Parathyroid Incidentaloma

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Received: 8 November 2011 / Accepted: 6 March 2012 / Published online: 28 March 2012
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Abstract Incidentalomas are lesions which are asymptomatic and detected incidentally during imaging or surgery. Parathyroid incidentalomas are a rare entity. Enlargement of gland without hyperfunction may be an early stage of disease. Symptomatology is usually non-specific or related to renal and skeletal system. Total serum calcium estimation may be used as a screening modality. Sestamibi scan is a more accurate imaging technique than USG. FNAB - PTH measurement is the most reliable minimally invasive nonsurgical test for parathyroid tissue verification. Incidentally discovered enlarged parathyroid gland may be removed to avoid a re-do surgery.

Keywords Incidentalomas · Parathyroid · Sestamibi Scan

Incidentalomas are the lesions which are asymptomatic and detected incidentally by an imaging or biochemical diagnostic test. With the advent of high resolution scanning for screening purposes as well as the increasing use of CT scan as a diagnostic modality, many asymptomatic masses are being discovered [1]. These masses are termed as “incidentalomas” and have been reported in many organs including pituitary, adrenal, thyroid and parathyroid glands, liver, heart, prostate and kidney [2, 3]. Though the occurrence of incidental tumors of other endocrine glands described here are well documented, but parathyroid incidentalomas are less common.

The incidental discovery of parathyroid tumors was first reported by Allie et al. in 1967 [4], while he was exploring the neck. The term “parathyroid incidentaloma” is used to indicate unexpected parathyroid adenomas that are

encountered during surgery [5, 6] but with the advent of high resolution ultrasound examination for thyroid lesion, parathyroid incidentaloma may be revealed prior to surgery.

Epidemiology

It's a rare entity and till now approximately 50 cases have been reported worldwide [7]. However, it is unusual to find an incidentally enlarged parathyroid gland during thyroid surgery. Abboud et al. encountered such findings in 1.9 % of 574 normocalcemic patients who underwent thyroidectomies at their institution over 8 year period [8]. In the series of Hellmen et al., incidental parathyroid enlargement has been reported in 1.5 % of 594 normocalcemic patients who underwent thyroid surgery, 9 patients had 11 enlarged parathyroid glands weighing 110 to 1,000 mg [9]. In another study by Carnaille et al., incidental parathyroid lesion was found in 0.58 % of thyroidectomies [5]. It's incidence during thyroid surgery varies between 0.2 % and 4.5 % [5–7]. As in all endocrine disease, the diagnosis of diseased parathyroid is based on two variables: parathyroid morphology and function. In autopsy studies of patients without primary hyperparathyroidism (PH) or thyroid disease, the incidence of parathyroid adenoma or hyperplasia varied from 1.9 % to 7.6 % of cases [5, 10], finding concordant with immunological studies [11]. The incidence of parathyroid incidentaloma in another study has been reported as 0.53 %. [12].

Etiology

Radiation appears to play a role in parathyroid disease. Tisell et al. had reported that 11 out of 100 patients who were treated with radiation for tuberculous cervical

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adenitis, developed hyperparathyroidism and four had asymptomatic hypercalcemia [13]. In another series, the authors have reported that out of 36 patients, who had parathyroid incidentalomas, 13 had a previous history of radiation [5]. Hence, parathyroid pathology should be suspected in patients who are scheduled to undergo thyroid surgery and have a previous history of exposure to radiation [14].

Natural History of Disease

Till now, more has been discovered about the natural history of PH and this information may help in deciding the best course of action when discovering “incidentaloma” during thyroid surgery. Hellman et al. in 1993 examined the structure and function of eleven enlarged parathyroid gland in 9 patients undergoing thyroid surgery with normal calcium levels, but he could find microscopic abnormality in only 8 out of 11 enlarged parathyroid glands. Further examination with monoclonal antibodies and measurement of cytoplasmic calcium concentration showed that all but one were also functionally abnormal [9]. Thereafter, two other groups, Carnaille et al. and Abboud et al. also examined histological and biochemical features of enlarged parathyroid glands found in otherwise normocalcemic patients and compared them with glands removed for “overt hyperparathyroidism”. Incidentalomas were found to occur in younger patients, are lighter in weight and biochemically and pathologically less hyperfunctioning, suggesting that these glands may represent an early stage of parathyroid disease [6, 8].

Clinical Features

Parathyroid incidentaloma appear to be more common in women than men with a ratio of 3:1 and 5:1 as reported in two series. [5, 6]. The symptoms and signs of hyperparathyroidism vary greatly and affect many systems, however, renal and skeletal systems are more commonly affected and many patients may also have gastrointestinal and neuromuscular symptoms. In a study of 70 cases of functioning parathyroid tumor, 5 patients initially admitted to the neurological institute for investigation of headache and neuromuscular weakness, were subsequently found to have hyperparathyroidism, 3 patients had symptoms of duodenal ulcer [15]. In general, the symptoms can be classified as follows:

- (i) Non-specific symptoms, like weakness, easy fatigability, weight loss and epigastric distress.
- (ii) Symptoms referable to kidney
- (iii) Symptoms referable to the skeleton system such as bone pain, pathological fractures and deformities.

Diagnosis

Development of accurate biochemical tests for parathyroid hormone as well as increased awareness of skeletal health with the use of bone profiling and density scans has led to an increased diagnosis of patients with Hyperparathyroidism. In the past, patients were diagnosed when symptoms developed, but today 80 % of patients with overt disease are asymptomatic. The definition of normal parathyroid gland is much debated. The total weight of a gland, which seems to be the most accurate gross criterion is estimated to be between 3 mg to 78 mg with a mean of 35 mg to 40 mg [6]. It was 50 mg in 995 autopsy cases [6]. Cost makes this policy unsuitable; however, calcium and intact parathormone (PTH) level may be normal in patients found to have enlarged parathyroids.

How to screen?

It's difficult to evaluate the real incidence of PH in thyroid disease [16]. The best screening for PH is total serum calcium level. In one series, hypercalcemia revealing PH was about 1 % of patients before they underwent cervicotomy for thyroid disease. Repeating this measurement or evaluating ionized calcium could improve the diagnosis of unknown PH. A better method would be to measure serum calcium and intact PTH (parathormone) levels before every thyroidectomy [8]. Cost of this policy is unsuitable, however, because calcium and PTH levels may be normal in patients found to have enlarged parathyroids.

Investigations

- (i) **Serum calcium and serum PTH:** Pre-operative work-up, including calcium and ionized PTH (iPTH) measurement, did not show parathyroid hyperfunction in 6 of 11 patients referred for thyroidectomy in a series of Abboud et al. and found to have enlarged parathyroid [8]. The inability to diagnose these lesions biochemically correlate well with their questionable significance. Calcium and intact PTH levels suggest less intense hyperparathyroidism.
- (ii) **Immunostaining:** It has been reported that as the weight of the gland increases, the hyperfunctioning of gland also increases. The result of Immunostaining of the glands favors this hypothesis. Hellman et al. found reduced expression of the antibody E₁₁ recognizing the calcium sensor of the parathyroid cells in hyperfunctioning parathyroid glands [10, 12]. These glands also showed a decreased cytoplasmic Ca⁺² response to elevation of external Ca⁺². The authors concluded that all but one gland had a patent functional abnormality [8]. For some authors [6], incidentally

found parathyroids had the same cellular disturbances as these found in overt PH but were not yet biochemically hyperfunctioning. Thus, gross enlargement of parathyroid could be the first step towards Hyperparathyroidism before biochemical disturbances develop.

- (iii) **Ultrasonography:** The role of sonography in the detection of parathyroid adenoma is controversial [17, 18]. It is accepted that its sensitivity and specificity is largely operator dependant and literature reports that 65–85 % of enlarged parathyroid gland may be seen by a skillful sonographer [19, 20]. The possibility of an enlarged parathyroid gland should always be considered when a hypoechoic, well-defined, oval, nodule is seen along the thyroid capsule. The incidence of parathyroid incidentaloma in a study was 0.53 % [12]. This figure is in agreement with the 0.45–0.6 % incidence of parathyroid adenomas incidentally found in patients undergoing surgery for thyroid disease [5]. However, in a series sonogram raised the possibility of parathyroid incidentaloma in about 2.2 % of patients undergoing thyroid sonography [13]. These studies indicate that sonography has a lower positive-predictive value in identifying parathyroid tissue in patients with thyroid disease.
- (iv) **Sestamibi Scan:** Sestamibi scintigraphy scan has been reported to be more accurate imaging technique [17, 21, 22]. In a study, the control group patients with parathyroid adenoma, the Sestamibi scintiscan showed the expected good sensitivity whereas, it missed almost half of parathyroid incidentalomas. The small size of the parathyroid gland may be one possible explanation for the low sensitivity of Sestamibi scanning [12].
- (v) **Routine frozen sections:** Frozen sections cannot always differentiate normal from abnormal lesions. Its main function is to determine if the removed specimen is parathyroid tissue. For this purpose, intra-operative fat staining can also be used [23].
- (vi) **FNAB-PTH:** Routine cytology with fine-needle aspiration has limited diagnostic value, so FNAB-PTH determination may be chosen for parathyroid tissue verification [24, 25]. In agreement with previous studies [24, 26]. Frasoldati A. in 1999 confirmed the role of combination of FNAB with PTH and Tg (thyroglobulin) determination in the identification of parathyroid incidentalomas. FNAB- PTH measurement may be considered the most reliable minimally invasive non-surgical test for parathyroid tissue verification [12].

Treatment

A positive correlation was found between the size of incidentalomas and serum PTH levels in patients studied by Frasoldati [12]. This is similar to other observations in

parathyroid incidentalomas [27], suggesting that larger incidentalomas are more likely to result in parathyroid hyperfunction. However, the optimal management of parathyroid incidentaloma remains unknown, as does the clinical significance of parathyroid incidentalomas. An established criterion for surgical treatment of asymptomatic hyperparathyroidism was discussed in 1991 NIH Consensus Development Conference. [28].

Whenever, any surgeon encounters a macroscopically abnormal parathyroid gland during thyroid surgery, he faces a dilemma, whether to remove it or not. There are risks in either scenario: should he remove the gland presuming it to be pathological or should he leave it in-situ, so that full investigations can be performed to confirm the parathyroid gland disease and this must be balanced by the surgeon when deciding what to do.

Risks of Removing the Gland The main risk is the development of hypocalcaemia postoperatively. If this were to be a hyperfunctioning adenoma then the risk is probably justified as the patient's hyperparathyroidism is cured. However, if it proves to be a normal gland, then the patient may have post-operative morbidity without any clinical benefit [29].

If Not Removed On the contrary, if abnormal gland is left-in-situ then the risk of needing to perform “re-do” surgery in the future to remove it. This may happen because the glands are overactive at surgery and was not picked-up pre-operatively, or the disease was pre-clinical or in its early phase and may turn up into overt hyperparathyroidism with time [30]. If an enlarged parathyroid gland is discovered incidently on ultrasound scan preoperatively, then the patient should undergo the following tests to detect any functional abnormality—serum calcium, FNAC, FNAB Parathormone, serum Parathormone and Sestamibi scan.

Complications

As reported by various studies approximately 10 % of patients develop temporary post-operative hypocalcaemia. These figures are almost similar to those seen in patients undergoing routine thyroid surgery, where the incidence of temporary hypocalcaemia after total thyroidectomy is quoted as 2–53 % [31]. As there are 4 parathyroid glands careful surgery to identify them and preserve the remaining glands should not result in increased risk of hypocalcaemia. Still, accidental removal of normal parathyroid tissue during thyroid surgery is reported to be 6–21 %. [31–33]. Patients who do become hypocalcaemic either temporarily or permanently, are treated with oral calcium and Vitamin D, if necessary [37].

Re-do surgery carries its own complications like higher chance of bleeding, damage to recurrent laryngeal nerve (<1 % in primary surgery and up to 10 % in re-do surgery) [30], post-operative hypocalcaemia due to inadvertent injury to normal parathyroid tissue either at original surgery or re-do operation [34].

Conclusion

To conclude, while doing thyroid surgery, one should carefully look for all 4 parathyroid glands and not only one should avoid accidental damage to glands but also abnormally enlarged gland should be identified. Gross enlargement of parathyroid glands could be the first step towards primary hyperparathyroidism (PH), before biochemical disturbances develop. In the absence of understanding the functional evaluation of these glands, it's recommended to remove all grossly enlarged parathyroid glands discovered during thyroidectomies in patients without the evidence of PH as long as at least 1 normal parathyroid gland remains. Estimation of serum calcium prior to thyroid surgery would be useful.

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