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Mediastinal Parathyroidectomy: Preoperative Management of Hyperparathyroidism

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1. Introduction

1.1 Anatomy and embryology of parathyroid glands

The normal parathyroid gland is oval or spherical in shape, has a distinct yellowish color, and averages 2x3x7 mm. The total mean weight of four normal parathyroids is about 150 mg. Majority of the population have four parathyroid glands typically located at the posterior capsule of the thyroid gland (Fig. 1; Fig.2), however in nearly 15% of individuals more than four glands are present. Phylogenetically, the parathyroid glands appear in amphibia, and arise from pharyngeal pouches III and IV. They may be arrested in the development as high as

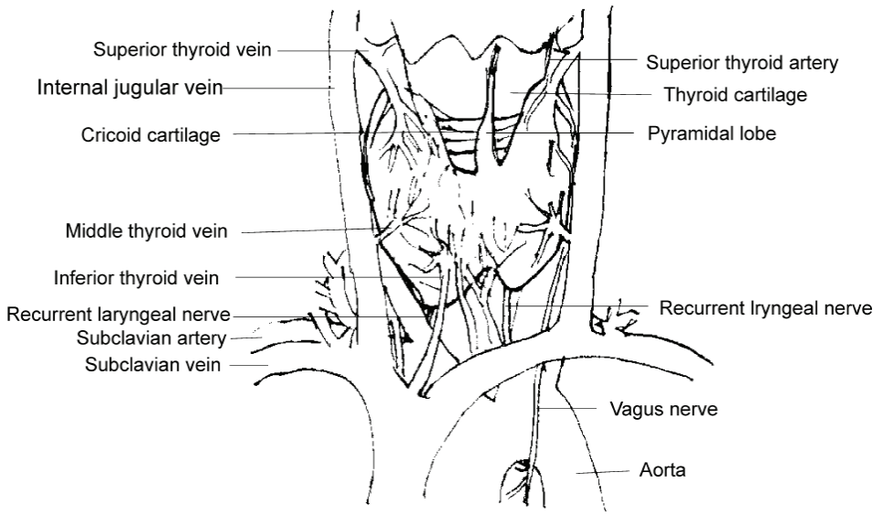

Fig. 1. Thyroid & parathyroid anatomy

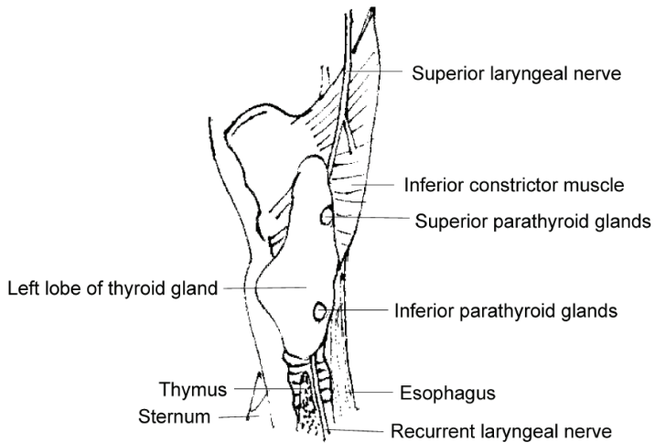

Fig. 2. Parathyroid glands anatomy. Left side view

at the level of the hyoid bone on the way of their descent to their typical location. Occasionally, parathyroids may be incorporated into the thyroid gland or thymus (intrathyroidal or mediastinal location). Lower (inferior) parathyroid glands (parathyroid III) may be found in the anterior mediastinum, while the upper (superior) parathyroids (parathyroid IV) usually remain in close association with the upper portion of the lateral thyroid lobes but may descend caudally along the esophagus into the posterior mediastinum (Fig. 3).

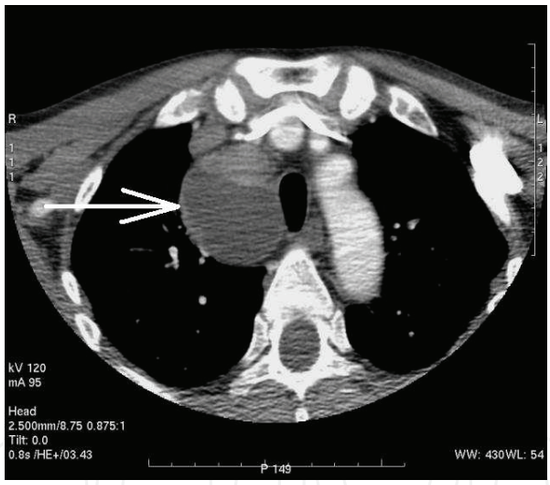

Fig. 3. Computed tomography scan showing a large mediastinal parathyroid adenoma (indicated with an arrow)

The parathyroid glands may lie in front of or behind the internal jugular vein and common carotid artery. Parathyroids are usually supplied by a branch of the inferior thyroid artery but may be supplied by the superior thyroid or, rarely, the thyroid ima arteries. The vessels can be seen entering a hilum-like structure, a feature that may be practically utilized to differentiate parathyroid glands from fat.

2. Physiology

Parathyroid glands secrete parathyroid hormone (PTH), which together with vitamin D, and calcitonin plays a vital role in precise regulation of calcium and phosphorus metabolism in

bone, kidney, and gut. PTH and calcitonin work in concert to regulate plasma levels of ionized calcium. Fall in the ionized calcium level stimulates the parathyroids to secrete more PTH, and inhibits the parafollicular cells within the thyroid to produce less calcitonin. The rise in PTH and fall in calcitonin stimulate increased resorption of calcium in the renal tubules and from bones, thus more calcium enters the blood, and ionized calcium levels normalize. PTH in the blood stream is heterogeneous and consists of the intact hormone, the amino terminal (N-terminal) fragment and the carboxyl terminal (C-terminal) fragment. C-terminal fragment is biologically inert, whereas N-terminal fragment maintains hormonal activity, however substantially lower than the intact hormone. Currently available diagnostic tests are capable of intact hormone level determination, which is important for reliability of the measurement in particular for intraoperative use.

3. Primary hyperparathyroidism

Primary hyperparathyroidism is a disease characterized by autonomous overproduction of PTH resulting in hypercalcemia. In majority of cases it is caused by a single parathyroid adenoma (80-85%), and less frequently by hyperplasia (10%), multiple adenomas (6%), or carcinoma (1%). Currently, primary hyperparathyroidism occurs in 0.1-0.3% of the general population and in unselected patients is considered the most common cause of hypercalcemia. It is almost three times more common in women than in men, with peak incidence between the third and fifth decades.

Excess production of PTH results in mobilization of calcium from bone and inhibition of the renal reabsorption of phosphate, leading to hypercalcemia and hypophosphatemia. Besides, it causes a wasting of calcium and phosphorus, which eventually may result in osseous mineral loss and osteoporosis. Other conditions which may be associated with hyperparathyroidism include nephrocalcinosis, nephrolithiasis, osteitis fibrosa cystica, pancreatitis, peptic ulcer, hypertension, and gout. Diagnosis of any of these diseases should evoke suspicion for hyperparathyroidism and the patient should be referred for more precise tests.

Hyperparathyroidism is occasionally associated with multiple endocrine neoplasia (MEN) type 1, or type 2. MEN type 1 is characterized by tumors of the parathyroid, pituitary, and pancreas (hyperparathyroidism, pituitary tumors, and islet cell pancreatic tumors) that may lead to gastrinoma (Zollinger-Ellison syndrome), glucagonoma, insulinoma (hypoglycemia), somatostatinoma, lipoma and pancreatic polypeptide tumors (PPomas). Adrenocortical tumors, carcinoid tumors, and multiple lipomas have also been reported in these patients. MEN type 2 is divided into 2 subtypes: MEN 2a and MEN 2b. MEN 2a is characterized by hyperparathyroidism associated with pheochromocytoma and thyroid medullary carcinoma. Hyperparathyroidism is rare in MEN 2b patients who often have multiple neuromas and a marfanoid habitus.

Parathyroid adenomas may range in weight from 65 mg to over 35 g, but occasionally the weight of these tumors may exceed 35g. Usually the size of the tumor parallels the degree of hypercalcemia (the larger the tumor, the more severe hypercalcemia). Microscopic examination of parathyroid adenomas shows chief cell, water cell, or, rarely, oxyphil cell type.

Primary parathyroid hyperplasia may be another cause of hyperparathyroidism. This condition involves all of the parathyroid glands, which vary considerably in size but are usually larger than normal. Microscopic examination may reveal two types: chief cell

hyperplasia and water-clear cell hyperplasia. Parathyroid carcinoma is rare but usually leads to severe hypercalcemia, and should be suspected at operation when the parathyroid gland is hard, has a whitish or irregular capsule, or shows signs of invasiveness. Rupture of the parathyroid tumor or breaching of the tumor capsule during rough dissection may result in seeding hyperactive tissue. This, and less frequently multiple embryologic rests may lead to a rare condition called parathyromatosis characterized by persistent hypercalcemia.

4. Signs and symptoms

Clinical signs and symptoms of hyperparathyroidism range from barely recognizable by patients, like muscle fatigablility, weakness, psychiatric disturbances, constipations, polydipsja and polyuria to severely impairing normal activities, like bone and muscle pains, nephrolithiasis, nephrocalcinosis, hypertension, peptic ulcer, pancreatitis or gout. Osteitis fibrosa cystica with bone pains and deformities, which was a prevailing symptom in patients with hyperparathyroidism a few decades ago, now became less frequent because majority of cases are detected early in the course of the disease. Also the incidence of renal complications decreased markedly and many patients are diagnosed by routine screening while still asymptomatic.

5. Laboratory tests

Serum calcium, parathyroid hormone and phosphates level are the principal laboratory tests used for the diagnosis of hyperparathyroidism. Elevated serum calcium and low phosphates are highly suggestive of hyperparathyroidism, however in about 50% of patients serum phosphates level is normal. Measurement of serum intact parathyroid hormone (PTH) concentration is the key test in diagnostic workout for patients with hypercalcemia, because the PTH level is low or nil in all cases except for those caused by primary hyperparathyroidism and familial hypocalciuric hypercalcemia, where PTH is markedly elevated.

Complementary laboratory tests include chlorides, protein electrophoretic pattern, alkaline phosphatase, creatinine, uric acid and urea nitrogen, urinary calcium, blood hematocrite and pH, serum magnesium and ESR. Sometimes, when previous tests are equivocal, measurement of nephrogenous cAMP, 1,25-hydroxy vitamin D levels and tubular resorption of phosphates may be helpful. Serum chloride concentration is elevated in nearly half of patients with hyperparathyroidism and may be a useful diagnostic clue. It's due to direct influence of PTH on the proximal renal tubule decreasing the resorption of bicarbonate, which leads to increased resorption of chloride. Other causes of hypercalcemia do not give rise in chloride concentration.

6. Secondary hyperparathyroidism

Secondary hyperparathyroidism (sHPT) is a condition characterized by excess secretion of parathyroid hormone stimulated by external factors, mainly hypocalcemia. Chronic renal failure is the most common cause of secondary hyperparathyroidism, as it results in hypocalcemia due to impaired conversion of vitamin D into active form, and excessive loss of calcium with urine. Sporadically sHPT may be caused by malabsorption, like chronic

pancreatitis, small bowel disease or malabsorbtion-dependent bariatric surgery. Prolonged stimulation of parathyroid tissue by hypocalcemia results in enlargement of parathyroids in the form of their hyperplasia and less frequently parathyroid adenoma.

7. Tertiary hyperparathyroidism

Tertiary hyperparathyroidism (tHPT) is a condition of autonomic excessive secretion of parathyroid hormone developing from secondary parathyroidism, that maintains despite restoration of renal function. It is caused by development of autonomous (unregulated) parathyroid function following a prolonged period of persistent parathyroid stimulation. It is no longer responsive to treatment by medication and requires surgical removal of three and a half parathyroid glands.

8. Indications for surgical treatment

Parathyroidectomy is currently recognized as the treatment of choice for patients with primary hyperparathyroidism. For virtually all these patients surgical resection of hyperactive parathyroid tissue is curative. It provides both metabolic improvement and symptoms relief. Medical observation is contraindicated. Furthermore, parathyroidectomy is recommended as early as possible in the course of the disease because once systemic complications such as renal dysfunction or hypertension develop, they tend to progress despite elimination of the underlying hyperparathyroidism.

9. Preoperative imaging techniques

Various techniques are currently available for parathyroid glands imaging. Noninvasive studies include ultrasonography, scintigraphy, computed tomography (CT) scanning, and magnetic resonance imaging (MRI). Scintigraphy with use of the radiopharmaceuticals technetium ^{99m}Tc sestamibi or technetium ^{99m}Tc tetrofosmin is widely recommended as the preferred imaging technique for parathyroids. Parathyroid selective arteriography or selective parathyroid venous sampling have been used occasionally as invasive techniques in select cases.

9.1 Ultrasonography

Parathyroid ultrasonography is currently the most easily accessible and a relatively inexpensive non-invasive test that is routinely used for the assessment of the thyroid and parathyroid glands. It is utilized for preoperative investigation in patients with hyperparathyroidism not only to localize and visualize enlarged parathyroids, but also to rule out thyroid nodules that may need to be evaluated prior to parathyroid surgery. For best results a high-frequency (7.5- or 10-MHz) linear ultrasound transducer should be available. The patient should be supine with the neck moderately hyperextended. It is recommended to start the evaluation from the carotid bifurcation superiorly and proceed down to the sternal notch inferiorly and to the carotid artery laterally.

Normal parathyroids are barely visualized with ultrasonography. Parathyroid adenomas appear on gray-scale images as hypoechoic or anechoic, discrete, oval masses. They are located posterior to the lobe of the thyroid gland and anterior to the longus colli muscles. Usually, the common carotid artery confines the parathyroid-bearing region laterally. An

echogenic line separating the thyroid tissue from the enlarged parathyroid gland can be often visualized. Cystic changes, lobulations, increased echogenicity due to fatty deposition, and occasional calcifications are more frequent in larger adenomas.
Parathyroid adenomas, in particular lesions larger than 1 cm in diameter, tend to be hypervascular, and therefore color Doppler ultrasonography is useful in localizing these enlarged glands. Besides, Doppler ultrasound can easily disclose the extrathyroidal vessel supplying parathyroid and this finding may constitute a road map to the otherwise inconspicuous gland.
Ultrasonography is efficient in diagnosing cervical parathyroid lesions with reported sensitivity up to 80% and specificity up to 90%, but fails to detect majority of parathyroid adenomas located in the mediastinum. Additionally, intrathyroidal lesions cannot be differentiated as a parathyroid adenoma or thyroid nodule based on imaging only, and a biopsy is required.

9.2 ^{99m}Tc sestamibi imaging

Nuclear imaging with use of ^{99m}Technetium (^{99m}Tc) sestamibi is currently approved as a standard technique for preoperative imaging of parathyroid glands. ^{99m}Tc sestamibi is a complex of the radioisotope technetium-^{99m}Tc with the ligand methoxyisobutylisonitrile (MIBI). ^{99m}Tc sestamibi, first applied as a myocardial perfusion agent, for parathyroids assessment is combined with either sodium iodide I^{123} or ^{99m}Tc pertechnetate in a procedure called subtraction scintigraphy. It is based on a fenomenon that ^{99m}Tc sestamibi is accumulated by both thyroid and abnormal parathyroids, whereas sodium iodide I^{123} and ^{99m}Tc pertechnetate are taken up by only thyroid tissue. To visualize parathyroids and differentiate them from thyroid tissue the sodium iodide I^{123} or ^{99m}Tc -pertechnetate image is subtracted from the ^{99m}Tc-sestamibi image.
Another, more recent imaging modality is the dual-phase technique with ^{99m}Tc sestamibi as the sole imaging agent. Both thyroid tissue and abnormal parathyroid tissue incorporate ^{99m}Tc sestamibi from circulating blood rapidly after intravenous administration. The test is based on the differential washout of ^{99m}Tc sestamibi from thyroid compared with abnormal parathyroids. The rate of washout from hyperactive parathyroid tissue, such as parathyroid adenoma, is much slower than that of normal thyroid tissue. Routine protocol includes intravenous administration of 20mCi of ^{99m}Tc Sestamibi and sequencial acquisition of early and delayed images of the neck and upper mediastinum. The early image, obtained 10-15 minutes after the injection, is called the thyroid phase as ^{99m}Tc sestamibi is rapidly taken up in the thyroid gland at this time. 1.5-3 hours after the injection the delayed image called the parathyroid phase is recorded. At this phase, ^{99m}Tc sestamibi has been washed out from thyroid but remains accumulated in the hyperactive parathyroid tissue, and this allows for localization of abnormal parathyroid glands. Planar images may be complemented with lateral or oblique acquisitions, or even SPECT images when appropriate equipment is applied. Sensitivity of the ^{99m}Tc sestamibi dual phase protocol has been reported to achieve 70-100%. Small or pedunculated, mobile adenomas may, however, be missed at this test.
^{99m}Tc sestamibi may also be used in minimally invasive parathyroid surgery, as an intraoperative adjunct facilitating localization of hyperactive parathyroid adenoma and confirming curative resection. The radionuclide is injected 1.5 to 3 hours prior to surgery, and a hand-held gamma probe is used to guide the incision, localize the abnormal gland and confirm identity of the resected parathyroid tissue ex-vivo. This technique called

intraoperative nuclear mapping proved to be successful, and is a standard procedure in a number of centers.

^{99m}Tc tetrofosmin is another radiopharmaceutical agent recently introduced into parathyroid imaging. It has a slightly different mechanism of accumulation in tissues, but imaging characteristics similar to those of ^{99m}Tc sestamibi. Also imaging protocols are similar with intravenous injections of 20-25 mCi of radionuclide prior to early (10-30 minutes) and delayed (1.5-3 hours) acquisition images.

9.3 Computed tomography (CT) scanning

Assessment of parathyroid glands with use of a typical CT protocol involves the acquisition of contiguous axial 2- to 3-mm images ranging from the hyoid bone down to the carina. Nonenhanced images of parathyroid adenomas have an attenuation similar to that of muscle. Substantial degree of enhancement is usually shown in parathyroid adenomas after administration of contrast material, as these lesions tend to be hypervascular structures. Typically, parathyroid adenomas present at CT as enlarged, enhancing, soft-tissue masses in the expected location of the parathyroids. The sensitivity of CT in detecting parathyroid adenomas attains 90%. However, the use of ionizing radiation and required intravenous administration of contrast material accompanied by associated risks are considered remarkable disadvantages of this imaging technique. Besides, thyroid nodule, tortuous vessel, or laterally displaced esophagus may be misidentified as a false-positive finding, whereas small or ectopic lesion, poor visualization of neck structures or distorted neck anatomy due to prior surgery may lead to false-negative result.

9.4 Magnetic resonance imaging

MRI is occasionally used for parathyroid imaging. A typical MRI protocol for the assessment of parathyroids involves axial images of the neck and mediastinum. Images are acquired using T1-weighted spin-echo sequences (short recovery time [TR], short echo time [TE]) followed by T2-weighted spin-echo sequences (long TR, long TE). Parathyroid adenomas are seen on MRI images as soft-tissue masses, whereas normal parathyroids are usually not detected. Parathyroid adenomas commonly have low-to-medium signal intensity on T1-weighted images and high signal intensity on T2-weighted images. After gadolinium contrast administration, abnormal parathyroid glands show strong enhancement on T1-weighted images, comparable to conventional T2-weighted imaging.

9.5 Parathyroid arteriography and venous sampling

Parathyroid arteriography and parathyroid venous sampling are invasive tests burdened by a remarkable risk of embolic stroke and spinal cord injury, and therefore should be considered only when the findings of noninvasive imaging modalities are nondiagnostic. Parathyroid adenomas, like many endocrine tumors, tend to be hypervascular and have a characteristic appearance on angiograms. They appear as round or oval lesions with smooth margins and dense vascular blush. Localization of parathyroid adenoma may be visualized with use of digital subtraction angiography (DSA) and/or conventional arteriography. Thyrocervical trunks and common carotid arteries should be subject to selective arteriography in typical cases. Ectopic mediastinal or thymic glands may be better identified by examination of internal thoracic arteries.

Selective venous sampling with parathyroid hormone measurement may be performed to determine the general location of hypersecreting parathyroid tissue. Right and left thymic veins, inferior thyroid veins, and vertebral veins have been reported to be sampled in this regimen. A 2-fold gradient in PTH concentration in the sampled vein as referenced to that of the peripheral vein confirms the location of hyperactive parathyroid tissue. Similar technique may also be used intraoperatively to confirm curative resection of parathyroid adenoma.

10. Preoperative anesthetic management

Since renal function is likely to be impaired in hyperparathyroidism, prior to surgical treatment hypercalcemic patients require thorough rehydration. In some of these patients urinary catheterization and central venous pressure monitoring may be indicated. After rehydration, loop diuretics may be administered to decrease renal calcium reabsorption and promote urinary excretion, which in result will alleviate hypercalcaemia. Excessive diuresis may in turn lead to increased maintenance fluid requirements. Corticosteroids, bisphosphonates, calcium chelators such as trisodium edentate, calcitonin, or even dialysis are occasionally indicated in severe cases. Hypertension, if present, should be controlled with fast-acting antihypertensive medication. In patients with end-stage renal failure, perioperative invasive central venous pressure monitoring may be helpful for thorough monitoring of circulatory system. Occasionally, tumors of other organs may secrete PTH, for example, bronchial or tracheal carcinomas. This condition is called pseudohyperparathyroidism and should be brought to attention preoperatively to avoid intreaoperative ventilatory problems in theses rare cases when the lesion occludes bronchial or tracheal lumen.

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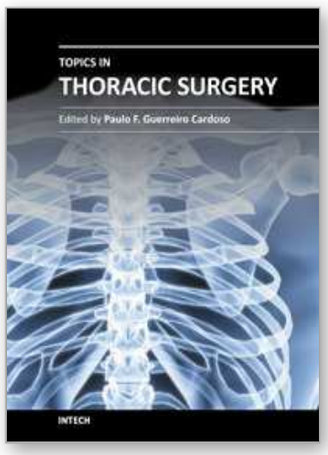

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