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EDITORIAL

Multigland primary hyperparathyroidism—frequently considered, seldom encountered

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Abstract

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Primary hyperparathyroidism (PHPT) is a common endocrine disorder. Though the vast majority of patients remain undiagnosed or are maintained on long-term follow-up because they are considered to be asymptomatic, an increasing number of patients are being referred for surgical treatment. In over 80 % of cases, one expects to find a single adenoma, of which at least two thirds can be localized preoperatively by a combination of sestamibi scans and ultrasonography, and, therefore, it is feasible to remove them through a minimally invasive parathyroidectomy. Many surgeons with low-volume practice defer an operation for patients with negative scans as they try to avoid the challenge of identifying a possible ectopic adenoma (not seen on scans) or the difficult management decisions in the presence of multigland disease. This last scenario might be encountered in 10–15 % of patients with PHPT and forces the surgeon to take important intraoperative decisions that impact on the likelihood of cure after parathyroidectomy.

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The recent symposium of the European Society of Endocrine Surgeons (ESES) focused on the diagnostic criteria and management challenges raised by multigland disease PHPT (MGD-PHPT). Three separate manuscripts published in this issue of LAS review the recent literature published on multigland disease in the context of hereditary and sporadic forms of PHPT [1, 2] and the secondary hyperparathyroidism in chronic renal failure [3].

Hereditary PHPT was first described over five decades ago in the context of multiple endocrine neoplasia type I syndrome (MEN 1). In recent years, mutations in at least 11 different genes have been identified as a cause for hereditary PHPT. The real frequency of these genetic syndromes might be underestimated because of the variable penetrance and expressivity of some of these mutations. There is a scarcity of prospective randomised studies in this area, and most information is derived from retrospective cohorts and case series treated at referral units. For the very rare variants of hereditary PHPT, only case reports or expert opinions have been published. As a consequence, the strength of recommendations made is often limited.

The review by Iacobone et al. [1] summarises the current understanding of the mechanisms through which these mutated genes lead to an excessive and dysregulated secretion of parathormone (PTH) either through the inactivation of tumour suppressor genes (in MEN 1, MEN 4, FIPHT, and HPT-JT), through the activation of oncogenes with an increase of cellular proliferation (in MEN 2A) or the dysregulation of the calcium set point with the loss of the normal feedback control on parathormone secretion (in FHH, ADMH and NSHPT). Awareness about the possibility of encountering such patients is increasingly important because the early

identification of the hereditary variants of HPT is crucial for the optimal clinical and surgical management of this subgroup of patients who have considerably higher rates of persistent and recurrent disease after attempted curative surgery. The genetic diagnosis is of vital importance also for the affected relatives who may be offered tailored management according to the presence of the associated mutations.

In the context of hereditary PHPT, the largest volume of knowledge has been accumulated over MEN 1—a disease characterized by tumours of the parathyroid glands, the pancreatic islets, the anterior pituitary gland that may coexist with adrenal and neuroendocrine tumours. Because the prevalence of MEN 1 is relatively high (2–3/100,000 population) and the vast majority of patients develop PHPT by the age of 50, most parathyroid surgeons are likely to encounter such cases in their practice.

The review by Iacobone et al. [1] covers the data based on which one can plan the extent of the operation for individual patients. The most commonly recommended initial operation remains subtotal parathyroidectomy (removing 3 + 1⁄2 glands) and concurrent bilateral cervical thymectomy. 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 has high rates of both recurrent and persistent PHPT. In younger patients, the expectation is that not all of the parathyroid glands would have developed adenomas/hyperplasia. If such patients are scanned and the disease is lateralized to one side of the neck, it would be reasonable to offer unilateral neck clearance (both glands from the ipsilateral neck as well as the cervical thymic horn are resected) despite the acknowledged risk of recurrent hypercalcaemia and a need to operate the contralateral side of the neck in future years. As an extreme of this step-wise conservative approach, a minimally invasive parathyroidectomy has been proposed as a first operation for young patients with MEN 1. The pros and cons for each of these four options are detailed in the paper by Iacobone et al. [1]. In this context, the multi-institutional French and Belgian GENEM study of 256 patients with MEN 1 and the Dutch MEN 1 study of 73 MEN 1 patients are to be commended as an example of multicenter collaborations that can provide data for evidence-based decisions regarding the extent of operations for MEN 1 patients. Furthermore, the Dutch MEN 1 study suggested possible 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. Thus, in the future, genotyping could guide the extent of initial parathyroidectomy for patients with MEN 1.

In contrast with the relatively significant number of patients with MEN1-related PHPT, few patients have been identified to be part of a syndrome first described only two decades ago—hyperparathyroidism-jaw tumour syndrome (HPT-JT). This rare autosomal dominant syndrome with incomplete penetrance and variable expression 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. To date, approximately 300 cases from 100 families have been reported. In contrast to other variants of hereditary disease, multiglandular involvement occurs rarely at initial surgery (20 % of cases) and many patients have a single benign parathyroid adenoma or a parathyroid carcinoma (a third of cases). Clinical suspicion confirmed through genetic testing (CDC73 germline analysis) will allow surgeons to inform patients preoperatively about the more extensive operation that might be necessary (e.g. en-block thyroid lobectomy if the macroscopic appearance raises the suspicion of parathyroid malignancy).

While in most cases of hereditary PHPT knowledge of the genetic abnormalities influences the extent of the operation, the diagnosis of hypercalcaemia related to familial hypocalciuric hypercalcaemia (FHH) should prevent embarking on parathyroidectomy. FHH is an autosomal dominant disorder with near-complete penetrance, but variable expressivity. An inactivating mutation of the gene that encodes the calcium-sensing receptor leads to lifelong mild hypercalcaemia associated with inappropriately high levels of PTH and a urinary calcium excretion that is inappropriately low in the presence of hypercalcaemia. There are currently three genetic types of FHH based on the mutation carried. 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, i.e. by offering parathyroidectomy to FHH patients misdiagnosed as sporadic PHPT.

Rather than being an updated summary of current knowledge on different genetic abnormalities leading to hereditary PHPT, the paper by Iacobone et al. aims to use the evidence available to answer clinically relevant questions. A pragmatic question is '*Should hereditary PHPT be managed differently from sporadic PHPT*?' and the affirmative answer is based on the fact that hereditary PHPT has an earlier onset, multiglandular

involvement and higher failure rate after routine surgical treatment; hence, patients at risk for hereditary PHPT should ideally be identified before surgery. The aim is not to strive for 'perfect cure' but to minimize the risk of recurrence after too limited operation yet mitigating the risk of life-long hypocalcaemia after too aggressive operation. 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. Though the strength of most of the recommendations made on behalf of ESES are limited due to the lack of level I evidence, this paper [1] represents a very useful guide for the practicing surgeon faced with a familial case of PHPT.

Sporadic MGD-PHPT is more common in clinical practice compared with the hereditary forms of PHPT. The real incidence of MGD is difficult to be defined because its estimates are influenced by several factors including the extent of parathyroid surgery (i.e. the use of routine bilateral neck exploration (BNE) or selective exploration), the experience and confidence of the operating surgeon to identify MGD and the experience of the pathologist to differentiate a (micro)adenoma from a normal gland. Furthermore, the evidence is unclear as to whether all enlarged parathyroid glands are hyperfunctioning, because no prospective study has been done without removing such glands to determine if patients are at risk for persistent or recurrent disease.

Barczyński et al. [2] summarise recent papers quoting an incidence of MGD ranging from 5–33 % and such contrasting figures rise into question the clinical significance of these additional enlarged glands. If all these enlarged glands would be functionally significant, the failure rate of minimally invasive parathyroidectomy (MIP) should be much higher than the reported figures. The authors emphasize the fact that negative preoperative localization studies are highly predictive of MGD (level III–V evidence). It is likely therefore that negative localization with sestamibi and ultrasound in PHPT infers a highly selected patient population with small parathyroid adenomas, an alarmingly high rate of negative exploration and an increased risk for persistent disease with outcome inferior than standards. For these reasons, some consider referring all patients with negative scans to a regional centre with higher workload/experience in parathyroid surgery. In such centres, it is more likely to exist the infrastructure for genetic testing which becomes desirable/compulsory when encountering MGD-PHPT in patients under the age of 40 with seemingly sporadic disease [2].

By definition, MGD-PHPT cannot be operated through a limited approach but rather through a bilateral neck exploration (BNE). Definite indications for BNE in non-familial PHPT disease are limited to patients with negative preoperative localization studies and those with inadequate decrease of intraoperative PTH (ioPTH) level following removal of the image-indexed parathyroid lesion. Relative indications for BNE include history of lithium therapy, history of head and neck irradiation or discordant preoperative localization studies [2]. Confirmation that all enlarged/overactive glands have been identified and excised should ideally be confirmed by ioPTH, but this technique is yet to be available in all units. Those who do not use ioPTH feel entitled to ignore this technique as it cannot identify patients with double adenomas because ioPTH provides false reassurance after the removal of the 'dominant' adenoma and a second (possible less active or with a lower calcium set point) becomes apparent only when persistent hypercalcaemia is demonstrated after an apparently successful minimally invasive parathyroidectomy.

It remains very likely therefore that surgery performed by an experienced parathyroid surgeon working in a high-volume parathyroid surgery centre is likely to be the main factor that leads to the best outcomes, with cure rates that can be similar (or only slightly worse) in patients with sporadic MGD when compared to those with single adenomas. The paper by Barczyński et al. [2] should provide the support needed during a 'difficult parathyroidectomy' and the summary recommendations should serve equally well surgeons deemed to be expert or beginner.

The last decade has seen a progressive decline in the involvement of surgeons in a condition always associated with multigland disease—the secondary hyperparathyroidism in patients with chronic renal failure. This is the topic covered by the third paper in this series of publications [3]. Progress in the medical treatment and hemodialysis protocols, adequate vitamin D replacement, the use of calcimimetics (cinacalcet), 'conservative' guidelines issued by nephrologists and increasing access to renal transplantation have all contributed to a decrease in the number of patients with severe SHPT deemed to benefit from parathyroidectomy. The paper by Lorenz et al. [3] reviews the selection criteria for parathyroidectomy suggested by the international practice guidelines (Kidney Disease Improving Global Outcome, KDIGO) and emphasizes that currently, surgery is restricted to those who fail medical treatment and its main indications are the correction of metabolic abnormalities rather than improving severity of symptoms or bone disease [3]. In parallel with an erosion of the role of surgeons in selecting the patients for surgery, there has been a strong influence of the medical community on the type of operation to be offered to individual patients. Such decisions are generally based on expert opinion and agreed local protocols because in the absence of large randomised controlled trials, the level of evidence in this field remains frustratingly low. The general agreement is that for patients expecting a renal transplant, the operation should be subtotal parathyroidectomy or total parathyroidectomy and autotransplant. Bilateral cervical thymectomy has been shown to reduce persistence and recurrence rate hence it is recommended [3].

Surgeons who are yet to decide what operation to offer can find very useful the analysis of a large volume of literature reviewed by Lorenz et al. [3]. As for MGD-PHPT, the evidence in favour of routine use of ioPTH is rather weak and the technique has even fewer proponents for its use in patients with secondary hyperparathyroidism. What is certain is that extreme emphasis should be placed on because of the potentially lethal perioperative morbidity associated with parathyroidectomy in this group of complex patients, in particular safe protocols for management of possible postoperative hypocalcaemia using routine postoperative supplementation of calcium and vitamin D [3].

This brief commentary fails to capture the extent to which the three papers published on behalf of ESES contribute to the current debates in the management of multigland hyperparathyroidism. With over 400 references quoted and a number of practical recommendations concluding each of these papers, the authors have provided the reader with an invaluable help when faced with a subgroup of very challenging patients.

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Compliance with ethical standards

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