Familial Isolated Hyperparathyroidism: Role of Intra Operative Parathormone Assay

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Abstract Primary Hyperparathyroidism (PHPT) has been reported to occur in members of same family either alone or in syndromic association. We report a family of patients with multi glandular disease wherein we have successfully used intra operative PTH (IOPTH) to assess the completeness of resection. Three members of one family were affected (One male and two females). Two of them had symptomatic disease whereas one was asymptomatic. Since the genetic studies are not available we used a combination of radiological, clinical and laboratory findings to rule out the other components of MEN syndromes. Extent of surgery in familial isolated hyperparathyroidism (FIHP) is controversial. Hence for confirmation of adequate parathyroid tissue resection we used IOPTH. Role of IOPTH has been well established in sporadic PHPT but controversial in multi glandular syndromes. IOPTH was successfully used to confirm the excision and establish cure.

Keywords Hyperparathyroidism · Intra operative PTH · Familial isolated hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) has been reported to occur in members of the same family. This occurs in MEN1 (multiple endocrine neoplasia), MEN2A, FIHP (familial

isolated hyperparathyroidism), and hyperparathyroidism-jaw tumor syndrome (HPT-jaw tumor). We report a family of patients with hyperparathyroidism wherein three members of the same family had PHPT without any other associated endocrinopathies. Even though these tumors are not rare, we have successfully used intraoperative PTH (IOPTH) to assess the completeness of resection. Use of IOPTH in setting of FIHP has not been very popular and has not been reported from India.

Case

A 34-year-old woman presented with weakness, muscle pain, and joint pains of 5 years' duration. No past history was suggestive of fractures and renal stones. Biochemical, hormonal, and radiological evaluation revealed PHPT. Bone mineral densitometry (BMD) done at the hip, lumbar spine, and wrist revealed osteoporosis. Ultrasonography (USG) neck and technetium Tc-99 m sestamibi (MIBI) revealed two foci of uptake in the neck. There were no features of pheochromocytoma and no clinical features of pancreatic endocrine tumors. The patient's mother was operated for PHPT 17 years ago. Detailed history revealed that her mother was operated for a histologically proven single parathyroid adenoma. After surgery she was healthy without any history of recurrence, hypertension, and visual disturbances. Her mother had expired following a road traffic accident at age of 51 years. Our patient (Case 1) has one brother and one sister who were asymptomatic with regards to hyperparathyroidism; however, both were screened for PHPT. The brother, a 40-year-old man, was also diagnosed biochemically to have PHPT (Case 2). However, the sister was having normal serum calcium and PTH levels, and she is under 6-monthly follow-up with serum calcium. The investigation profiles of both the patients are shown in Table 1.

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Table 1 Profiles of both the patients

	Case 1	Case 2
Serum calcium (8.4–10.2 mg%)	12.5 mg%	10.6 mg%
Serum phosphorus	1.9 mg%	3.2 mg%
Serum alkaline phosphatase (40–140 IU/ml)	339 IU/ml	113 IU/ml
Serum PTH (15–65 pg/ml)	537 pg/ml	137 pg/ml
Serum Vitamin D (<15 µm/dl suggests gross deficiency)	14.315 µm/dl	11.215 µm/dl
Serum prolactin (<400 mU/l)	38 mU/l	17 mU/l
Serum creatinine	0.6 mg%	0.8 mg%
BMD	T score: Lumbar spine –4.4 Hip –3.7 Forearm –5.2	Normal range

Absence of hyperacidity with diarrhea, absence of hypoglycemic attacks, and normal contrast-enhanced computed tomography (CECT) of the pancreas were used to rule out endocrine tumors of pancreas. Normal serum prolactin and absence of visual symptoms ruled out pituitary pathology. The patient was normotensive and had normal 24-h urinary metanephrines, which ruled out pheochromocytoma. The absence of thyroid nodule and normal serum calcitonin ruled out the MEN 2A components. Since the genetic studies were not available, we used a combination of radiological, clinical, and laboratory findings to rule out the other components of MEN syndromes. Orthopantomogram was carried out to rule out the fibromas of the mandible as seen in HPT-jaw tumor syndrome. Case 2 also underwent the same evaluation as Case 1, and no other associated endocrinopathies were identified. We used a combination of USG thyroid and sestamibi scanning for all cases of biochemically proven hyperparathyroidism. In Case 1 imaging revealed double adenoma, whereas in Case 2 only left inferior adenoma was identified. Four-gland exploration was planned in view of the family history and also presence of double adenoma. Currently, the management of FIHP is controversial, and hence the management options were discussed with the patients and their relatives. They were reluctant to undergo total parathyroidectomy with autotransplantation to the forearm, and hence we decided to proceed with excision of the enlarged glands and combine with IOPTH. IOPTH was measured at baseline, 10 and 20 min after excision of the first tumor (T1, Fig. 1) and also 20 min after excision of the second tumor (T2, Fig. 1). Since the conventional criteria of 50 % drop may not be accurate in multigland disease, we used 80 % drop in PTH as the cut-off value. In Case 1, both inferior parathyroid glands were enlarged and excision resulted more than 80 % drop. However, in Case 2, when the first gland was excised as localized by the imaging, the drop was marginal, and once the second gland was excised, the 80 % cut-off was achieved (Fig. 1). We did not employ the intraoperative frozen section since our previous experience with the procedure had been limited to the fact

that the pathologist was able to confirm parathyroid tissue but not able to differentiate between hyperplasia and adenoma. Postoperative hungry bone syndrome was seen in Case 1 who had raised alkaline phosphatase and low BMD; however, Case 2 did not have hungry bone syndrome. At two years of follow-up, both patients are having normal serum calcium.

Discussion

PHPT is sporadic in vast majority of the cases. However, it is essential for the surgeon managing PHPT to know that it may occur in familial settings. The commonly associated conditions are MEN1, MEN2A, FIHP, HPT-jaw tumor syndrome, autosomal dominant mild hyperparathyroidism (ADMH), and neonatal severe hyperparathyroidism (NSHPT) [1]. The management in the familial setting is different from the sporadic cases. A patient with two of the three principal endocrine gland tumors (pituitary, parathyroid, and pancreas) is said to have MEN1, and it is called familial if one of the first-degree relatives has one of the three principal glands involvement [1]. MEN2A has PHPT as one of its components in 25 % cases; however, it is associated with medullary thyroid cancer (in

Fig. 1 Fig depicts the iPTH levels at baseline (0 minute), 10 minutes and 20 minutes after excision of 1st tumor and then 20 minutes after excision of 2nd tumor in the two cases.

100 %) and pheochromocytoma (in 50 %) [2]. FIHP has been linked to MEN1 gene, HRPT2 gene, and the calcium-sensing receptor gene (CASR). HPT-jaw tumor is an autosomal dominant disorder and has been linked to the HRPT2 gene and is highly associated with parathyroid cancer [3]. It is also characterized by renal cysts, ossifying fibromas of the maxilla, and uterine fibromas. About 80 % of these patients develop PHPT of which 15 % have carcinoma [3]. Diagnosis of FIHP requires that the patient and at least one of the first-degree relatives should be diagnosed with PHPT with abnormal parathyroid histology but without clinical manifestation of MEN1 or HPT-jaw tumor syndrome [3]. In our cases we had ruled out MEN1 due to the negative CECT of pancreas with no symptoms of insulinoma/gastrinoma. Pituitary lesion was ruled out in view of the normal prolactin and absence of symptoms such as headache and visual disturbances. MEN2A was ruled out due to the negative serum calcitonin and normal 24-h urinary metanephrines. HPT-jaw tumor was ruled out due to the lack of other associated conditions such as renal cysts and ossifying fibromas of the mandible. Ideally, genetic testing for menin gene (MEN1), RET-proto-oncogene (MEN2A), HRPT2 gene (HPT-Jaw tumor syndrome), and CASR gene has to be done to correctly diagnose the condition; however, a combined clinical, radiological, and hormonal evaluation may be needed in areas of resource limitation. In such cases it is also of utmost importance that the patient is ensured a cure. For this, additional intraoperative measures are needed. Intraoperative visualization of all four glands, intraoperative frozen section, and IOPTH—all help in achieving intraoperative cure. IOPTH has become a routine in surgery for sporadic PHPT [4]. Even though controversy exists, the Miami criterion of 50 % drop from the highest pre-excision value of PTH is widely accepted [5] for sporadic PHPT. False-positive [6] and false-negative [7] IOPTH assay reports have been shown to occur in multiglandular disease like MEN1. Because of this, the IOPTH has been controversial in multiglandular disease. To overcome this, 80 % reduction of the PTH was suggested as criteria for adequate excision of parathyroid tissue in multiglandular disease [1]. In our two cases, we used IOPTH and 80 % cut-off for

ensuring short-term cure. Even though the extent of parathyroidectomy in MEN1 and MEN2A is clearly defined, in other cases like FIHP it is controversial [1]. There is grade C recommendation that excision of adenoma if one or two glands are enlarged and subtotal parathyroidectomy if all four glands are enlarged to be performed [1]. However, in such cases, ensuring adequate parathyroid tissue excision can be done with IOPTH as in our case. Even though the follow-up is short (2 years) and recurrence is still a possibility, we could ensure short-term cure with IOPTH.

In conclusion, high index of suspicion can pick up familial PHPT. It is important to rule out MEN syndromes clinically and with locally available resources. The management in familial settings is different from sporadic ones. Localization studies are indicated even in familial settings. Less than total/subtotal parathyroidectomy can be performed in FIHPT with IOPTH to ensure cure. Lifelong follow-up is needed to detect recurrence.

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