionate representation of genetic syndromes in young patients, we performed a subgroup analysis of patients with sporadic PHPT. The 53 patients with MEN described above were excluded, leaving patients with presumed sporadic PHPT. Cohort comparison was performed by age group (Table 3).

The exclusion of MEN patients obviated the statistically significant differences between younger and older patients in rates of prior parathyroidectomy (4.7 vs. 4.7%,

$p = 0.992$), bilateral neck exploration (77.0 vs. 73.8%, $p = 0.224$), ectopic gland location (12.8 vs. 10.2%, $p = 0.145$), single adenoma (78.3 vs. 78.4%, $p = 0.001$), hyperplasia (9.2 vs. 9.9%, $p = 0.001$), median size of the dominant gland (1.4 vs. 1.5 cm, $p = 0.197$), and cure rates (95.2 vs. 96.8%, $p = 0.377$). Median serum PTH became statistically, but not clinically, significantly different between age groups (83 vs. 87 pg/mL, $p = 0.007$).

Exclusion of patients with MEN did not change the statistically significant difference between groups in terms of male sex (35.4 vs. 22.6%, $p < 0.001$), family history of hyperparathyroidism (3.1 vs. 1.0%, $p = 0.001$), median 24-h urinary calcium (320 vs. 280 mg, $p = 0.007$), bone demineralization (20.2 vs. 57.3%, $p < 0.001$), non-specific symptoms (56.5 vs. 68.2%, $p < 0.001$), localization by all imaging (51.6 vs. 59.7%, $p = 0.005$), or by ultrasound (29.8 vs. 35.4, $p = 0.045$) and rates of negative exploration (6.1 vs. 2.4%, $p = 0.001$) between younger and older patients, respectively. Rates of localization by sestamibi scan (58.1 vs. 59.5%, $p = 0.611$) and median mass of dominant excised gland (324.5 vs. 373 mg, $p = 0.915$) remained similar between groups.

Factors Associated with Increased Risk of MGD

Multivariate logistic regression analysis was performed to identify preoperative factors that conferred increased risk of MGD versus single-gland disease (Table 4) in both the total population of PHPT patients and the subgroup of sporadic PHPT patients. For the entire population with PHPT, MEN conferred the greatest risk of MGD (OR 6.3, 95% CI 3.1–12.7). Other significant risk factors included male sex (OR 1.3, 95% CI 1.0–1.5), a positive family history of PHPT (OR 2.7, 95% CI 1.6–4.8), history of prior parathyroidectomy (OR 2.2, 95% CI 1.6–3.0), and non-localization by imaging (OR 1.8, 95% CI 1.5–2.1). By univariate and multivariate analysis, younger age was not associated with higher rates of MGD.

In the sporadic PHPT cohort, a positive family history of PHPT in the absence of MEN was associated with the highest risk of MGD (OR 4.0, 95% CI 2.2–7.3). Male sex (OR 1.3, 95% CI 1.0–1.6), prior parathyroidectomy (OR 2.2, 95% CI 1.6–3.0), and non-localization by imaging (OR 1.7, 95% CI 1.5–2.1) also remained significant. Patients with none of these risk factors ($n = 1642$) had a 14.9% incidence of MGD; one risk factor ($n = 2191$) increased the rate to 21.7%, two risk factors ($n = 424$) increased the rate to 25.7%, and three risk factors ($n = 24$) increased the rate to 33.3% (Fig. 1). To eliminate potential confounding from patients with prior parathyroidectomy, subset analysis was performed in patients undergoing initial parathyroidectomy, and excluding subjects with prior parathyroidectomy. On multivariate regression, we found that a positive family history of PHPT remained associated with the highest risk of MGD (OR 3.8, 95% CI 2.0–7.1).

TABLE 2 Cohort characteristics of patients with MEN undergoing parathyroidectomy for PHPT

	MEN1 (<i>n</i> = 48)	MEN2A (<i>n</i> = 5)
<i>Preoperative findings</i>		
Sex		
Female	28 (58.3)	4 (80)
Male	20 (41.7)	1 (20)
Age, years		
Median (IQR)	39.5 (30.5–54.5)	34 (28–39)
Mean (SD)	42.9 (14.6)	33.4 (10.6)
Family history of HPT	25 (52.1)	2 (40.0)
Prior parathyroidectomy	29 (60.4)	2 (40.0)
Serum Ca, mg/dL [median (IQR)]	10.7 (10.4–11.1)	10.1 (10.1–11.2)
24-h urinary Ca, mg [median (IQR)]	293 (262–401)	422 ^a
Serum PTH, pg/mL [median (IQR)]	122.5 (85.1–178.9)	47 (19.8–56)
Signs and symptoms		
Nephrolithiasis	21 (43.8)	0 (0.0)
Abnormal DXA scan	10 (20.8)	0 (0.0)
DXA scan performed	15 (31.3)	0 (0.0)
Non-specific symptoms	31 (64.6)	1 (20.0)
Localization by imaging		
Localized	28 (58.3)	2 (40.0)
Localized by ultrasound	18 (37.5)	2 (40.0)
Localized by sestamibi	41 (85.4)	4 (80.0)
<i>Intraoperative findings</i>		
Operative approach		
MIP	4 (8.5)	0 (0.0)
BLNE	43 (91.5)	5 (100.0)
Ectopic gland	4 (8.5)	0 (0.0)
<i>Postoperative findings</i>		
Pathology		
Single adenoma	6 (12.8)	3 (75.0)
Double adenoma	3 (6.4)	0 (0.0)
Hyperplasia	36 (76.6)	1 (25.0)
Inconclusive	2 (4.3)	0 (0.0)
Dominant gland		
Median size (IQR), cm	1.15 (0.6–1.7)	0.7 (0.55–0.9)
Median mass (IQR), mg	211 (65–760)	118 (56.3–302)
Cure	37 (90.2)	4 (100.0)

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *IQR* interquartile range, *MIP* minimally invasive parathyroidectomy, *BLNE* bilateral neck exploration, *MEN* multiple endocrine neoplasia, *PHPT* primary hyperparathyroidism, *HPT* hyperparathyroidism, *PTH* parathyroid hormone

^aIQR not reported because 24-h urinary calcium was only available for one of five patients

Male sex (OR 1.3, 95% CI 1.0–1.6) and non-localization by imaging (OR 1.8, 95% CI 1.5–2.2) also remained significant.

To investigate the relationship between young age and heritable germline mutations, a subgroup analysis was performed in patients < 30 years of age (*n* = 121). We found that a diagnosis of MEN syndrome was the only significant risk factor for MGD among all patients with PHPT (OR 39.5,

95% CI 4.3–361). Male sex, positive family history, prior parathyroidectomy, and non-localization by imaging were no longer significant. Among patients < 30 years of age with sporadic hyperparathyroidism (*n* = 14; i.e. excluding those with a history of MEN), male sex, prior parathyroidectomy, and non-localization by imaging were not associated with an increased risk of MGD.

TABLE 3 Cohort characteristics of patients undergoing parathyroidectomy for sporadic primary hyperparathyroidism, by age group

	Total population (n = 3833)	Group A: age 18–40 years (n = 322)	Group B: age >40 years (n = 3511)	p-value
<i>Preoperative findings</i>				
Sex				
Female	2967 (77.4)	208 (64.6)	2759 (78.6)	< 0.001
Male	866 (22.6)	114 (35.4)	752 (22.6)	< 0.001
Age, years [mean (SD)]	59.3 (12.8)	32.6 (5.9)	61.7 (10.2)	–
Family history of HPT	45 (1.2)	10 (3.1)	35 (1.0)	0.001
Prior parathyroidectomy	179 (4.8)	15 (4.7)	164 (4.7)	0.992
Serum Ca, mg/dL [median (IQR)]	10.8 (10.4–11.2)	10.8 (10.4–11.3)	10.8 (10.4–11.2)	0.001
24-h urinary Ca, mg [median (IQR)]	285 (185–406)	320 (225–419)	280 (181–404)	0.007
Serum PTH, pg/mL [median (IQR)]	86.3 (53.6–123)	83 (57.3–117)	87 (53–124)	0.007
Signs and symptoms				
Nephrolithiasis	634 (16.5)	66 (20.5)	568 (16.2)	0.116
Abnormal DXA scan	2077 (54.2)	65 (20.2)	2012 (57.3)	< 0.001
Non-specific symptoms	2576 (67.2)	182 (56.5)	2394 (68.2)	< 0.001
Localization by imaging				
Localized	2261 (59.0)	166 (51.6)	2095 (59.7)	0.005
Localized by ultrasound	1338 (34.9)	96 (29.8)	1242 (35.4)	0.045
Localized by sestamibi	2277 (59.4)	187 (58.1)	2090 (59.5)	0.611
<i>Intraoperative findings</i>				
Operative approach				
MIP	992 (25.9)	74 (23.1)	918 (26.2)	0.224
BLNE	2838 (74.1)	247 (77.0)	2591 (73.8)	0.224
Ectopic gland	398 (10.4)	41 (12.8)	357 (10.2)	0.145
<i>Postoperative findings</i>				
Pathology				
Single adenoma	2976 (78.4)	246 (78.3)	2730 (78.4)	0.001
Double adenoma	345 (9.1)	20 (6.4)	325 (9.3)	0.001
Hyperplasia	375 (9.9)	29 (9.2)	346 (9.9)	0.001
Inconclusive	102 (2.7)	19 (6.1)	83 (2.4)	0.001
Dominant gland				
Median size (IQR), cm	1.5 (1.1–2.0)	1.4 (1.0–1.9)	1.5 (1.1–2.0)	0.197
Median mass (IQR), mg	368.5 (182–791)	324.5 (153–741.8)	373 (185.2–794)	0.915
Cure	3475 (96.7)	276 (95.2)	3199 (96.8)	0.377

Data are expressed as n (%) unless otherwise specified

SD standard deviation, IQR interquartile range, MIP minimally invasive parathyroidectomy, BLNE bilateral neck exploration, HPT hyperparathyroidism

Impact of a Positive Family History of PHPT

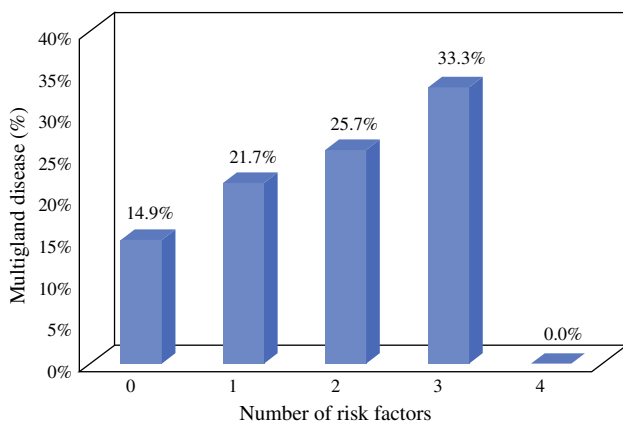
We sought to further determine the impact of a positive family history in sporadic PHPT. Subgroup analysis of patients with a positive family history demonstrated high rates of MGD in both young patients (40 vs. 14.4%, $p = 0.524$) and older patients (51.3 vs. 18.8%, $p = 0.057$)

compared with corresponding age groups without a family history, although this did not reach statistical significance. Rates of bilateral neck exploration were high in the setting of a family history in both young patients (100% vs. 76.2%, $p = 0.205$) and older patients (85.7 vs. 73.7%, $p = 0.339$), although these results were not significantly different between groups.

TABLE 4 Reduced multivariate analysis of factors associated with multigland disease

	OR	95% CI
<i>PHPT</i>		
Male sex	1.3	1.0–1.5
Family history of PHPT	2.7	1.6–4.8
MEN	6.3	3.1–12.7
Prior parathyroidectomy	2.2	1.6–3.0
Non-localized by imaging	1.8	1.5–2.1
<i>Sporadic PHPT</i>		
Male sex	1.3	1.0–1.6
Family history of PHPT	4.0	2.2–7.3
Prior parathyroidectomy	2.2	1.6–3.0
Non-localized by imaging	1.7	1.5–2.1

OR odds ratio, CI confidence interval, PHPT primary hyperparathyroidism, MEN multiple endocrine neoplasia

**FIG. 1** Incidence of multigland disease in sporadic PHPT patients, by number of risk factors. PHPT primary hyperparathyroidism

DISCUSSION

This is the largest published series to analyze the profile of familial and sporadic PHPT in young adults and to identify independent predictors of MGD.

Adult PHPT typically afflicts women in the fifth or sixth decade of life; the female to male ratio was 2.8:1 in patients with sporadic PHPT.¹⁰ The literature on sex ratios in young patients is mixed due to inconsistent use of age ranges and the inclusion of patients with genetic syndromes. A slight male predominance (female to male ratio approximately 0.9:1) has been identified in pediatric patient populations with PHPT;^{2–4,11} this literature is inclusive of cases of neonatal hyperparathyroidism and other inherited disorders that have no sex predilection. The slightly higher proportion of affected males observed may reflect the small number of published cases. Large studies of sporadic PHPT

in adolescent and young adult patients have found a sex distribution midway between published rates for the pediatric and geriatric populations. One review summarizing 230 published cases of PHPT in patients < 20 years of age found a moderate female predominance of 1.3:1.⁷ Studies specifically analyzing patients under the age of 40 years have demonstrated comparably high proportions of male patients.^{12,13} A contemporary analysis of the National Inpatient Sample database found a female to male ratio ranging from 1.17 to 1.83 for patients under age 40 years.¹⁰ Our data were consistent with these findings, with a female to male ratio of 1.8:1 in PHPT patients 18–40 years of age, and a 3.6:1 ratio in patients older than 40 years of age. These ratios remained unchanged after exclusion of patients with known inherited endocrinopathies. On multivariate analysis of predictors of MGD, male sex was independently associated with higher rates of MGD in both the total population of PHPT and in sporadic PHPT.

In our study cohort, signs and symptoms of PHPT differed based on age. Younger patients reported lower rates of non-specific symptoms, and had lower rates of bone mineral density loss but higher rates of nephrolithiasis compared with older patients. Prior studies have identified high rates of nephrolithiasis and nephrocalcinosis in pediatric and adolescent populations, compared with the overall population of PHPT patients.⁷ The relatively elevated incidence of end-organ disease may reflect a delay in diagnosis due to low utilization of routine screening serum chemistries in children. An analogous phenomenon has been well-documented in the changing epidemiology of adult PHPT. Historically, < 20% of adult patients were asymptomatic at diagnosis, with 51–57% experiencing nephrolithiasis, 36% with hypercalciuria, and 10–23% with overt skeletal disease.¹⁴ With the introduction of multi-channel analysis and automated serum calcium levels in the 1970s, both the incidence of PHPT and the proportion of asymptomatic patients rose dramatically. Today, the majority of adult PHPT patients are identified on routine blood testing and up to 95% of patients are asymptomatic at the time of diagnosis.¹⁵

Conflicting literature exists on symptom profiles of adult patients aged 40 years or younger. Consistent with our study, Sneider et al. found higher rates of nephrolithiasis but lower rates of bone pain in young patients.¹³ Joshua et al. found no statistically significant difference in renal, musculoskeletal, or neurocognitive symptoms between younger and older patients.¹² Adam et al. noted higher rates of symptoms in younger patients, but did not differentiate based on organ systems.¹⁶ In our study, we identified significantly higher rates of nephrolithiasis in young patients, and young patients were less likely to present with non-specific symptoms or bone demineralization. This may reflect overall better bone mineral

density in young patients, or alternatively, may reflect ascertainment bias as fewer young patients underwent DXA scan.

Some series have found lower rates of successful preoperative localization in pediatric populations compared with adults.¹⁷ In our patient population, we found lower rates of successful localization by imaging in young patients with PHPT. Non-localization by imaging was an independent risk factor for MGD on multivariate analysis of both PHPT and sporadic PHPT. This finding is consistent with prior studies that have identified a 31% incidence of MGD in patients with negative preoperative imaging studies compared with patients with one positive imaging study (3.6%) or patients with two concordant imaging studies (0%).¹⁸ Interestingly, Joshua et al. found that ultrasound was more sensitive than sestamibi (96 vs. 57%, $p < 0.05$) in patients 40 years of age or younger, and attributed this to lower rates of thyroid pathology to obstruct sonographic imaging of the parathyroid glands.¹² We found that although sestamibi was markedly less likely to localize successfully in young patients, more young patients had localizing sestamibi scans than ultrasound studies.

In our population of all patients with PHPT, a known diagnosis of MEN was the strongest predictor of MGD on multivariate analysis. This is consistent with published literature identifying higher rates of MGD in patients with inherited endocrinopathies.^{19,20} In our population of patients with presumed sporadic PHPT, a positive family history of PHPT was associated with increased incidence of MGD, with an odds ratio of 4.0. Although patients with MEN1 and MEN2A were excluded from the study population, it is possible that our analysis included people with undiagnosed inherited disorders. One large study identified undiagnosed MEN1 in 1.6% of patients presenting for surgical evaluation of PHPT.²¹ Another rare cause of PHPT is Familial Isolated Primary Hyperparathyroidism (FIHP), defined as inherited PHPT in the absence of other endocrinopathies. FIHP is a clinical diagnosis and is not associated with a single genetic abnormality, although mutations in the *MEN1* gene have been identified in some FIHP kindreds.²² Like MEN, FIHP is associated with high rates of MGD;²³ the exact incidence of FIHP is difficult to quantify as it has primarily been reported in small series. Because of the diagnostic uncertainty, FIHP was not captured in our dataset and therefore was not excluded from the study population. Given the large number of young patients with a positive family history in our cohort of young patients with sporadic PHPT, it seems unlikely that undiagnosed MEN or FIHP accounts entirely for the higher incidence of MGD in this population. Our results suggest

that a positive family history of PHPT may confer an increased risk of MGD even in the absence of known genetic syndromes.

Our data suggest that patients aged 40 years or younger with a positive family history of PHPT may have a 40% rate of MGD. This finding is consistent with prior observations from the Mayo Clinic. In 1997, Barry et al. noted a high prevalence of MGD (70%) as well as recurrent or persistent disease (43%) in 'familial hyperparathyroidism', defined as patients with one or more first-degree relatives with PHPT in the absence of MEN.²⁴ Their recommendation was for routine subtotal parathyroidectomy and transcervical thymectomy in all 'familial' patients. This approach incurs an elevated risk of hypocalcemia; in patients with high suspicion for MGD, we favor bilateral neck exploration with identification and excision of all affected gland(s). We suggest that young adult PHPT patients with a family history of PHPT should be counseled on their elevated risk of MGD. Testing for genetic susceptibility syndromes should be performed as clinically indicated. This population may benefit from routine bilateral neck exploration performed by an experienced endocrine surgeon; patients with double adenoma should undergo resection of the abnormal glands, while patients with four-gland hyperplasia should undergo debulking surgery with selective three-gland resection or subtotal parathyroidectomy. In contrast, young adult patients without a family history of PHPT do not appear to have higher rates of MGD and may be managed similarly to older adult patients.

CONCLUSIONS

In our population, young patients with PHPT did not have increased risk of MGD. However, even in the absence of a known inherited susceptibility gene, young adult patients with a family history of PHPT had a higher incidence of MGD. Age alone in the absence of a positive family history should not determine the need for bilateral neck exploration or subtotal parathyroidectomy. Patients with a positive family history of PHPT in the absence of a genetic syndrome should be counseled regarding their elevated rates of MGD, and may benefit from routine bilateral neck exploration and selective three gland resection or subtotal parathyroidectomy. Additional factors including male sex, prior parathyroidectomy, and non-localization by imaging were associated with increased risk for MGD. Patients with multiple co-occurring risk factors may benefit from counseling.

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