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ORIGINAL ARTICLE

Familial parathyroid tumours—comparison of clinical profiles between syndromes

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Abstract

Introduction Primary hyperparathyroidism (PHPT) caused by parathyroid tumours is mostly sporadic, with a genetic cause identified in 5–10% of cases. Familial parathyroid tumours can be included in complex syndromes, such as multiple endocrine neoplasia (MEN) type 1, 2A and 4 or hyperparathyroidism-jaw tumour syndrome (HPT-JT).

Objective Characterisation of the familial parathyroid tumours followed-up at our centre and comparison of the different clinicopathological manifestations between the syndromes.

Methods Retrospective analysis of 48 patients with familial parathyroid tumours harbouring *RET* ($n=11$), *CDC73* ($n=20$) and *MEN1* ($n=17$) germline mutations was performed.

Results Cases of PHPT in MEN2A syndrome presented with lower serum PTH (sPTH) and serum calcium (sCa) levels at diagnosis (sPTH = 108.0 (IQR 53.3) pg/mL, sCa = 10.6 ± 1.1 mg/dL) than MEN1 (sPTH = 196.9 (IQR 210.5) pg/mL, sCa = 11.7 ± 1.2 mg/dL) ($p=0.01$, $p=0.03$, respectively) or HPT-JT cases (sPTH = 383.5 (IQR 775.8) pg/mL, sCa = 12.9 ± 1.8 mg/dL) ($p=0.01$; $p<0.001$, respectively). There was a statistical difference in sCa levels between MEN1 and HPT-JT ($p=0.02$), but not between sPTH ($p=0.07$). The predominant first manifestation of the syndrome in MEN1 was gastroenteropancreatic neuroendocrine tumour (GEP-NET) in 47.1% of the cases, in MEN2A was medullary thyroid cancer (90.9%) and in HPT-JT was PHPT in 85% patients. In MEN1 syndrome, the number of affected parathyroid glands was significantly higher than in MEN2A ($p<0.001$) and HPT-JT ($p=0.01$).

Conclusion The first manifestation of the syndrome in MEN1 cases was GEP-NET and not PHPT. Although presenting at similar ages, patients with MEN2A exhibit less severe biochemical and clinical PHPT at diagnosis than the other familial syndromes.

Keywords Parathyroid tumour · Familial primary hyperparathyroidism · Multiple endocrine neoplasia · Hyperparathyroidism-jaw tumour

Introduction

Primary hyperparathyroidism (PHPT) is a disorder caused by the inappropriate secretion of parathyroid hormone (PTH) from one or more abnormal parathyroid glands, leading to increased serum calcium (sCa) levels [1]. Symptomatic and untreated PHPT can present as nephrolithiasis, low bone mineral density, gastrointestinal or muscular-skeletal complaints [2]. Additionally, neurocognitive dysfunction and cardiovascular morbidity and mortality are increased in patients with PHPT [3]. It is a common endocrine disorder with a higher prevalence in females and in the elderly population. In Europe, it has an estimated prevalence of 3 per 1000 people [4]. Most of the cases of PHPT are sporadic, with a reported rate of the inherited form of 5–10% [2].

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Hereditary PHPT can manifest as a familial solitary endocrinopathy, also known as familial isolated PHPT (FIHP), or as part of a complex endocrine syndrome [5]. Familial syndromes associated with parathyroid tumours are all autosomal dominant inherence and, to date, there are four multisystem syndromes with parathyroid involvement identified: multiple endocrine neoplasia (MEN) type 1, 2A and 4 and hyperparathyroidism-jaw tumour syndrome (HPT-JT) [5, 6]. These hereditary forms of PHPT result from the inactivation of tumour suppressor genes in MEN1 (*MEN1* gene), MEN4 (*CDKN1B* gene), FIHP (*MEN1*, *CDC73*, *GCM2* genes) and HPT-JT (*CDC73* gene) or from the activation of an oncogene in MEN2A (*RET* gene) [7]. Genetic testing for germline mutations involved in familial PHPT is helpful in clinical practice since it will provide proper screening for other non-parathyroid tumours related to the syndrome and identification of family members who may be asymptomatic carriers of the mutation [5]. In MEN2 syndrome, due to the high penetrance of MTC, a proper screening can have a major impact on patient survival, allowing an early or prophylactic thyroidectomy [8].

Clinicopathological features common to familial PHPT include multiglandular involvement and an earlier age of onset than the sporadic form [3]. However, depending on the syndrome, PHPT will also have specific features, with different clinical presentations and surgical management [5, 6]. Therefore, our aim was to characterise familial parathyroid tumours followed at our centre and to compare clinicopathological manifestations between syndromes.

Materials and methods

Study population

We performed a retrospective analysis of the familial parathyroid tumours cases followed in our centre. Cases were retrieved from *RET*, *CDC73* and *MEN1* genetic tests, performed at our institution between 1975 and 2020. Then through clinical records, cases of PHPT were identified, and only patients followed at our endocrine department were included. Our cohort included 12 MEN1 families, 6 MEN2 and 7 HPT-JT.

Demographics, symptoms at diagnosis, biochemical and densitometric parameters and imaging studies were collected from the medical records, as well as medical and surgical treatments, pathology exams and postoperative data.

Low bone mineral density (BMD) was defined as a *T* or *Z* score under − 1, depending on the age of the evaluated patient.

Patients were considered to have a total parathyroidectomy if all identified parathyroid glands were removed and a subtotal parathyroidectomy if three or more parathyroid glands were resected, with one or a partial gland left behind. Any lesser resection from the above mentioned was considered selective resection.

Biochemical cure was defined as the presence of normal sCa [normal range (NR): 8.4–10.2 mg/dL] and sPTH (NR: 12.0–65.0 pg/mL) levels for at least 6 months after surgery, persistent disease was defined as elevated sCa and SPTH levels within 6 months from parathyroidectomy, and recurrence as elevated sCa 6 months or later after parathyroidectomy. Permanent hypoparathyroidism was defined as SCa lower than 8.4 mg/dL lasting for more than 6 months.

At our centre, genetic testing is offered according to standard practice guidelines and includes: PHPT occurring before the age of 40 years; multiglandular disease, parathyroid carcinoma or atypical parathyroid adenomas, first relatives of known mutation carriers and index cases with two or more endocrine tumours associated with MEN syndrome [5, 9, 10].

The study was approved by the Ethics Committee of our centre. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data. Confidentiality was kept throughout the study and all patients or representatives signed informed consent for genetic analysis.

Genetic testing methods

Initially, the genetic testing in patients with familial PHPT was performed using single-strand conformational polymorphism analysis (SSCP) combined with manual Sanger sequencing (performed only for amplicons with abnormal SSCP bands) or, when DNA samples showed no abnormal SSCP bands, using manual Sanger sequencing for all amplicons, to detect point mutations or small insertions and deletions (INDELs). Southern blot analysis was used for the detection of large deletions/insertions (copy number variations—CNVs), but mainly in an investigational scope [11]. With the development of the technologies and sequencing platforms, we started to use automatic Sanger sequencing [12], together with multiplex ligation-dependent probe amplification (MLPA) for the detection of CNVs. In 2014, we implemented the use of next-generation sequencing (NGS) analysis of multi-gene panels in our laboratory, which was still combined with MLPA [13]. NGS technologies have facilitated multi-gene panel testing to detect germline DNA variants in patients with familial PHPT. Presently, we have implemented the use of a NGS multi-gene panel to identify both small sequence alterations and CNVs. Automatic Sanger sequencing and MLPA are only performed to confirm a positive result obtained by NGS. Most initial cases, with undetected genetic alterations, were reanalysed later, using more comprehensive and sensitive technical approaches.

Only recently, in 2020, *GCM2* genetic testing became part of the standard NGS gene panel.

Statistical analysis

Data management and statistical analysis were performed using Excel Software Microsoft ® and SPSS 23 IBM ®. Categorical variables are shown as absolute number and percentage; continuous normally distributed variables data are shown using mean and standard deviation (SD) and non-normally distributed variables data as median and interquartile range (IQR). All variables were checked for normality of distribution using Shapiro–Wilk test. Categorical variables were analysed using the Pearson's Chi-square test and Fisher's exact test as appropriate. Continuous variables were compared using the one-way ANOVA statistic test. A p value < 0.05 was considered statistically significant.

Table 1 Clinical characteristics of the patients

Number of patients	48
Age at PHPT diagnosis, mean ± SDS, years	40.0 ± 15.5
Gender: male; female	24; 24
Follow-up, median (IQR), months	146.5 (240.0)
Syndrome, *n* (%)	
MEN1	17 (35.4)
MEN2A	11 (22.9)
HPT-JT	20 (41.7)

HPT-JT hyperparathyroidism-jaw tumour syndrome, *IQR* interquartile range, *MEN1* multiple endocrine neoplasia type 1, *MEN2A* multiple endocrine neoplasia type 2A, *PHPT* primary hyperparathyroidism, *SDS* standard deviation

Results

We found 48 patients with a familial form of PHPT, including 24 females (50.0%) and 24 males (50.0%), with a median follow-up of 146.5 (IQR 240.0) months. MEN1-related PHPT syndrome was found in 17 (35.4%) patients, MEN2A in 11 (22.9%) and HPT-JT in 20 (41.7%) patients (Table 1). Germ line mutations identified in our cohort are listed in Table 2. No *CDKN1B* mutations were found in MEN1-related PHPT.

In the MEN1 group, the first manifestation of the syndrome occurred at a mean age of 37.7 ± 17.6 years. In eight (47.1%) patients, the first manifestation was a gastroenteropancreatic neuroendocrine tumour (GEP-NET) and in five (29.4%) PHPT. GEP-NET was the most common first manifestation of MEN1 in index cases (66.7%), while in non-index cases, it was PHPT (50%). Mean age at diagnosis of PHPT was 43.1 ± 14.2 years and 35.3% of the patients were detected by screening of mutation carriers. Nephrolithiasis was the most frequent complication (47.1%). Most

Table 2 List of germline mutations identified in our cohort

Gene (transcript)	Exon	Mutation	Classification	Number of patients
RET (NM_020975)	e10	c.1832G > A p.(Cys611Tyr)	Pathogenic	2
	e11	c.1900 T > C p.(Cys634Arg)	Pathogenic	4
	e11	c.1901G > A p.(Cys634Tyr)	Pathogenic	2
MEN1 (NM_130803)	e2	c.1A > T p.(Met1Leu)	Pathogenic	3
	e3	c.640C > T p.(Gln214*)	Pathogenic	1
	e3	c.643_646del p.(Thr215Serfs*13)	Pathogenic	3
	e5	c.810del p.(Trp270Cysfs*16)	Likely Pathogenic	1
	e7	c.978C > A p.(Tyr326*)	Pathogenic	1
	e9	c.1213C > T p.(Gln405*)	Pathogenic	1
	e9	c.1321_1323dup p.(Trp441dup)	Likely Pathogenic	1
	e10	c.1372C > T p.(Gln458*)	Likely Pathogenic	1
	e10	c.1393C > T p.(Arg465*)	Pathogenic	1
	e10	c.1444del p.(Glu482Lysfs*82)	Likely Pathogenic	1
	del exon 7–3'UTR		Pathogenic	2
CDC73 (NM_024529)	e3	c.306G > A p.(=)	Likely Pathogenic	1
	e4	c.356del p.(Gln119Argfs*14)	Likely Pathogenic	11
	e7	c.520_523del p.(Ser174Lysfs*27)	Likely Pathogenic	1
	e8	c.766_767del p.(Val256Lysfs*10)	Pathogenic	6
	Whole-gene deletion		Pathogenic	1

Genetic test result not available in four patients

patients underwent surgical intervention (76.5%). Regarding histopathological data, parathyroid hyperplasia (46.1%) and adenoma (38.5%) were the most common findings. Parathyroid carcinoma was observed in one patient. Postsurgical evaluation was available in 12 patients: 3 of them presented with persistent PHPT, 2 with recurrence and 5 with permanent hypoparathyroidism (Table 3). Hypoparathyroidism was found in four (57,1%) patients submitted to total/subtotal parathyroidectomy and in one (16,7%) patient submitted to selective resection of parathyroids. We found an association between surgical selective resection of parathyroid and persistence/recurrence of PHPT (80% in selective resection vs 12.5% in total/subtotal parathyroidectomy; $p = 0.01$).

Of the 11 patients with MEN2A syndrome, 6 were females and 5 were males. The first manifestation of the syndrome occurred at a mean age of 31.3 ± 19.5 years and PHPT was diagnosed at a mean age of 43.9 ± 19.2 years. Medullary thyroid carcinoma (MTC) was the most common first manifestation of the syndrome in ten cases (90.9%) and in both index (100%) and non-index (85.7%) cases. In one case, the first manifestation was pheochromocytoma. All eight patients submitted to surgical intervention underwent selective parathyroid gland resection, and pathology confirmed parathyroid adenoma in seven (87.5%). Recurrence was observed in one (12.5%) patient, and disease persistence did not occur (Table 4).

In HPT-JT patients ($n = 20$), most had PHPT as the first manifestation of the syndrome (85.0%), occurring at a mean age of 35.1 ± 13.6 years. PHPT was the predominant form of HPT-JT's first manifestation in both index (83.3%) and non-index cases (85.7%). Ossifying fibroma of the maxilla and/or mandible was reported as the first manifestation in two (10.0%) patients. An equal female to male ratio was observed. Of the 17 patients who underwent surgery, parathyroid selective resection was the most frequent surgical approach in ten (58.8%) patients, followed by subtotal parathyroidectomy and total parathyroidectomy in three patients (17.6%). Parathyroid adenoma was the most frequent histological diagnosis, and parathyroid carcinoma occurred in four (23.5%) patients. Postsurgical evaluation was available in 16 patients, with 2 having persistent PHPT, 4 recurrence and 5 permanent hypoparathyroidism (Table 5).

Regarding sPTH and sCa levels, we observed that these were lower at diagnosis in patients with MEN2A syndrome (sPTH = 108.0 (IQR 53.3) pg/mL, sCa = 10.6 ± 1.1 mg/dL) than in MEN1 (sPTH = 196.9 (IQR 210.5) pg/mL, sCa = 11.7 ± 1.2 mg/dL) ($p = 0.01$, $p = 0.03$, respectively) or in HPT-JT (sPTH = 383.5 (IQR 775.8) pg/mL, sCa = 12.9 ± 1.8 mg/dL) ($p = 0.01$; $p < 0.001$, respectively). sCa levels were significantly higher ($p = 0.02$) in HPT-JT (12.9 ± 1.8 mg/dL) than in MEN1 (11.7 ± 1.2 mg/dL) but sPTH (383.5 (IQR 775.8) pg/mL in HPT-JT and 196.9 (IQR 210.5) pg/mL in MEN1) did not reach statistical

Table 3 Clinicopathological characteristics of MEN1 patients

Number of patients,	17
Index cases, *n* (%)	9 (52.9)
Age at first manifestation of MEN1, mean ± SDS, years	37.7 ± 17.6
Age at PHPT diagnosis, mean ± SDS, years	43.1 ± 14.2
Sex: male; female, *n* (%)	9 (52.9); 8 (47.1)
Follow-up, median (IQR), months	66.0 (198)
First manifestation of MEN1, *n* (%)	
GEP-NET neuroendocrine tumour	8 (47.1)
PHPT	5 (29.4)
Pituitary adenoma	4 (23.5)
First manifestation of MEN1 in index cases, *n* (%)	
GEP-NET neuroendocrine tumour	6 (66.7)
PHPT	1 (11.1)
Pituitary adenoma	2 (22.2)
First manifestation of MEN1 in non-index cases, *n* (%)	
GEP-NET neuroendocrine tumour	2 (25)
PHPT	4 (50)
Pituitary adenoma	2 (25)
Diagnosis of PHPT, *n* (%)	
Screening of mutation carriers	6 (35.3)
Clinical manifestations of PHPT	7 (41.2)
Routine blood analysis	4 (23.5)
Serum PTH, median (IQR), pg/mL	196.9 (210.5)
Serum calcium, mean ± SDS, mg/dL	11.7 ± 1.2
Complications of PHPT, *n* (%)	
Nephrolithiasis	8 (47.1)
Low bone mineral density	3 (17.6)
Chronic renal insufficiency	2 (11.8)
Surgical intervention, *n* (%)	13 (76.5)
Parathyroid selective resection	5 (38.5)
Subtotal parathyroidectomy	3 (23.1)
Subtotal parathyroidectomy and thymectomy	2 (15.4)
Total parathyroidectomy	2 (15.4)
En bloc resection of the parathyroid tumour and ipsilateral hemithyroidectomy	1 (7.7)
Histology, *n* (%)	
Hyperplasia	6 (46.1)
Adenoma	5 (38.5)
Carcinoma	1 (7.7)
Atypical adenoma + adenoma	1 (7.7)
Postoperative hypoparathyroidism, *n* (%)	5 (41.7)
Persistence of PHPT, *n* (%)	3 (25)
Recurrence of PHPT, *n* (%)	2 (16.7)

GEP-NET, gastroenteropancreatic neuroendocrine tumour; IQR, interquartile range; MEN1, multiple endocrine neoplasia type 1; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; SDS, standard deviation

Table 4 Clinicopathological characteristics of MEN2A patients

Number of patients	11
Index cases, *n* (%)	3 (27.3)
Age at first manifestation of MEN2A, mean ± SDS, years	31.3 ± 19.5
Age at PHPT diagnosis, mean ± SDS, years	43.9 ± 19.2
Sex: male; female, *n* (%)	5 (45.5); 6 (54.5)
Follow-up, mean ± SDS, months	200.9 ± 133.0
First manifestation of MEN2, *n* (%)	
MTC	10 (90.9)
Pheocromocytoma	1 (9.1)
First manifestation of MEN2 in index cases, *n* (%)	
MTC	3 (100)
First manifestation of MEN2 in non-index cases, *n* (%)	
MTC	7 (87.5)
Pheocromocytoma	1 (12.5)
Diagnosis of PHPT, *n* (%)	
Screening of mutation carriers	9 (81.8)
Clinical manifestations of PHPT	2 (18.2)
Serum PTH, median (IQR), pg/mL	108.0 (53.3)
Serum calcium, mean ± SDS, mg/dL	10.6 ± 1.1
Complications of PHPT, *n* (%)	
Nephrolithiasis	2 (18.2)
Low bone mineral density	1 (9.1)
Chronic renal insufficiency	1 (9.1)
Surgical intervention, *n* (%)	8 (72.7)
Parathyroid selective resection	8 (100)
Histology, *n* (%)	
Adenoma	7 (87.5)
Hyperplasia	1 (12.5)
Postoperative hypoparathyroidism *n* (%)	3 (37.5)
Persistence of PHPT, *n* (%)	0
Recurrence of PHPT, *n* (%)	1 (12.5)

IQR interquartile range, *MTC* medullary thyroid carcinoma, *MEN2A* multiple endocrine neoplasia type 2A, *PHPT* primary hyperparathyroidism, *PTH* parathyroid hormone, *SDS* standard deviation

difference ($p = 0.07$). PHPT was the first manifestation of the syndrome in more patients with HPT-JT syndrome than in MEN1 ($p = 0.001$) and MEN2A syndrome ($p < 0.001$). PHPT-mediated organ damage was more frequent in HPT-JT ($p = 0.02$). The number of affected parathyroids was higher in MEN1 than in MEN2A ($p < 0.001$) and HPT-JT syndrome ($p = 0.01$). There were no differences between syndromes concerning age at PHPT diagnosis, sex or postoperative features like hypoparathyroidism, persistence, or recurrence of PHPT (Table 6).

Discussion

Hereditary PHPT represents approximately 5–10% of all cases of PHPT, in which a germline mutation in *MEN1*, *CDC73*, *CDKN1B, RET* or *GCM2* can be the underlying cause [2, 14]. In our cohort of 48 patients with familial parathyroid tumours, HPT-JT was the most prevalent syndrome, followed by MEN1 and MEN2A syndrome.

PHPT affects more than 93% of patients with MEN1 and in most of the cases, it is the first manifestation of the syndrome (> 67%) [15]. However, as far we know, there is no study that has compared the first manifestation of the syndrome in index cases vs non-index cases. In our cohort, surprisingly, the most reported first manifestation in index cases was a GEP-NET, instead of PHPT. In non-index cases, on the other hand, PHPT was the first manifestation of the syndrome. Our institute is an oncology centre, and this may have constituted a bias in our study, leading to GEP-NET being one of the main causes of referral and, therefore, the first manifestation of MEN1 in index cases. MEN1-related PHPT differs from the sporadic form in many clinical features: younger age at presentation, equal male/female ratio and common affection of multiple parathyroid glands [10]. Indeed, in our series, we observed an equal proportion of

Table 5 Clinicopathological characteristics of HPT-JT patients

Number of patients	20
Index cases, *n* (%)	6 (30.0)
Age at first manifestation of HPT-JT, mean ± SDS, years	33.3 ± 13.1
Age at PHPT diagnosis, mean ± SDS, years	35.1 ± 13.6
Sex: male; female, *n* (%)	10 (50);10 (50)
Follow-up, median (IQR), months	216.5 ± 277.0
First manifestation of HPT-JT, *n* (%)	
PHPT	17 (85.0)
Ossifying fibroma of the maxilla and/or mandible	2 (10.0)
Unknown	1 (5.0)
First manifestation of HPT-JT in index cases, *n* (%)	
PHPT	5 (83.3)
Unknown	1 (16.7)
First manifestation of HPT-JT in non-index cases, *n* (%)	
PHPT	12 (85.7)
Ossifying fibroma of the maxilla and/or mandible	2 (14.3)
Diagnosis of PHPT, *n* (%)	
Screening of mutation carriers	9 (45.0)
Clinical manifestations of PHPT	10 (50.0)
Unknown	1 (5.0)
Serum PTH, median (IQR), pg/mL	383.5 (775.8)
Serum calcium, mean ± SDS, mg/dL	12.9 ± 1.8
Complications of PHPT, *n* (%)	
Nephrolithiasis	13 (65.0)
Low bone mineral density	6 (30.0)
Chronic renal insufficiency	4 (20.0)
Surgical intervention, *n* (%)	17 (85.0)
Parathyroid selective resection	10 (58.8)
Subtotal parathyroidectomy	3 (17.6)
Total parathyroidectomy	2 (11.8)
Total parathyroidectomy with autotransplantation	1 (5.9)
Unknown	1 (5.9)
Histology, *n* (%)	
Adenoma	10 (58.8)
Carcinoma	4 (23.5)
Atypical adenoma	2 (11.8)
Hyperplasia	1 (5.9)
Postoperative hypoparathyroidism, *n* (%)	5 (31.3)
Persistence of PHPT, *n* (%)	2 (12.5)
Recurrence of PHPT, *n* (%)	4 (25.0)

HPT-JT, hyperparathyroidism-jaw tumour syndrome; IQR, interquartile range; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; SDS, standard deviation

female and male patients and the mean number of involved parathyroid glands was 2.7 ± 0.9. The diagnosis of PHPT occurred at a younger age than the sporadic form (50 to 75 years) [10], though slightly later than the mean age reported in the literature [15–17]. Our explanation for the late diagnosis of PHPT is related to the high proportion of index cases (52.9%) in our MEN1 cohort who were referred to our centre because of the GEP-NET, with a diagnosis of PHPT only after starting the investigation for the NET. They probably had PHPT for a long time, but it was never diagnosed. Furthermore, as these index cases were diagnosed at an advanced age, so were a good proportion of their family members, initiating surveillance later in life. MEN1-related PHPT is mainly caused by diffuse hyperplasia of the parathyroid glands and parathyroid carcinoma is very rare (< 1%) [15]. We detected one case of parathyroid carcinoma. In this case, the patient already had a preoperative suspicion of parathyroid carcinoma for a severe biochemical PHPT, and an *en bloc* resection of the tumour together with the ipsilateral thyroid lobe was done. Half of our patients were submitted to total or subtotal parathyroidectomy, with selective resection of the involved parathyroids in the other half. Recurrence and persistence were observed in 16.7% and 25% of the operated PHPT, and we found a higher prevalence of disease persistence in patients only submitted to selective resection (80%) than to total/subtotal parathyroidectomy (12.5%) similarly to the published literature [15, 18].

PHPT in MEN2A syndrome is typically diagnosed after MTC's presentation or concurrently with it, and this was confirmed in our series [19]. The hypercalcemia is usually mild [8] and, in our study, it was the lowest of the three syndromes. Contrary to MEN1 syndrome, in which multiglandular disease involvement usually occurs [3], single-gland adenoma is the most common presentation in MEN2 [19]. Several options have been described concerning the intraoperative management of parathyroid glands in this syndrome; however, a conservative approach is defended by most authors, with selective resection of only enlarged parathyroid glands, avoiding total parathyroidectomy [7]. According to the recommendations, all MEN2A patients in our cohort were submitted to parathyroid selective resection.

PHPT is a highly penetrant clinical feature of HPT-JT and almost 100% of patients develop PHPT, typically in late adolescence or early adulthood [20]. Multiglandular involvement at initial surgery occurs only in 20% of cases, with later affection of other parathyroids in 23.9% of cases [7]. In our series, we observed a recurrence rate of 25%. Most HPT-JT patients were submitted to parathyroid selective resection. Due to the potential for malignancy and PHPT recurrence, prophylactic total parathyroidectomy or subtotal parathyroidectomy with autotransplantation has been considered in the past [7, 21]. However, total parathyroidectomy is not always successful and is associated with an increased morbidity due to permanent postsurgical hypoparathyroidism. Furthermore, the recent finding of frequent uniglandular involvement in this syndrome did not support this approach [7, 20]. As such, if parathyroid cancer is not suspected, all parathyroid glands should be identified at surgery and only

Table 6 Comparison between features of MEN1, MEN2A and HPT-JT

	MEN1	MEN2A	HPT-JT	*p* value
Age at first manifestation of the syndrome, mean ± SDS, years	37.7 ± 17.6	31.3 ± 19.5	33.3 ± 13.1	0.39
Age at PHPT diagnosis, mean ± SDS, years	43.1 ± 14.2	43.8 ± 19.2	35.1 ± 13.6	0.22
Female, *n* (%)	8 (47.1)	6 (54.5)	10 (50.0)	0.93
PHPT as first manifestation of the syndrome, *n* (%)	5 (29.4)$^{\Upsilon,¤}$	0$^{\Upsilon}$,*	17 (85.0)$^{¤}$*	$^{¤}$ **0.001** $^{\Upsilon}$ 0.13 * **< 0.001**
Serum PTH, median (IQR), pg/mL	196.9 (210.5) $^{\Upsilon,¤}$	108.0 (53.3) $^{\Upsilon}$,*	383.5 (775.8)$^{¤}$*	$^{¤}$ 0.07 $^{\Upsilon}$ **0.01** ***0.01**
Serum calcium, mean ± SDS, mg/dL	11.7 ± 1.2$^{\Upsilon,¤}$	10.6 ± 1.1 $^{\Upsilon}$,*	12.9 ± 1.8$^{¤}$,*	$^{¤}$**0.02** $^{\Upsilon}$**0.03** * **< 0.001**
Complications of PHPT at diagnosis, *n* (%)	8 (47.1)	2 (18.2)	12 (60)	0.06
Complications of PHPT, *n* (%)				
Nephrolithiasis	8 (47.1)$^{\Upsilon,¤}$	2 (18.2)$^{\Upsilon}$,*	13 (65.0)$^{¤}$*	$^{¤}$0.19; $^{\Upsilon}$0.12; ***0.02**
Low bone mineral density	3 (17.6)	1 (9.1)	6 (30.0)	0.29
Chronic renal insufficiency	2 (11.8)	1 (9.1)	4 (20.0)	0.63
Histology, *n* (%)				
Adenoma	6 (46.2)	7 (87.5)	10 (58.8)	0.42
Carcinoma	1 (7.7)	0	4 (23.5)	0.21
Hyperplasia	6 (46.2)	1 (12.5)	1 (5.9)	0.06
Total number of involved parathyroids, mean ± SDS	2.7 ± 0.9 $^{\Upsilon,¤}$	1.1 ± 0.3$^{\Upsilon}$*	1.6 ± 1.1$^{¤}$,*	$^{¤}$**0.01** $^{\Upsilon}$ **< 0.001** *0.23
Postoperative hypoparathyroidism, *n* (%)	5 (41.7)	3 (37.5)	5 (31.3)	0.97
Persistence of PHPT, *n* (%)	3 (24)	0	2 (12.5)	0.24
Recurrence of PHPT, *n* (%)	2 (16.7)	1 (12.5)	4 (25)	0.91

HPT-JT hyperparathyroidism-jaw tumour syndrome, *IQR* interquartile range, *MEN1* multiple endocrine neoplasia type 1, *MEN2A* multiple endocrine neoplasia type 2A, *PHPT* primary hyperparathyroidism, *PTH* parathyroid hormone, *SDS* standard deviation

$^{\Upsilon}$Comparison between MEN1 and MEN2A

*Comparison between MEN2A and HPT-JT

$^{¤}$Comparison between MEN1 and HPT-JT

the abnormal ones should be resected [18, 22]. The risk of parathyroid carcinoma is a hallmark of HPT-JT syndrome, with a reported rate of 15–20% in the literature [21]. In our cohort, we documented a slightly higher incidence, of 23.5%.

Our study was retrospective and spanned for a long period of time which allowed for a prolonged follow-up of our patients. On the other hand, it led to a greater heterogeneity in the cohort and in the therapeutic approaches of PHPT over the years within each syndrome. Furthermore, due to the rarity of these syndromes, our study population was relatively small, which may have provided insufficient statistical power to detect significant differences. Nevertheless, this is one of the few studies in the literature that describes and compares hyperparathyroid patients within familial syndromes providing additional important information about clinical behaviour of PHPT in these syndromes.

In conclusion, in our analysis, PHPT was not the most frequent first manifestation of the MEN1 syndrome, as commonly believed. MEN2A showed the least severe form of familial PHPT, with HPT-JT being the most aggressive in terms of hypercalcemia and prevalence of carcinoma.

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Data availability statement The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval This study was approved by the local Ethics Committee of Instituto Português de Oncologia de Lisboa Francisco Gentil.

Informed consent Informed consent was waived because of the retrospective nature of the study.

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