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REVIEW ARTICLE

Hereditary hyperparathyroidism—a consensus report of the European Society of Endocrine Surgeons (ESES)

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Abstract
Background Hereditary hyperparathyroidism has been reported to occur in 5–10 % of cases of primary hyperparathyroidism in the context of multiple endocrine neoplasia (MEN) types 1, 2A and 4; hyperparathyroidism-jaw tumour (HPT-JT); familial isolated hyperparathyroidism (FIHPT); familial hypocalciuric hypercalcaemia (FHH); neonatal severe hyperparathyroidism (NSHPT) and autosomal dominant moderate hyperparathyroidism (ADMH). This paper aims to review the controversies in the main genetic, clinical and pathological features and surgical management of hereditary hyperparathyroidism.
Methods A peer review literature analysis on hereditary hyperparathyroidism was carried out and analyzed in an evidence-based perspective. Results were discussed at the 2015 Workshop of the European Society of Endocrine Surgeons devoted to hyperparathyroidism due to multiple gland disease.
Results Literature reports scarcity of prospective randomized studies; thus, a low level of evidence may be achieved.
Conclusions Hereditary hyperparathyroidism typically presents at an earlier age than the sporadic variants. Gene penetrance and expressivity varies. Parathyroid multiple gland involvement is common, but in some variants, it may occur metachronously often with long disease-free intervals, simulating a single-gland involvement. Bilateral neck exploration with subtotal parathyroidectomy or total parathyroidectomy + autotransplantation should be performed, especially in MEN 1, in order to decrease the persistent and recurrent hyperparathyroidism rates; in some variants (MEN 2A, HPT-JT), limited parathyroidectomy can achieve long-term normocalcemia. In FHH, surgery is contraindicated; in NSHPT, urgent total parathyroidectomy is required. In FIHPT, MEN 4 and ADMH, a tailored case-specific approach is recommended.

Keywords Hereditary primary hyperparathyroidism · Familial primary hyperparathyroidism · Multiple gland disease · MEN 1 · MEN 2 · MEN 4 · HPT-JT · FIHPT · FHH · NSHPT · ADMH · Parathyroidectomy

Introduction

Primary hyperparathyroidism (pHPT) is a common endocrine disorder, which in approximately 90 % of cases arises sporadically with a peak incidence in the sixth decade of life and caused by over 80 % by a solitary benign adenoma. One tenth of pHPT occurs in a genetic and hereditary setting where it tends to present earlier and more frequently with multiglandular involvement. Hereditary pHPT usually occurs in a familial setting, but family history may be absent, underestimated or misdiagnosed. The most common hereditary variants are part of syndromes where the pHPT is

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associated with other endocrine and non-endocrine neoplasms: multiple endocrine neoplasia (MEN) type 1, 2A or 4 and hyperparathyroidism-jaw tumour syndrome (HPT-JT). Less frequently, it may be found without any syndromic association including familial isolated hyperparathyroidism (FIHPT), familial hypocalciuric hypercalcaemia (FHH), neonatal severe hyperparathyroidism (NSHPT) and autosomal dominant moderate hyperparathyroidism (ADMH) (Tables 1 and 2) [1].

In the last decades, an increasing number of specific gene mutations have been identified as responsible for various hereditary types of pHPT which as a consequence has swelled the amount of hereditary pHPT. To date, mutations in at least 11 different pathogenic genes have been identified as a cause of hereditary pHPT. The disease is usually transmitted by an autosomal dominant pattern (Table 1) [1, 2]. However, the variable penetrance and expressivity of the genes and the finding of variants of hereditary pHPT of an unknown genetic cause suggest that the real frequency of these diseases may be underestimated [3].

An excessive and dysregulated secretion of parathormone (PTH) represents the pathogenetic basis of hereditary forms of pHPT with either the inactivation of tumour suppressor genes (in MEN 1, MEN 4, FIPHT and HPT-JT) or the activation of oncogenes with an increase of cellular proliferation (in MEN 2A) or the dysregulation of the calcium set point with loss of the normal feedback control on PTH secretion (in FHH, ADMH and NSHPT) [1].

The diagnosis of hereditary pHPT should be confirmed by a genetic testing preceded by the appropriate genetic counselling. The early identification of hereditary variants of pHPT is crucial for the optimal clinical and surgical management of hereditary pHPT patients who present a very different set of challenges to sporadic pHPT as reflected by the considerably higher rate of persistent and recurrent disease after attempted curative surgery. The identification of hereditary disease is of vital importance also for both affected relatives who may be offered tailored management according to the presence of the associated mutations [2].

Despite the increasing number of identified variants of hereditary pHPT, better understood epidemiology, molecular pathogenesis, the pattern of parathyroid involvement (benign vs. malignant, single-gland vs. multiglandular involvement), the indications for and optimal timing and type of surgical treatment (focused vs. bilateral exploration, selective vs. extensive parathyroidectomy) remain stubbornly controversial. This represents the incentive behind this paper that aims to summarize and analyze the literature focusing on epidemiology, main genetic, clinical and pathological features and surgical management of hereditary pHPT in an evidence-based perspective.

Table 1 Clinical syndromes and genetic defects in hereditary hyperparathyroidism

Disease/OMIM	Gene/protein	Chromosomal location	Type of germline mutation
MEN 1/131100	*MEN1/Menin*	11q13	Inactivating
MEN 2A/ 171400	*RET/c-RET*	10q11.21	Activating
HPT-JT/ 145001	*CDC73/parafibromin*	1q31.2	Inactivating
FIHPT/145000	*MEN 1*, *CDC73*, *CASR*, *CDKN1A, CDKN2B*, *CDKN2C*, *other genes*	11q13, 1q31.2, 3q21.1	Inactivating
FHH types 1, 2, 3/145980, 145981, 600740	*CASR*, *GNA11*, *AP2S1/ calcium-sensing receptor*	3q21.1, 19p13.3, 19q13.2–q13.3	Inactivating
NSHPT/ 239200	*CASR/calcium-sensing receptor*	3q21.1	Inactivating
ADMH/ 601199	*CASR/calcium-sensing receptor*	3q13.3-q21.1	Atypically inactivating
MEN 4/610755	*CDKN1B*, *other genes/ P27*, *KIP1*	12p13.1	Inactivating

MEN multiple endocrine neoplasia, *HPT-JT* hyperparathyroidism-jaw tumour syndrome, *FIHPT* familial isolated hyperparathyroidism, *FHH* familial hypocalciuric hypercalcaemia, *NSHPT* neonatal severe hyperparathyroidism, *ADMH* autosomal dominant moderate hyperparathyroidism

Materials and methods

A Medline search of articles focusing on hereditary pHPT was performed using PubMed via the National Library of Medicine up to December 2014 and further expanded. Levels of evidence and possible grades of recommendation were considered according to the criteria stated by a modified Sackett's classification [4] and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system [5]. According to Sackett's classification, the strength of a recommendation was graded "A" when supported by studies with a level of evidence I (meta-analysis or large randomized trials with clear cut-off results and low risk for error); "B" when supported by level II studies (small randomized trials and moderate to high risk for error) and "C" when supported by level III (non-randomized, prospective with contemporaneous control trials), level IV (non-randomized trials with historical controls, retrospective analysis) or level V studies (case series without controls, expert opinion). In the GRADE system, the strength of recommendations has been defined as "strong" or "weak"; the quality of the evidence has been indicated by cross-filled circles: "⊕OOO" denotes very-low-quality evidence (any estimate of effect is very uncertain); "⊕⊕OO", low quality (further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate); "⊕⊕⊕O", moderate quality (further

Table 2 Main clinical features in hereditary hyperparathyroidism

Disease	Age at onset (years)	Parathyroid involvement	Parathyroid pathology	Associated diseases	Surgical strategy
MEN 1	20-25	MGD	Hyperplasia/ multiple adenomas	Pituitary, gastroenteropancreatic, thymus, adrenal, breast tumours	SPTX or TPTX with autologous reimplantation + transcervical thymectomy
MEN 2A	>30	Single/MGD	Hyperplasia/ adenoma(s)	Medullary thyroid carcinoma, pheochromocytoma	Selective resection during thyroidectomy (or MEN 1 type PTX in case of MGD)
HPT-JT	>30	Single/MGD	Adenoma(s) (cystic)/ carcinoma	Jaw tumours, uterine and renal involvement	Single gland disease: focused parathyroidectomy, MGD: SPTX or TPTX, carcinoma: en block enlarged resection
FIHPT	Not reported	Single/MGD	Hyperplasia/ adenoma(s)	–	Surgery tailored to the intraoperative findings
FHH	At birth	MGD	Mild hyperplasia	–	No surgery
NSHPT	At birth	MGD	Severe hyperplasia	–	TPTX
ADMH	45	Single/MGD	Hyperplasia/ adenoma(s)	–	Surgery tailored to the intraoperative findings
MEN 4	>35	MGD	Hyperplasia/ adenoma(s)	Pituitary, gastroenteropancreatic, thymus, adrenal tumours	SPTX or TPTX with autologous reimplantation + transcervical thymectomy

MEN multiple endocrine neoplasia, *HPT-JT* hyperparathyroidism-jaw tumour syndrome, *FIHPT* familial isolated hyperparathyroidism, *FHH* familial hypocalciuric hypercalcaemia, *NSHPT* neonatal severe hyperparathyroidism, *ADMH* autosomal dominant moderate hyperparathyroidism, *MGD* multiglandular disease, *SPTX* subtotal paratyroidectomy, *TPTX* total parathyroidectomy

research is likely to have an important impact on confidence in the estimate of effect and may change the estimate) and "⊕⊕⊕⊕", high quality (further research is very unlikely to change the confidence in the estimate of effect).

The review of the literature led to the production of a draft document that was presented and discussed at the 2015 Workshop of the European Society of Endocrine Surgeons devoted to hyperparathyroidism due to multiple gland disease held in Varna (Bulgaria), May 28–30, 2015, and finally revised.

Results

The analysis of the literature focusing on hereditary pHPT revealed the scarcity of prospective randomized studies. In most cases, only retrospective cohorts and case series are available; in some variants of hereditary pHPT, because of rarity, only case reports or expert opinions have been published. As a consequence, frequently only a low level of evidence may be offered for conclusions; thus, the subsequent strength of recommendations is often limited.

MEN 1

MEN 1 (OMIM # 131100) is a syndromic variant of hereditary pHPT. It is the most frequent form of familial pHPT characterized primarily by tumours of the parathyroid glands; the pancreatic islets; the anterior pituitary gland which may coexist with adrenocortical tissue growth and neuroendocrine tumours of the thymus, lungs and stomach [6]. Non-endocrine manifestations of MEN 1 include angiofibromas, collagenomas, lipomas, leiomyomas and meningiomas; more recently, breast cancer has been described as an associated disease [7]. The prevalence of MEN 1 is 2–3/100,000 with equal sex distribution. The risk of MEN 1 in patients with apparently sporadic endocrine tumours can be predicted according to the age of onset, type of tumour and family history [8].

Genetic features

MEN 1 is an autosomal-dominant inherited syndrome, caused by germline mutations of the *MEN 1* gene which is located on chromosome 11 (11q13). The *MEN 1* gene encodes for *Menin* and is a tumour suppressor gene.

Clinical features

pHPT occurs in 75–95 % of MEN 1 patients, and it is usually the first manifestation of MEN 1 syndrome [6]. The onset of pHPT in MEN 1 is typically between ages 20 and 25 years and caused by parathyroid hyperplasia or multiple usually benign adenomas. All individuals with MEN 1 syndrome can be virtually expected to have hypercalcaemia by the age 50 years [1]. Pituitary tumours occur from 15 to 55 % [9] of which prolactinoma is the most common pituitary tumour. Multiple non-secreting or secreting (gastrinomas, insulinomas) gastroenteropancreatic tumours occur in more than 50 % of

cases. The age-related penetrance for all clinical features surpasses 50 % by age 20 years and 95 % by age 40 years [9].

Diagnosis

The presumed affected individual should be genetically tested first in order to determine the mutation involved. If a pathogenetic mutation is identified within a kindred, family members at risk for carrying this mutation should undergo DNA testing following the appropriate counselling and informed consent procedures that will include informing the at risk individual of the advantages and disadvantages of testing. In the case of patients under the age of consent, the parents of a child at risk for being mutation carriers can decide whether the child's DNA will be tested or not. Other first-degree family members, parents, brothers and sisters of a patient share half of their genes with the proband and have a risk of 50 % of carrying the *MEN 1* disease gene. Second- and third-degree relatives share one fourth and one eighth of their genes with the proband, respectively, and have a risk of 25 and 12.5 %. The extended family risk also has to be addressed.

According to the updated MEN 1 consensus published in 2012, a practical definition of a MEN 1 patient is a patient with at least two of the three main MEN 1-related endocrine tumours (i.e. parathyroid adenomas, gastroenteropancreatic endocrine tumours and pituitary adenoma) [9, 10]. A MEN 1-suspected patient is defined as having multiple lesions within one MEN 1-related organ and/or a MEN 1-associated lesion at a young age (<30 years) [11].

Thus, MEN 1 gene mutation analysis should be offered to

- Clinically demonstrated MEN 1 patients to confirm the diagnosis;
- MEN 1-suspected patients;
- Relatives of MEN 1 patients with a confirmed *MEN 1*-gene germline mutation, after risk estimation and genetic counselling;
- Relatives of patients with clinically proven or highly suspected MEN 1, without an identified *MEN 1*-germline mutation or declining mutation analysis, after risk estimation and genetic counselling.
- *MEN 1* genetic analysis has been also suggested in pHPT patients with parathyroid adenomas before age of 40 years, multiglandular parathyroid involvement or persistent or recurrent pHPT.

Surgical treatment

Several surgical approaches in MEN 1-related pHPT have been reported (Table 3) [12–32]. In general, the most commonly recommended initial operation for MEN 1 patients with pHPT is bilateral neck exploration with the aim of a subtotal parathyroidectomy, removing 3+1⁄2 glands and leaving a vascularized remnant from the most normal-appearing gland marked [33–35]. Concurrent bilateral cervical thymectomy is recommended due to the 15 % chance of finding parathyroid tissue in the cervical thymus and because thymic carcinoid tumours occur in this population [36], mainly in male patients. Intraoperative PTH assay is recommended in reoperative surgery to confirm that cure has been achieved while its benefit is unproven especially in first-time surgery. Cryopreservation of resected parathyroid tissue—although controversial—may be considered especially in reinterventions.

Total parathyroidectomy has the lowest risk of persistent and recurrent pHPT but inevitably comes with the highest risk of permanent hypoparathyroidism. Equally, anything less than subtotal parathyroidectomy appears to have the highest rate of both recurrent and persistent pHPT [30, 36]. A total parathyroidectomy with autotransplantation to the brachiocephalic muscle in the forearm is a more aggressive option with a high risk of permanent hypoparathyroidism and a hypothetically lower risk of recurrent pHPT. The cited advantage is the potentially easier reoperation to find and resect regrown autografts from the muscle of the forearm, in comparison to remnant regrowth in the neck, but this may not offset the higher risk of permanent hypoparathyroidism and recurrence may occur in the neck as well as the forearm causing a diagnostic dilemma. As a consequence, despite it being used in some centres, this is not considered the most appropriate approach in MEN 1 patients [3].

Given the surgical strategies adopted and the multigland nature of the disease in MEN 1 patients, standard preoperative localization studies including cervical ultrasound and nuclear scintigraphy or more recent additions such as computed tomography, magnetic resonance imaging (MR) and positron emission tomography scans are infrequently contributory in first-time surgery except for their ability to occasionally identify ectopic or supranumerary parathyroid. Imaging remains mandatory in the case of reoperation for persistent or recurrent pHPT [37].

A third option that can be adopted when there is unilateral disease dominance of localization studies is the option of a "unilateral neck clearance" where both glands from the ipsilateral neck as well as the cervical thymic horn are resected, with the expectation that if reoperation is required, it will be limited to the contralateral virgin neck. This approach, however, remains controversial since, like focused surgery, it is likely to decrease the time to recurrence and is more likely to be associated with persistence although intraoperative PTH measurement as an adjunct may be a useful option.

The final option, although controversial, would be a minimally invasive targeted single-gland resection in patients with clear preoperative localization studies showing one enlarged parathyroid gland. It has been reported that a significant

Table 3 Results of parathyroidectomy in MEN 1 patients

Author (year)	Operation	Patients (*n*)	Permanent hypocalcaemia, *n* (%)	Persistent pHPT, *n* (%)	Recurrent pHPT, *n* (%)	Follow-up (months)
Prinz (1981) [12]	SPTX	12	4 (33 %)	2 (17 %)	1 (8 %)	Unclear
Rizzoli (1985) [13]	<SPTX	41	–	21 (51 %)	7 (17 %)	Overall 7.8 (1.3–12)
	SPTX/TPTX	20	–	2 (10 %)	3 (15 %)	
Malmaeus (1986) [14]	<SPTX	21	1 (5 %)	5 (24 %)	13 (62 %)	Overall
	SPTX	6	–	–	2 (33 %)	6.5 (1–14)
	TPTX	3	3 (100 %)	–	–	
Riordain (1993) [15]	<SPTX	30	Overall 7	5 (17 %)	2 (7 %)	Overall 6.7
	SPTX	54	Overall 7	–	3 (6 %)	(2.5–11.1)
Cougard (1994) [16]	<SPTX	37				Overall 4.6
	SPTX	43	–	–	–	
	TPTX	11	–	–	–	
Hellman (1998) [17]	<SPTX	26	–	9 (35 %)	16 (62 %)	8.2±3.9
	SPTX	9	–	2 (22 %)	4 (44 %)	9.1±3.9
	TPTX	15	15[a] (100 %)	–	3 (20 %)	5.2±2.8
Burgess (1998) [18]	SPTX	37	9 (24 %)	3 (8 %)	7 (19 %)	8
Dotzenrath (2001) [19]	<SPTX	13	2 (15 %)	–	3 (23 %)	54 (12–180)
	SPTX	25	3 (12 %)	–	3 (12 %)	54 (12–180)
Arnalsteen (2002) [20]	<SPTX	13	2 (13 %)		4 (31 %)	37±34
	SPTX	66	–		5 (38 %)	50±54
Elaraj (2003) [21]	<SPTX	13	2 (15 %)	[b]	6 (46 %)	5.3
	SPTX	63	16 (26 %)		20 (32 %)	6.1
	TPTX	16	7 (46 %)		4 (25 %)	6.1
Langer (2004) [22]	<SPTX	14	–	–	–	132 (6–240)
	SPTX	5	–	–	–	151 (84–264)
	TPTX	15	–	–	–	36 (6–192)
Lambert (2005) [23]	<SPTX	13	4 (31 %)	–	12 (92 %)	4
	SPTX	14		–	6 (43 %)	4.6
	TPTX	4		–	2 (50 %)	4.6
Lee (2006) [24]	<SPTX	11	1 (9 %)	–	–	7 (0.5–19.5)
	SPTX	5	3 (60 %)	–	1	6.9 (1.5–15.5)
	TPTX	6	3 (50 %)	–	–	7.7 (2–11.5)
Hubbard (2006) [25]	<SPTX	4	–	–	1 (25 %)	152 (8–285)
	SPTX	21	2 (10 %)	–	1 (5 %)	62 (8–192)
	TPTX	4	1 (25 %)	–	2 (50 %)	167 (18–226)
Tonelli (2007) [26]	TPTX	45	10 (22 %)	–	5 (11 %)	80±62
Norton (2008) [27]	<SPTX	35	1 (3 %)	15 (43 %)	16 (46 %)	20.7±1.9
	SPTX	40	4 (10 %)	5 (13 %)	18 (45 %)	14.5±1.5
	TPTX	9	2 (22 %)	–	5 (56 %)	9.9±1.5
Salmeron (2010) [28]	SPTX	69	3 (4 %)	–	9 (13 %)	75 (9–300)
Waldmann (2010) [29]	<SPTX	13	0	3 (23 %)	6 (46 %)	84(36–180)
	SPTX	11	5 (45 %)	0	2 (18 %)	118(32–132)
	TPTX	23	5 (22 %)	1 (4 %)	1 (4 %)	84(4–204)
Schreinemaker (2011) [30]	<SPTX	29	2 (7 %)	9 (31 %)	17 (59 %)	99 (44–162)
	SPTX	17	4 (24 %)	1 (7 %)	11 (65 %)	144 (71–207)
	TPTX	6	4 (67 %)	1 (17 %)	–	16 (4–201)
Pieterman (2012) [39]	<SPTX	17	4 (24 %)	9 (53 %)	9 (53 %)	Overall 51 (21–78)
	SPTX	23	9 (39 %)	4 (17 %)	4 (17 %)	
	TPTX	32	21 (66 %)	6 (19 %)	6 (19 %)	

Table 3 (continued)

Author (year)	Operation	Patients (*n*)	Permanent hypocalcaemia, *n* (%)	Persistent pHPT, *n* (%)	Recurrent pHPT, *n* (%)	Follow-up (months)
Versnick (2013) [31]	<SPTX	6	–	–	–	19
	SPTX	10	4 (40 %)	–	3 (30 %)	106
	TPTX	10	6 (60 %)	–	3 (30 %)	133
Lairmore (2014) [32]	SPTX	17	2 (12 %)	1 (6 %)	4 (24 %)	7.5±5.7
	PTPX	15	1 (7 %)	–	2 (13 %)	7.5±5.7

Follow-up are shown as mean or median, with range or SD (±)

pHPT primary hyperparathyroidism, *SPTX* subtotal parathyroidectomy, *<SPTX* less than subtotal parathyroidectomy, *TPTX* total parathyroidectomy, – not available

[a] Permanent hypopara but recovery in 1–7 years

[b] Two patients with persistent disease in total population; six lost at follow-up

proportion of MEN 1 patients may not have recurrence after resection of only one enlarged gland and that recurrence may not occur for many years [31, 38]. This approach may be an option, but the patient should be aware of the increased risk for persistent or recurrent disease which is likely to occur sooner compared to patients who had undergone a more extensive parathyroidectomy [3].

The preferred approach is guided by the actually best available data on the subject: a Dutch study including 73 MEN 1 patients showed that in case of removal of less than three parathyroid glands, the risk of persistent or recurrent pHPT was 53 %, whereas this risk was only 17 % when the resection was subtotal and 19 % when the resection was total. Persistent hypoparathyroidism occurred in 24, 39 and 66 % of patients who underwent resection of less than three parathyroid glands, subtotal resection and total resection, respectively [39]. The multiinstitutional French and Belgian GENEM study including 256 MEN 1 patients showed that since 1990, the majority (51 %) of patients underwent subtotal parathyroidectomy. After operation, 19 % had persistent disease and 15 % had postoperative hypocalcemia [36]. Lairmore recently published a randomized, prospective trial comparing subtotal and total parathyroidectomy with autotransplantation. Over a period of 16 years, 32 patients were included in this study cohort. The overall rate of recurrent pHPT was 19 %, without any significant differences between subtotal and total parathyroidectomy + autotransplantation groups (24 vs. 13 %, respectively). Overall permanent hypoparathyroidism was 9 % (12 % in the subtotal parathyroidectomy vs. 7 % in the total parathyroidectomy + autotransplantation group). The study shows comparable outcomes for MEN 1 patients treated by either approach, but subtotal parathyroidectomy may have advantages because it involves only one surgical incision and avoids an obligate period of transient postoperative hypoparathyroidism [32].

Reoperations for recurrent pHPT in MEN 1 usually involve limited exploration to avoid the higher risk of recurrent laryngeal nerve injury in a scarred neck. Reoperations are guided by prior operative and pathological findings and the results of preoperative localization studies. Recent preliminary findings from the Dutch MEN 1 study suggested genotype-phenotype correlations for the manifestation of pHPT in MEN 1 patients; after less than a subtotal parathyroidectomy, patients with nonsense or frameshift mutations in exons 2, 9 and 10 had a significantly lower risk of persistent or recurrent pHPT compared to those with other mutations [39]. Thus, genotyping that may be useful in the future to guide the extent of initial parathyroidectomy and to achieve a more de-escalating strategy, especially in young patients, could be advocated.

MEN 2

MEN 2A (OMIM # 171400) is a rare genetic disease (with a prevalence of less than 2.5/100,000 of general population), characterized by the presence of medullary thyroid carcinoma (100 % of cases), pheochromocytomas (approximately 50 %) and tumours of the parathyroid glands (20–40 %) [10, 15, 40–44]. It is clinically distinct from the other two variants of MEN 2 such as familial medullary thyroid carcinoma or MEN 2B where pHPT is absent. Thus, MEN 2-related hyperparathyroidism is considered an infrequent syndromic variant of hereditary pHPT, since it is significantly less common than in MEN 1. It is not the dominant part of the disease; subsequently, it has a different management pathway.

Genetic features

MEN 2A is an autosomal dominant inherited tumour syndrome due to germline activating mutations of the *RET* proto-oncogene. This activating gene maps to chromosome

10q11.21 and has 21 exons. It encodes a tyrosine kinase receptor, whose activity is increased in MEN 2 mutation with oncogenic properties, including growth and differentiation signals.

There is a genotype-phenotype correlation in MEN 2. In fact, pHPT is more frequent in patients with *RET* mutation at codon 634. It is observed in a minority of patients with mutations of codons 609, 611, 618, 620, 790, 791 and 804. It is rare in patients with mutations of codons 630, 649, 768, 790, 804 and 891 and is absent in mutations of codons 883, 913 or 922 (MEN 2B). There is no genotype-phenotype relation in terms of severity of pHPT and genetic abnormality [10, 40, 44, 45].

Clinical features

Age of onset of pHPT is slightly younger in MEN 2 than in the sporadic counterpart since it presents typically in the fourth decade (35–41 years, range 5–77 years). It is more frequent in females than in males (ratio 1.5 to 2.6), suggesting the presence of additional hormonal factors. The disease is most often a mild form of pHPT, at least milder than in MEN 1, and it is clinically asymptomatic in 42 to 84 % of cases.

MEN 2A-related pHPT is characteristically identified at the time of medullary thyroid carcinoma and/or pheochromocytoma workup (75–85 % of cases). pHPT is rarely the first manifestation of MEN 2 (4–8 % of cases) [1, 10, 15, 40, 42–44].

The anatomo-pathological nature of MEN 2-related pHPT is not as predictable as in MEN 1: parathyroid multiglandular involvement is less frequent, and the volume of the affected glands tends to be smaller. A single adenoma is found in 27 to 54 % of cases; double adenomas are less frequent (1–17 %). About one half of the patients develop enlargement of all four glands, either diffuse hyperplasia or association of hyperplasia and adenoma(s). Enlarged glands are occasionally discovered at the time of thyroidectomy in normocalcemic patients. Ectopic and supernumerary glands are found in 15.7 and 8.6 % of cases, respectively; one case of parathyroid carcinoma has been reported [1, 10, 15, 40–44].

Diagnosis

MEN 2 should be clinically suspected in all cases where medullary thyroid carcinoma and/or pheochromocytomas are present; such patients should be also screened for pHPT. The diagnosis should be confirmed by *RET* mutation analysis.

Thus, *RET* genetic screening should be performed in all patients with personal or familial history of medullary thyroid carcinoma, pheochromocytoma or at risk of non-sporadic pHPT (young patient, multiglandular parathyroid involvement, familial pHPT). Patients should be screened for pHPT at the time of screening for pheochromocytoma: by age 11 in the ATA-H categoy (*RET* mutation 634) and by age 16 in those in the ATA-MOD category (other *RET* mutations) [10, 40, 45].

Surgical treatment

Surgery is the treatment of choice for MEN 2-related pHPT. Medical therapy should be considered only in those rare patients with poor medical status or with persistent or recurrent disease. Therefore, surgery seems justified in symptomatic MEN 2-related pHPT, as it is in sporadic patients. In asymptomatic patients, resection of enlarged parathyroid glands found at the time of thyroidectomy for medullary thyroid carcinoma is probably justified since empirically it is likely to avoid reoperation for persistent or recurrent pHPT. Evaluation of parathyroid function prior to thyroidectomy and intraoperative evaluation of all four parathyroid glands was mandatory [10, 41, 45]. Parathyroidectomy if required should be performed at the time of thyroidectomy for medullary thyroid carcinoma which, in turn, should be addressed after adrenal surgery for phaeochromocytoma. Thus, pHPT is the last concern in MEN 2A patients [45].

Several options have been reported regarding the intraoperative management of parathyroid glands. Selective resection has been reported in 42 to 60 % of cases, subtotal parathyroidectomy in 22 to 39 % and total parathyroidectomy in 11 to 17 % [1, 15, 40, 42–44].

Most authors favour a “conservative approach” including selective resection of only grossly enlarged parathyroid glands and autograft of normal glands devascularized during the thyroidectomy, avoiding total parathyroidectomy (unless all four glands are obviously abnormal and preservation of an in situ parathyroid remnant is not possible) [15, 42]. Only Herfarth in 1996 suggested routine total parathyroidectomy with heterotopic transplantation [44].

In 2015, the American Thyroid Association has published guidelines [45] suggesting a “selective approach” with resection of only grossly enlarged glands. When all four glands are enlarged, the choice is left between subtotal or total parathyroidectomy + autotransplantation in patients with pHPT diagnosed at the same time of planned thyroidectomy for medullary thyroid carcinoma.

In patients without pHPT at the time of thyroidectomy, prophylactic parathyroidectomy is not considered an option. Accidentally devascularized normal parathyroid glands should be autografted into the forearm or into the sternocleidomastoid muscle according to the family history and type of mutation. In children, indications are the same as in adults. However, all these recommendations have a limited strength, since they are based on expert opinion [45].

For decision making, it must be kept in mind that it is probably easier to manage a mild asymptomatic recurrent pHPT than a permanent hypocalcemia.

No evident recommendations are available in the literature concerning the role of thymectomy in MEN 2A patients [15, 42, 44]. The role of routine thymectomy is debatable but might be selectively adopted in cases of multiglandular disease, in order to resect potential supernumerary and/or ectopic glands.

Cryoconservation, currently practiced infrequently at a few medical centres, is not mandatory [45]; it has been suggested as a routine tool or done only in cases of reoperation [42, 44, 46]. However, the rate of successful reimplantation remains very low 1 year after excision; thus, storage may be not a cost-effective strategy.

Intraoperative qPTH assay is probably not useful because a focused parathyroidectomy cannot be done at the time of total thyroidectomy for medullary thyroid carcinoma, which requires exploration of all parathyroid glands for preservation. It may be useful in case of reoperations [37].

Equally, preoperative localizing studies may have a limited role at initial surgery in MEN 2A, aiming to detect, as in MEN 1, ectopic parathyroid glands using MIBI scintiscan, although the diagnostic yield is likely to be low.

The relevant literature suggest high cure rates for MEN 2A-related pHPT, ranging from 77 to 100 %, including a rate of permanent hypoparathyroidism around 20 %, while persistent pHPT is reported between 3 and 11 %, but publication bias is likely given the absence of well-constructed research studies [1, 15, 42–44]. Similar results are reported independently of the extent of resection, but it is likely that the rate of hypoparathyroidism is increased by neck nodal dissection of the level VI performed for medullary thyroid carcinoma. pHPT tends to recur rarely (and mildly) within more than 5 years of follow-up (0–12 %) [15, 42–44], except in Tonelli's series (21 %) [1].

Recurrent and persistent pHPT are related to inadequate gland resection, ectopic or supernumerary glands.

In case of recurrent or persistent pHPT, and in case of previous operation for medullary thyroid carcinoma, imaging studies and even interventional radiology are required before surgery is considered [37, 45]. In such cases, medical treatment may be an option, mainly in surgical high-risk patients and in those with mild and stable pHPT. Selective resection of enlarged gland(s) appear to be a pragmatic strategy to minimize the risk of hypoparathyroidism. qPTH intraoperative assay, thymectomy and cryoconservation may be an option in such situations [37].

HPT-JT syndrome

HPT-JT syndrome (OMIM # 145001) is a rare autosomal dominant syndrome with incomplete penetrance and variable expression. It is characterized by single/multiple parathyroid tumours occurring at an earlier age, a relatively high prevalence of carcinomas and atypical adenomas, ossifying fibromas of mandible and/or maxilla, uterine tumours and less frequently, a variety of renal lesions [47, 48]. To date, less than 300 cases from approximately 100 families have been reported (Table 4). HPT-JT syndrome was first described in 1990 [49], but the genetic marker has been identified only in 2002 [50]; for these reasons, its real incidence is still unknown and might be underestimated.

Genetic features

HPT-JT is linked to germline inactivating mutations in the tumour suppressor gene *CDC73* (formerly *HRPT2*), which encodes for parafibromin, a ubiquitously expressed protein with antiproliferative properties. Several reports have demonstrated a loss of parafibromin expression in HPT-JT-related adenomas and in sporadic parathyroid carcinoma carrying somatic *CDC73* mutations [51–54]. No genotype-phenotype correlations for *CDC73* mutations have been formally established to date. However, it has been suggested that missense mutations are more likely to be associated with the disease without typical associated features (FIHPT), whereas mutations causing gross parafibromin disruption are more likely associated with the classical HPT-JT phenotype [55, 56].

Clinical features

pHPT is the main finding of HPT-JT syndrome [47, 48, 55–57] and is found in almost 100 % of mutation carriers [55–57]. The prevalence of pHPT increases with age, and whilst the onset is typically in early adulthood, the earliest reported age is 7 years [58]; the earliest parathyroid carcinoma has been found at the age of 20. However, the onset may be delayed until the sixth decade, and some older healthy mutation carriers have been reported. pHPT is usually mild, but, in the case of parathyroid carcinoma, severe hypercalcaemic crises may occur [59]. pHPT in HPT-JT is usually caused by a single benign parathyroid adenoma, which is often cystic or has atypical histologic features [60]. In contrast to other variants of familial disease, parathyroid carcinoma may be found in 21.6 % of cases (Table 4) [47, 48, 50, 53, 54, 56–58, 60–99]. Multiglandular involvement occurs rarely at initial surgery (20 % of cases); a second parathyroid tumour may occur metachronously in the years to decades after the appearance of the first tumour (23.9 % of cases) (Table 4). The frequent single-gland involvement (76 % of cases at onset) (Table 4) supports the hypothesis that *CDC73* is an oncosuppressor gene and that biallelic inactivation is required for tumour development [100]. The rather low prevalence of multiglandular parathyroid involvement, either synchronous or metachronous, suggests that *CDC73* germline mutations may offer a predisposition to neoplastic progression and a

Table 4 Review of the literature focusing on hyperparathyroidism-jaw tumour syndrome

Author (year)	Kindred (*n*)	Patients with pHPT (*n*)	Single-gland involvement (*n*)	Synchronous multiglandular involvement (*n*)	Recurrences (*n*)	Jaw tumour (*n*)	Parathyroid carcinoma (*n*)	Renal involvement (*n*)	Uterine involvement (*n*)
Carpten (2002) [50]	14	66	NA	NA	NA	30	11	18	NA
Shattuck (2003) [61]	3	3	NA	NA	NA	NA	3	NA	NA
Howell (2003) [62]	3	7	NA	NA	0	0	3	0	NA
Simonds (2004) [63]	1	4	4	0	0	0	1	0	NA
Cetani (2004) [64]	2	4	3	1	NA	0	0	0	NA
Villablanca (2004) [65]	2	9	7	2	3	0	0	0	NA
Cavaco (2004) [66]	6	9	5	1	0	2	0	2	NA
Howell (2004) [67]	1	2	2	0	NA	1	0	NA	NA
Bradley (2005) [47]	2	9	NA	NA	NA	11	2	0	6
Moon (2005) [68]	1	2	2	0	NA	1	2	NA	NA
Gimm (2006) [57]	1	3	1	1	1	NA	1	NA	NA
Mizusawa (2006) [56]	3	7	6	0	1	1	1	0	0
Aldred (2006) [69]	1	3	3	0	0	2	0	NA	NA
Bradley (2006) [47]	5	5	4	1	NA	2	0	0	1
Juhlin (2006) [53]	1	1	1	NA	NA	NA	0	NA	NA
Guarnieri (2006) [70]	1	4	4	0	1	NA	1	0	2
Kelly (2006) [60]	1	3	2	1	2	NA	2	NA	NA
Yamashita (2007) [71]	1	1	1	0	0	1	0	NA	NA
Cetani (2007) [72]	1	1	1	0	1	0	0	0	NA
Cetani (2007) [73]	2	3	NA	NA	NA	NA	3	NA	NA
Raue (2007) [74]	1	2	1	1	NA	1	1	NA	NA
Cetani (2008) [75]	1	1	1	0	NA	0	1	NA	NA
Sarquis (2008) [76]	3	11	5	6	6	1	1	4	5
Guarnieri (2008) [77]	3	3	3	0	1	0	3	3	3
Howell (2009) [78]	1	1	1	0	0	NA	NA	NA	NA
Silveira (2009) [79]	1	9	3	6	6	0	1	4	5
Schmidt (2009) [80]	1	1	1	0	0	1	0	NA	NA
Iacobone (2009) [99]	3	16	15	0	3	1	1	1	8
Rekik (2010) [81]	1	1	1	0	0	1	0	0	1
Panicker (2010) [82]	1	5	NA	NA	NA	1	0	0	1

Table 4 (continued)

Author (year)	Kindred (*n*)	Patients with pHPT (*n*)	Single-gland involvement (*n*)	Synchronous multiglandular involvement (*n*)	Recurrences (*n*)	Jaw tumour (*n*)	Parathyroid carcinoma (*n*)	Renal involvement (*n*)	Uterine involvement (*n*)
Veiguela (2010) [83]	1	7	NA	NA	NA	3	1	0	2
Cavaco (2011) [84]	2	2	2	0	1	0	2	0	0
Pichardo-Lowden (2011) [58]	1	1	1	0	1	0	0	1	NA
Frank-Raue (2011) [85]	7	11	9	1	1	8	3	0	2
Cascon (2011) [86]	1	3	NA	NA	NA	3	0	NA	NA
Siu (2011) [87]	2	2	2	0	0	0	1	0	NA
Domingues (2012) [88]	1	1	1	0	0	0	0	0	NA
Guerrouani (2013) [89]	1	1	1	0	NA	1	0	NA	NA
Bricaire (2013) [90]	NA	19	NA	NA	NA	4	5	4	6
Kutcher (2013) [91]	1	1	0	1	0	1	1	1	NA
Ghemigian (2013) [92]	1	3	3	0	0	0	0	NA	NA
Abdulla (2013) [93]	1	1	0	1	1	1	0	NA	NA
Pazienza (2013) [94]	3	7	7	0	0	0	0	1	1
Kong (2014) [95]	1	2	0	2	1	1	0	NA	2
Chiofalo (2014) [96]	1	2	2	0	0	1	1	0	NA
Korpi Hyovalti (2014) [97]	1	7	NA	NA	NA	NA	2	2	NA
Sriphrapradang (2014) [98]	1	1	1	0	NA	1	1	0	NA
Mehta[a] (2014) [48]	7	16	11	5	4	2	6	3	2
TOTAL	101	283 (95 %)	117 (76 %)	30 (20 %)	34 (23.9 %)	83 (30.5 %)	61 (21.6 %)	44 (13.3 %)	47 (57.3 %)

NA not available

[a] Some cases have been previously included in Carpten [50]

second hit or other genetic or epigenetic events are necessary to the development of parathyroid tumours [61, 62, 101].

Despite the nomenclature of the syndrome, jaw tumours are evident only in a minority of cases (30.5 %) (Table 4), which may contribute to the underdiagnosis of the disease [99]. Ossifying fibromas of the mandible or maxilla may present as an enlarging visible or palpable mass, whereas others are detected only on jaw X-ray. Although benign, these tumours can disrupt normal dentition and be of significant cosmetic concern. Tumours may occasionally be bilateral/multifocal and may recur and continue to enlarge if not treated. They usually appear to be radiographically radiolucent and develop before the third decade of life [85, 90]. They must be differentiated by the brown tumours associated with severe pHPT, that resolve after curative parathyroidectomy [71].

Several non-endocrine tumours may be also present in HPT-JT patients, with uterine involvement being the second most common clinical feature (57.3 % of affected women) (Table 4). Some of these tumours (leyomiomas, endometrial hyperplasia, adenomyosis) are very common also in the general population; others (adenosarcomas, adenofibromas, multiple adenomyomatous polyps) are less frequent. Interestingly, most of these tumours appear to have a common embryological origin from the mesodermal Mullerian duct system. The

absence of parafibromin expression also in uterine polyps seems to support the pathogenetic role for *CDC73* mutations in HPT-JT-related uterine involvement [47–76, 99].

Renal involvement may be found in 13.3 % of HPT-JT patients (Table 4). Hamartomas, polycystic disease, Wilms tumours and adenocarcinomas have been reported. Cysts have also been observed in association with rare solid tumours, which were histologically similar to mixed epithelial-stromal tumours or adult mesoblastic nephroma or hamartomatous-type tumours [66, 77]. Finally, pancreatic adenocarcinoma, testicular mixed germ cell tumours, thyroid and colon carcinomas have been reported, but it is not clear that these tumours are present in a higher frequency in HPT-JT syndrome than in the general population [99].

Diagnosis

The diagnosis of HPT-JT must be confirmed by genetic testing. *CDC73* germline analysis should be performed in cases of hereditary pHPT with negative genetic testing for MEN 1, in cases of personal and/or familial history of HPT-JT syndrome (ossifying jaw fibroma and other associated conditions, such as Wilms tumour or other genitourinary disease). Equally, genetic analysis is appropriate in pHPT with cystic, atypical and/or malignant parathyroid histology, in children diagnosed with ossifying fibroma(s) of the maxilla or mandible, pHPT with the absence of nuclear parafibromin staining in parathyroid tumour and pHPT with young onset (age <40 years), multiglandular or recurrent pHPT [64, 99].

Following the initial diagnosis, it is necessary to establish the extent of the disease by evaluating standard end organ damage of pHPT but also the assessment for jaw tumours (panoramic jaw X-ray), renal lesions (renal ultrasound examination or MR) and uterine tumours (pelvic ultrasound examination, CT or MR) starting at reproductive age [99].

Surgical treatment

The optimal surgical approach to pHPT in HPT-JT syndrome has not yet been established and remains controversial. Extensive parathyroid surgery (bilateral neck exploration and subtotal parathyroidectomy or total parathyroidectomy ± autotransplantation) has been proposed in the past, because of the risk of multiglandular involvement and malignancy [70, 76]. Autotransplantation has been considered a risky procedure because it may allow the seeding and dissemination of parathyroid cancer cells [48]. Recently, because of the finding of frequent single-gland involvement, lower risk of parathyroid carcinoma and synchronous multiglandular involvement at onset, more limited approaches and parathyroid excisions have been proposed, in order to decrease the risk of permanent hypoparathyroidism [48, 99, 101, 102]. In the case of preoperative imaging techniques localizing concordantly a single-gland involvement, when a parathyroid malignancy is unlikely, a focused approach with selective parathyroidectomy has been proposed as in sporadic pHPT [99, 101, 102]. This strategy might have the potential advantage of causing lower risk of hypoparathyroidism and minimal tissue trauma, facilitating reoperations in case of recurrent pHPT. In all cases, because of the risk of recurrent and/or new disease, a regular lifelong serum testing for biochemical evidence of pHPT is recommended every 6 months [100–102]. In case of suspicion of parathyroid carcinoma (large and infiltrating parathyroid neoplasm, extremely elevated serum calcium and PTH levels), an en bloc resection including the ipsilateral thyroid lobe, the adjacent soft tissues and possibly the omolateral parathyroid should be performed, taking to prevent fracture of the tumour, which could seed the local area [59, 99, 103]. Dissection of the central compartment lymph nodes might be required in case of suspicion of nodal involvement [59], and reoperations may be required in case of recurrences [103].

MEN 4

MEN 4 (OMIM # 610755) is a syndromic variant of hereditary pHPT; it has been identified following the description of the so-called MEN X by Fritz in 2002 in rats that developed multiple paragangliomas, pheochromocytomas (100 %), bilateral thyroid C cell neoplasia, multiple parathyroid hyperplasia, pituitary adenoma (100 %) and bilateral cataracts [104, 105]. These lesions overlap the spectrum of human MEN 1 and MEN 2, but no mutation of either *RET* nor *MEN 1 genes* have been found in the affected animals. Equally, MEN 4 has been found and described in MEN 1-like patients in the absence of a MEN 1 mutation.

The genetic disease was identified in 2006 as a mutation of the *CDKN1B* gene [106]. It is a very rare disease, with less than 15 cases reported in the literature to date (probably less than the number of publications on the subject). MEN 4 accounts for 1.5 to 3.7 % of MEN-related phenotypes without MEN 1 mutation [107, 108].

Genetic features

MEN 4 is caused by autosomal dominant mutations of the *CDKN1B* gene mapped to 12p13 [105]. This gene encodes the ubiquitous p27 (Kip1) protein, made of 198 amino acids. It belongs (with p21 and p57) to the KIP/CIP family of cyclin/cyclin-dependent kinase inhibitors, regulating the cell cycle from G1 to S phases. Also, *Menin* and *RET* are components of the p27-dependent pathway that regulates a tissue-specific cell proliferation [109]. Nine different germline mutations have been reported by the end of 2014 [109–112]. Inactivating mutations of the *CDKN1B* produce a truncated p27 cell cycle inhibitor. Mutation of additional cyclin genes are under

investigation. Somatic mutations of the gene have been found in sporadic parathyroid adenomas [113].

Clinical features

Very few data are available in the literature, mainly focused on the genetics of case reports or reviews [106–108, 110–115]. All clinically affected patients are female; only one male is an asymptomatic carrier to date. The age of onset of clinical expression is 20 years later than in MEN 1 (range 36–79 years), therefore often around the age of the menopause. pHPT has a high penetrance (81 %) and is often the first endocrinopathy at onset. The disease is described as multiglandular in most cases. Pituitary adenoma is the second most common tumour type (46 % of cases), usually non-functioning. Other tumours include gastric and bronchic carcinoids, neuroendocrine tumours of the duodeno-pancreas and the cervix, testicular cancer, adrenal tumours, renal angiomyolipoma. No MEN 2-related tumour (pheochromocytoma, paraganglioma, medullary thyroid neoplasia), described in MEN X rats has been reported in MEN 4 humans. No genotype-phenotype relationship has been established.

Diagnosis

MEN 4 should be suspected in patients with MEN 1 phenotype and without MEN 1 gene mutation. In these cases, a focused genetic testing is recommended

Surgical treatment

No definitive conclusion can be drawn from the literature concerning the optimal surgical management, because of the small number of patients reported as operated on, none of them being diagnosed as MEN 4 before the operation, as the genetic test was not available. From the case reports, it appears that the patients were managed as sporadic or atypical familial pHPT, according to the local practice.

Only one case was clearly described as having pHPT, reoperated on twice for recurrences (four adenomas). The final operation was total parathyroïdectomy + thymectomy + autotransplantation of parathyroid tissue in the subcutaneous of the forearm, with permanent hypoparathyroidism [110]. Thus, resection similar to that performed in MEN 1 has been proposed [1]. The scarce clinical publications make it impossible to give strong recommendations on preoperative and intraoperative management of MEN 4 patients since none has yet been diagnosed before surgery.

FIHPT

FIHPT (HRPT1) (OMIM # 145000) is a non-syndromic and uncommon form of hereditary pHPT characterized by familial clusters typically with early onset pHPT but characteristically in the absence of other endocrine syndromic manifestations [116]. The prevalence of this condition remains unknown, and it is thought to represent either a stand-alone non-syndromic entity or an incomplete expression of one of the genetic syndromes that include pHPT within their profile. The endocrine syndromes of which FIHPT can play a part include MEN 1 and HPT-JT and arguably FHH. It remains unclear how many additional rarer genotypes may also exist [117].

Genetic features

FIHPT appears to be inherited in an autosomal dominant fashion, but the specific gene responsible remains elusive although the *MEN 1*, *CDC73* and calcium-sensing receptor (*CASR*) mutations have been found in a significant number of the kindreds [41, 118]. For this reason, FIHPT can be postulated as the cause of pHPT only when the other possible genetic variants have been excluded. This is achieved via a thorough clinical review of the proband and a family historical review. Emphasis should primarily be placed on excluding features typical of MEN 1 syndrome such as pituitary and pancreatic disease but also the presence of a history of recurrent pHPT or multiple gland disease at surgery. The features of HPT-JT syndrome should be sought including histologically proven parathyroid atypical adenomas and cancers, fibrous jaw tumours as well as kidney cysts and neoplasms. Gene mutational testing can then be performed after appropriate counselling to confirm or exclude the incomplete expression of a syndromic form of hereditary pHPT. Thus, the recommended gene tests include those for *MEN 1*, *CASR* and *CDC73* mutations.

Surgical treatment

At surgery, FIHPT may be either caused by a single adenoma, or multiple gland disease, often with asymmetry [119]. The rarity of this condition is such that no truly evidence-based surgical strategy can be provided and the disease is best treated empirically [102]. However, whilst forms of image-guided focused surgery are an option, visualization of all four parathyroid glands is the approach most likely to provide the most long-term cure.

FHH

FHH is a non-syndromic genetic disorder transmitted by autosomal dominant inheritance with near-complete penetrance but variable expressivity. It is characterized in most cases by a dysregulation of the phosphor-calcic metabolism caused by an inactivating mutation of the gene that encodes the *CASR* [120]. The condition is characterized by lifelong mild hypercalcaemia associated with inappropriately

unaccommodated levels of PTH and a urinary calcium excretion that is inappropriately low in the presence of the corresponding hypercalcaemia. Typically, the patients have a normal vitamin D and unaffected bone mineral density [121, 122].

There are currently three genetic types of FHH based on the chromosomal mutation carried. FHH type 1 (OMIM # 145980) is responsible for 65 % of cases and is due to inactivating mutations in the *CASR* gene localized on chromosome 3: 3q21.1. The *CASR* gene encodes the calcium-sensing receptor the loss of whose function results in a reduction in the sensitivity of parathyroid and renal cells to the serum calcium concentration, and hypercalcaemia is perceived as normal [120]. The remaining 35 % of FHH patients have mutations on chromosome 19: either mutation *GNA11* (19p13.3) seen in FHH type 2 (OMIM # 145981) or more rarely *AP2S1* (19q13.2–q13.3) seen in FHH type 3 (OMIM # 600740). Presumably, there are also additional genes with similar effects that have not yet been discovered. FHH may be very rarely caused by autoantibodies against the calcium-sensing receptor in patients that do not have a mutation [123]. In FHH type 2, very marked hypocalciuria is typical. The characteristic of FHH type 3 is that of a co-existent mild hypophosphatemia and the usual elevated plasma PTH concentrations. Of clinical importance is that offspring of FHH type 1 carriers are at a higher risk of developing neonatal severe primary hyperparathyroidism, a condition that can be life-threatening.

FHH is usually asymptomatic, but symptoms such as fatigue, weakness, excessive thirst and poor concentration may be experienced as well as relapsing pancreatitis, chondrocalcinosis and premature vascular calcification [124]. The serum biochemistry and possible symptoms mimic pHPT, but importantly, FHH is not associated with end organ damage at the renal or bone level; indeed, bone mineral density may even be improved.

FHH is a considerably more common than many surgeons undertaking parathyroid surgery realize since it is responsible for up to 2 % of patients with hypercalcaemia [125]. It should therefore be excluded in all patients prior to contemplating parathyroid surgery [2]. The index of suspicion is greatest in the presence of mild hypercalcaemia along with normal or slightly elevated PTH, relative hypocalciuria and normal serum phosphate levels. FHH should be distinguishable from pHPT in most cases by assessment of urinary calcium excretion via the 24-h urine calcium to creatinine clearance ratio (UCCR), calculated using the formula below [126] although this is not without pitfalls:

$$\frac{\text{Urine Calcium (mmol/l)} \times [\text{Plasma Creatinine (umol/1)}/1000\,]}{\textbf{Plasma Calcium (mmol/l)} \times \textbf{Urine Creatinine (mmol/l)}}$$

A UCCR value of <0.01 is diagnostic of FHH [2] but captures no more than 65 % of cases and perhaps misclassifies around 4 % of patients with pHPT as FHH [126]. For this reason, caution is required and a careful evaluation of the clinical as well as biochemical picture in each patient is required.

Exclusion of FHH in particular should always be also considered in the presence of persistent hypercalcaemia despite surgical removal of hypercellular parathyroid glands or when four apparently normal parathyroids are encountered at surgery. Indeed, the parathyroid glands in most cases of FHH appear normal or mildly hyperplastic [127] although overt parathyroid gland enlargement and hyperplasia have also been noted [128].

When the diagnosis of FHH is made, first-degree family members should be screened for serum calcium concentrations. If found to be hypercalcaemic, *CASR* mutation analysis preceded by genetic counselling should be offered. Unfortunately, the absence of a mutation on genetic testing does not exclude the diagnosis of FHH [125] since *CASR* gene mutations may not be detected in up to 30 % of cases depending on the assay. As FHH is a benign condition, prenatal testing is not recommended. As de novo mutations are frequently described, the *CASR* gene must also be sequenced in the presence of typical biological features even in the absence of a familial history of hypercalcaemia.

As FHH is usually asymptomatic and does not appear to harm the patient, treatment is not necessary. Indeed the only potential harm in FHH patients appears to be iatrogenic. The hypercalcaemia seen in FHH does not respond to diuretics or bisphosphonates, and surgery is usually of no value. For those with constantly very elevated serum calcium concentrations or in those with NSHPT or relapsing pancreatitis, a total parathyroidectomy may be of benefit only in very carefully selected cases. Furthermore, pregnant women with FHH must be identified, as in the developing foetus, a context of marked hypercalcaemia leads to the inhibition of endogenous secretion of PTH and a high risk of developing severe hypocalcaemia and potentially neonatal tetany during the first days of life. In newborns of two FHH parents, calcium levels should be monitored for the first days of life as NSHPT can also develop. FHH does not lower life expectancy and has a benign, stable course.

NSHPT

NSHPT (OMIM # 239200) is a rare, extreme form of FHH. It typically presents within a few days of birth and if undiagnosed or suboptimally treated is associated with the death of over half of neonates with the disease.

NSHPT like FHH is most commonly caused by loss-of-function mutations in the *CASR* gene [129]. Whereas heterozygous inactivating mutation of the *CASR* gene leads to FHH and mild hypercalcaemia, NSHPT is caused by homozygous

mutations. In some cases, only a single abnormal allele is present and characterized by a severe phenotype [130].

NSHPT presents within 6 months of life with hypotonia, intestinal dysmotility and failure to thrive associated with severe hypercalcaemia, skeletal demineralization, fractures and respiratory distress. Biochemically, it is associated with a low fractional excretion of urinary calcium and very elevated serum levels of PTH [131]. NSHPT is associated with life-threatening hypercalcaemia that requires urgent treatment with intravenous saline and bisphosphonates on a pediatric high dependency unit. This offers at best a short-lived improvement in preparation for an urgent life-preserving total parathyroidectomy [132] where typically massive hyperplastic parathyroids are encountered [133]. More recently, the observation that some patients with NSHPT may respond to high levels of extracellular calcium, a phenomenon that can be amplified by calcimimetics, has led to the use of cinacalcet as another temporizing measure either alone or with a bisphosphonate [134]. Once the emergency situation has been resolved if the genetic abnormality is not already diagnosed, then a genetic counselling review with testing is appropriate.

ADMH

Autosomal dominant mild hyperparathyroidism (ADMH) (OMIM # 601199) is a non-syndromic variant of hereditary pHPT, first reported over a decade ago in a large Swedish family [135] but has been subsequently very infrequently convincingly diagnosed. An overlap with FIHPT is possible given the very similar phenotypes. An atypical germline inactivation isolated to the intracytoplasmic tail domain of *CASR* was identified, but the phenotype is characterized by the absence of relative hypocalciuria and the possibility of nephrolithiasis and hypermagnesaemia. The treatment of ADMH is a parathyroidectomy tailored to the intraoperative findings [102].

Summary and recommendations

In conclusion, after presenting the results of this review in an evidence-based perspective at the European Society of Endocrine Surgeons 2015 Workshop (May 28–30, Varna, Bulgaria), a set of conclusions were agreed upon, followed by the recommendation grade and evidence level.

Is parathyroid multiglandular involvement constant in hereditary pHPT?

Multiglandular involvement is more frequent in hereditary pHPT than sporadic disease. In hereditary pHPT, it is assumed that all parathyroid tissue has a predisposition to be affected. The multiglandular involvement may be present synchronously at onset or may occur metachronously with a widely variable interval in keeping with Knudsen's two-hit hypothesis. For these reasons, highly increased persistent and recurrent disease rate may occur after surgery, especially when the suspicion of hereditary disease is not preoperatively available. In some cases (HPT-JT syndrome, MEN 2, ADMH), an asymmetric hyperplasia or an apparent single-gland involvement may occur, because of the influence of genetic and epigenetic with also a very long disease-free interval after limited parathyroidectomy (evidence level: IV; GRADE: ⊕⊕OO).

Should hereditary pHPT be managed differently from sporadic HPT?

Hereditary pHPT is different from sporadic pHPT, because of the earlier onset, increased multiglandular involvement and higher failure rate after routine surgical treatment, and should be managed differently from usual sporadic pHPT. For these reasons, patients at risk for hereditary pHPT should ideally be identified before surgery [3] (recommendation level: C, evidence level: IV; GRADE: weak, ⊕⊕OO).

What is the optimal diagnostic strategy in suspected hereditary pHPT? Indication for genetic testing

Hereditary pHPT may be suspected on clinical grounds due to the young age of onset, a positive family history of pHPT or syndrome-related endocrinopathies (gastroenteropancreatic, pituitary, corticoadrenal or neuroendocrine tumours in MEN 1 and MEN 4; medullary thyroid carcinoma or pheochromocytoma in MEN 2; ossifying jaw fibroma or genitourinary involvement in HPT-JT syndrome), personal positive history of syndrome-related endocrinopathies, parathyroid multiglandular (or malignant) involvement and persistent or recurrent pHPT after removal of affected parathyroids [3, 136].

Approximately 5–10 % of patients presenting with apparently sporadic (non-familial and non-syndromic) pHPT before the age of 40 years may have a germline *MEN 1*, *CDC73* or *CASR* mutation [137, 138]. However, some patients with apparently sporadic pHPT in the sixth to ninth decades have germline mutations of genes encoding cyclin-dependent kinase inhibitors, presumably due to the variable penetrance and expressivity of the putative genes [2, 139].

However, a positive family history may be absent in hereditary pHPT because the affected relatives may not have been adequately investigated or may have died before the diagnosis of pHPT. Alternatively, pHPT may be due to a de novo germline mutation in the patient (with subsequent absent family history but increased risk of hereditary pHPT in the children of the patient) or because of the incomplete penetrance and variable expressivity of the putative gene [2, 140].

The diagnosis of hereditary pHPT should be confirmed, whenever possible, by genetic testing of the appropriate gene preceded by counselling [2].

Genetic testing has a pivotal role for early identification of mutation carriers, the earlier identification of associated tumours, appropriate clinical and biochemical surveillance, timing and surgical strategy, early identification of healthy and/or asymptomatic mutation carriers among relatives (with subsequent earlier surgical treatment) and identification of relatives who do not harbour the familial germline mutation and can be excluded from follow-up, with the associated lower costs and disease-related anxiety [2, 9, 140]. Ideally, whenever possible, genetic confirmation should be performed preoperatively because the results could impact the surgical strategy [3]. However, it should be noted that genetic testing is a complex issue and not ubiquitously available; it may require a long time to achieve a diagnostic conclusion, that may, in turn, cause an unacceptable delay of surgical treatment. Furthermore, it is still not able to identify all variants of hereditary disease (because of still unknown putative genes or rare disease-causing mutations in a gene); thus, DNA testing should be individualized [140, 141].

The prevailing view is that genetic testing should be offered to patients diagnosed with pHPT under the age of 40 years, those with a parathyroid multiple gland involvement, those with a family history of HPT or family/personal history of related endocrinopathies and in cases of persistent or recurrent pHPT after excision of an affected gland. FHH should be primarily excluded in all cases.

Furthermore, more specifically, *Menin* genetic testing should be offered to patients with at least two of the three major MEN 1-associated lesions (parathyroid adenomas, pancreatic islet cell tumours, pituitary adenomas), multiple lesions within one MEN 1-related organ and/or a MEN 1-associated lesion at a young age (<35 years) [6, 11].

RET analysis should be performed in all patients with a personal or familial history of medullary thyroid carcinoma: pheochromocytoma. *CDC73* germline analysis should be performed in cases of familial pHPT with negative genetic testing for MEN 1, in cases of personal and/or familial history of HPT-JT syndrome (ossifying jaw fibroma or other associated conditions, such as Wilms tumour or other genitourinary disease), pHPT with cystic, atypical and/or malignant parathyroid histology, in children diagnosed with ossifying fibroma(s) of the maxilla or mandible and in pHPT with absence of nuclear parafibromin staining in parathyroid tumour as demonstrated by immunohistochemistry [140]. Cyclin genes testing should be performed in patients with MEN 1 phenotype, without *Menin* mutation.

The absence of clinical manifestations of hereditary or syndromic forms of pHPT and any genetic abnormalities within the known genes would indicate that the likelihood of a MEN syndrome, HPT-JT syndrome or FHH is less than 5 % [9, 45].

First-degree relatives of a pHPT patient with a mutation should be identified and offered genetic counselling and appropriate gene testing, and individuals who have inherited the mutation should be offered periodic biochemical screening, even if asymptomatic [2] (recommendation level: C, evidence level: IV; GRADE: weak; ⊕⊕OO).

What is the optimal surgical management in hereditary pHPT?

Because of the potential parathyroid multiglandular involvement at long term in hereditary pHPT, theoretically, the definitive cure can be obtained only by a total parathyroidectomy, with resultant permanent hypoparathyroidism. However, total parathyroidectomy is clearly not always successful but anything less than total excision leaves potentially abnormal tissue and therefore the risk of recurrence. However, given the morbidity related to permanent hypoparathyroidism, the surgical approach should be governed by a pragmatic compromise tailored to the patient with the aim of achieving the longest possible normocalcemia without permanent hypoparathyroidism, in a so-called Goldilocks operation (not too much and not too little) [3]. Thus, the aim of surgery in hereditary pHPT is not to achieve a simple surgical cure but to obtain and maintain normocalcaemia for the longest time possible, avoiding iatrogenic hypocalcaemia, minimize surgical morbidity and facilitate future surgery for recurrent disease [3, 102]. Because of the different genetics (different gene expression, penetrance, asynchronous multiglandular involvement), the approach should be tailored to the gene involvement, the patient's wishes and surgeon's experience [3].

Thus, in case of *MEN 1-related pHPT*, a subtotal parathyroidectomy with a bilateral transcervical thymectomy, removing 3+1⁄2 glands and leaving a viable remnant from the most normal-appearing gland is the most usually recommended surgical strategy; alternatively, a total parathyroidectomy and forearm autotransplantantion with bilateral transcervical thymectomy might be performed but appears less popular (recommendation level: B, evidence level: II; GRADE: strong: ⊕⊕⊕O).

In case of *MEN 2-related pHPT*, selective resection of enlarged gland(s) found during thyroidectomy for MTC is the recommended procedure. When all four glands are enlarged, the choice is left between subtotal or total parathyroidectomy + autotransplantation (recommendation level: C, evidence level: IV; GRADE: weak; ⊕OOO).

In case of *HPT-JT syndrome*, when preoperative localization is negative, a bilateral neck exploration is recommended, with subtotal parathyroidectomy or total parathyroidectomy (with or more frequently without autotransplantation). In the presence of concordant imaging suggestive of single-gland involvement, a focused approach with selective parathyroidectomy may be performed (recommendation level: C, evidence level: IV; GRADE: weak; ⊕OOO). In all cases, because of the risk of recurrent and/or new disease and possible

malignant involvement, a regular lifelong biannual serum testing for biochemical evidence of pHPT is recommended.

In case of suspicion of parathyroid carcinoma, an en bloc resection including the ipsilateral thyroid lobe and adjacent soft tissues with a view to avoiding fragmentation of the tumour is recommended (recommendation level: C, evidence level: IV; GRADE: strong; ⊕⊕OO).

In case of *MEN 4-related HPT*, resection similar to that performed in MEN 1 should be performed (recommendation level: C, evidence level: V; GRADE: weak; ⊕OOO).

In case of *FIHPT*, since it may be either caused by single adenoma, or asymmetric multiple gland disease, bilateral neck exploration with visualization of all four parathyroid glands is the approach most likely to provide the most long-term cure (recommendation level: C, evidence level: V; GRADE: weak; ⊕OOO).

FHH should be diagnosed before surgery, and no surgical treatment should be performed (recommendation level: C, evidence level: IV; GRADE: weak; ⊕OOO).

In case of *NSHPT*, when a hypercalcaemic crisis occurs, an urgent life-preserving total parathyroidectomy without parathyroid fragment implants is recommended (recommendation level: C, evidence level: V; GRADE: weak; ⊕OOO).

In case of *ADMH*, the treatment is a parathyroidectomy tailored to the intraoperative findings (recommendation level: C, evidence level: V; GRADE: weak; ⊕OOO).

Future directions

Only a minimal number of genes causing hereditary pHPT are known, to date; it is likely that in the future, several additional genes (with genotype-phenotype correlations) will be identified. In the past, a multiglandular involvement has been assumed in hereditary pHPT, requiring a systematic four-gland exploration. Recent advances in genetics seem to suggest more tailored approach, according to gene involvement, patient's age and wishes. Further researches are needed to expand a more personalized surgery.

Compliance with ethical standards

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