Notes & Comments
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ABOUT THE GUIDELINE FOR DIAGNOSIS AND TREATMENT OF PRIMARY HYPERPARATHYROIDISM IN A COUNTRY WITH ENDEMIC GOITER

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Abstract

Endemic goiter and primary hyperparathyroidism are two common endocrine disorders, and, consequently, they could coexist in many European countries. The prevalence of nodular goiters is increased in the patients with primary hyperparathyroidism, ranging widely between 22 to 70%, with higher prevalence in endemic goiter areas.

Romania is a country having both endemic goiter and a high prevalence of vitamin D deficiency. Coexisting vitamin D deficiency is associated with more cases of symptomatic primary hyperparathyroidism or may mask a primary hyperparathyroidism, serum calcium being in the normal range.

Because of the frequent association of parathyroid adenomas with thyroid nodules, the optimal imaging combination is 99mTc-sestamibi and ultrasonography. Thyroid nodules can give false positive results at preoperative scintigraphy because they trap and retain 99mTc-sestamibi similarly as parathyroid adenomas.

Bilateral neck exploration (*vs* minimally invasive parathyroidectomy) is probably necessary in the treatment of primary hyperparathyroidism associated with nodular goiter, because nodular goiters increases the difficulty of preoperative localization of parathyroid lesion(s).

Keywords: primary hyperparathyroidism, nodular goiter, parathyroidectomy, thyroidectomy, iodine deficiency, vitamin D deficiency.

INTRODUCTION

Primary hyperparathyroidism is due to excessive secretion of parathyroid hormone (PTH) by at least one enlarged parathyroid gland, being caused by a single parathyroid adenoma in about 80 to 85% of cases (1). Since the introduction of routine serum calcium measurement in the 1970s, this disorder has become one of the most

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common endocrine diseases in the world (2). Iodine deficiency is the world's most common endocrine disorder (3). Consequently, because primary hyperparathyroidism and endemic goiter are two common endocrine diseases, they coexist in many European countries, including Romania.

In Europe, the estimated prevalence of primary hyperparathyroidism is 3 per 1000 overall, reaching 21 per 1000 in women 55 — 75 years old (4). Most of the patients with primary hyperparathyroidism are asymptomatic (5) and the classical picture of "moans, groans and stones" is rarely seen today (6). Regarding symptomatic patients, those with serum calcium in excess of 13 mg/dl are at increased risk of premature death due to hypercalcemic crisis (7). The diagnosis of primary hyperparathyroidism is confirmed by demonstrating persistent hypercalcemia in the presence of elevated parathormone (PTH) concentrations.

In the context of the debate around consensus Guidelines already proposed by the Romanian Society of Endocrinology (8-10), we consider necessary a consensus guideline for diagnosis and treatment of primary hyperparathyroidism in a country having both iodine deficiency and a high prevalence of vitamin D deficiency.

PRIMARY HYPERPARATHYROIDISM ASSOCIATED WITH NODULAR ENDEMIC GOITER

The prevalence of nodular goiter was reported in an average 38.1% of hyperparathyroid patients, ranging widely between 22 and 70% and even more in endemic goiter regions (11-13).

A difficult matter in the patients with associated nodular endemic goiter is that about 2 — 3% of parathyroid adenomas are intrathyroidal, usually within the lower pole of the thyroid gland (14). In a study group of 125 consecutive patients with

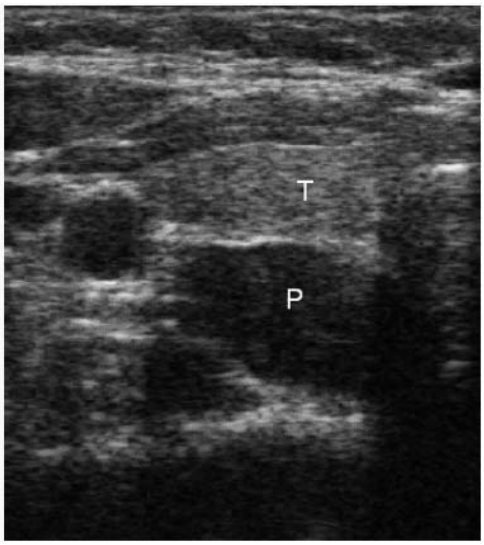

Figure 1. Neck ultrasound suggesting a parathyroid (P) lesion (2.9 cm) behind the left thyroid lobe (T).

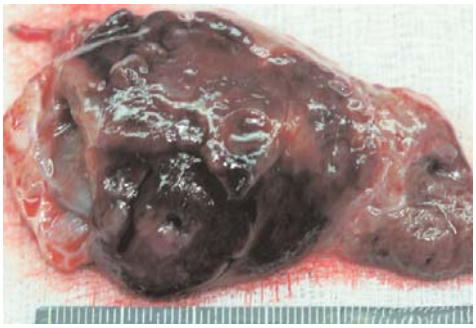

Figure 2A. A large parathyroid adenoma (54.5 g).

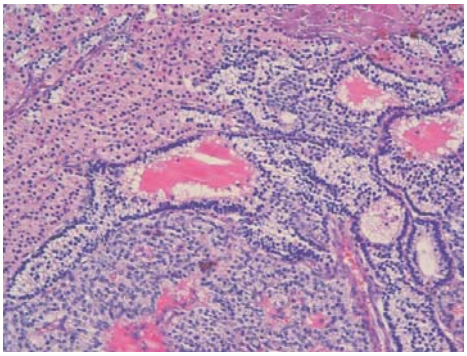

Figure 2B. Microscopic aspect of a chief cell parathyroid adenoma.

primary hyperparathyroidism, thyroidectomy has always been carried out soon after parathyroidectomy in 60% of the patients (15). In one of our patients with primary hyperparathyroidism and a diffuse goiter, a parathyroid adenoma (2.9 cm) mimicked a thyroid nodule (Fig. 1); parathyroid adenoma was palpable because the parathyroid lesion was associated with a small diffuse goiter.

Coexisting differentiated thyroid carcinoma and primary hyperparathyroidism were found in 3.3 — 6% (16-18), causing difficulties in the diagnosis, preoperative localization and management of primary hyperparathyroidism. One of the largest parathyroid adenomas (54.5g) from the Pathology department collection of our National Institute of Endocrinology was found in one of our cases (Figs 2A,2B). Parathyroid carcinoma is a rare tumor responsible for 1% of the patients with primary hyperparathyroidism and, interestingly, are usually small (from 1.5 to 27g in weight) (19,20); the precise diagnosis of malignancy is made when local or distant metastases are found (19). On the other hand, it was reported a large parathyroid functioning carcinoma (1200g) presenting as a substernal goiter (19).

Because of the frequent association of parathyroid adenomas with nodular goiter, the optimal imaging combination is 99mTc-sestamibi and ultrasonography (14). Thyroid nodules can give false positive results at preoperative scintigraphy because they can trap and retain 99mTc-sestamibi similarly as parathyroid adenomas (14). In areas with high prevalence of nodular endemic goiter, dual tracer subtraction protocols (with I123/99mTc-sestamibi or 99mTcO4/99mTc-sestamibi) are generally preferred for preoperative localization of parathyroid lesions (14), but these protocols are not yet available in Romania.

PRIMARY HYPERPARATHYROIDISM ASSOCIATED WITH VITAMIN D DEFICIENCY

In a representative osteoporosis population from Romania it was found a very

high prevalence of vitamin D deficiency and insufficiency (21).

Although asymptomatic primary hyperparathyroidism commonly occurs in countries that use multichannel screening tests, symptomatic disease is common in other geographic areas, where access to multichannel screening is limited (5). In addition, the high prevalence of vitamin D deficiency in these countries may fuel the processes associated with overactivity of the parathyroid glands, leading to more cases of symptomatic disease (5).

It must be stressed that coexisting vitamin D deficiency may cause the serum calcium level to fall into the normal range, which leads to diagnostic uncertainity (22); in these patients, primary hyperparathyroidism is masked by vitamin D deficiency (23). Vitamin D deficient patients undergoing parathyroidectomy are also at increased risk of postoperative hypocalcemia and "hungry bone syndrome" (22).

In Romania there is a clear discrepancy between the estimated incidence of primary hyperparathyroidism in a population of more than 20 millions (around 4000 patients diagnosed per year) and the average number of patients (40 cases/year) admitted in the "C.I. Parhon National Institute of Endocrinology" (24). A limited access to multichannel screening tests and an increased prevalence of coexisting vitamin D deficiency might contribute, at least in part, to the above mentioned discrepancy which was found in Romania.

REVISED CONSENSUS GUIDELINES (2008)

Many patients with primary hyperparathyroidism are asymptomatic. According to new Guidelines (2008), there is general agreement that the patients with asymptomatic primary hyperparathyroidism should undergo surgery if the following 4 criteria are present (25):

- they are younger than 50 years
- serum calcium has been maintained at more than 1mg/dl above the upper limit of normal range
- have a T-score of — 2.5 or less at any site and/or previous fracture fragility
- have a creatinine clearance reduced to less than 60ml/min.

Only about 20% of the patients with primary hyperparathyroidism meet indications for surgical intervention if these guidelines are used (24).

On the other hand, for patients with asymptomatic primary hyperparathyroidism who do not meet the above mentioned criteria, some authors recommend long term monitoring to identify about a quarter (27%) of the patients will show progression of disease over time (26).

For the Romanian Guidelines for the diagnosis and treatment of primary hyperparathyroidism we recommend the same 4 criteria mentioned above (25) regarding the group of patients with asymptomatic primary hyperparathyroidism who should undergo surgery. Because about a quarter of the patients with asymptomatic primary hyperparathyroidism will show progression of the disease

over time (26), the annual evaluation and follow-up is recommended, in the patients without surgical indication, using serum calcium and PTH, DEXA measurement, creatinine clearance and renal ultrasound.

SURGICAL THERAPY OF PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism can be cured by an experienced endocrine surgeon in 95% of cases (27). Unsuccessful surgery with persistent hyperparathyroidism due to inadequate preoperative or intraoperative localization may be observed in 5 to 10% of patients, reoperation being associated with increased morbidity (28). In a study performed on 30 patients with primary hyperparathyroidism, a bilateral neck exploration was required in 15 patients and a minimally invasive parathyroidectomy was possible in 15 cases; nine of the patients with bilateral neck exploration showed thyroid pathology (29).

In comparison with bilateral neck exploration, minimally invasive parathyroidectomy was associated with a 50% reduction in operating time, a 7-fold reduction in length of hospital stay, is achieved through a small skin incision (around 2 cm) and can be performed under local or general anesthesia (24).

Rapid intraoperative parathyroid hormone (RIOPTH) monitoring predicts complete removal of all hypersecreting tissue by means of a significant parathyroid hormone decrease (15). It must be added that false positive results may occur in patients with multiglandular disease (15), i.e. multiple parathyroid adenomas or parathyroid hyperplasia.

PROPOSALS TO ADOPT IN A COUNTRY WITH ASSOCIATED ENDEMIC NODULAR GOITER

For Romania, a country with endemic goiter and a high prevalence of vitamin D deficiency, we have some suggestions:

1. Because of the frequent association of parathyroid adenomas with thyroid nodules, the optimal imaging combination is 99mTc-sestamibi and ultrasonography (14). However, thyroid nodules can give false positive results at preoperative scintigraphy because they trap and retain 99mTc-sestamibi similarly as parathyroid adenomas (14). Cervical ultrasonography is useful in the preoperative detection of nodular goiter in the patients with primary hyperparathyroidism (12).

2. In our country, with a high prevalence of vitamin D deficiency, preoperative measurement of 25 - hydroxyvitamin D is required.

3. Bilateral neck exploration (vs minimally invasive parathyroidectomy, the alternative strategy) is necessary in the patients with associated multinodular goiter or heterolateral uninodular goiter, because nodular goiters increases the difficulty of preoperative and intraoperative localization of parathyroid lesion(s) (30). Bilateral

neck exploration is also preferred when multiglandular disease (parathyroid gland hyperplasia or double adenomas) cannot be excluded (30).

4. When primary hyperparathyroidism is associated with a nodular goiter, thyroidectomy is indicated for 3 reasons: (a) in order to remove a potential compressive goiter, (b) when a thyroid carcinoma is suspected or (c) when intrathyroidal parathyroid adenoma cannot be excluded.

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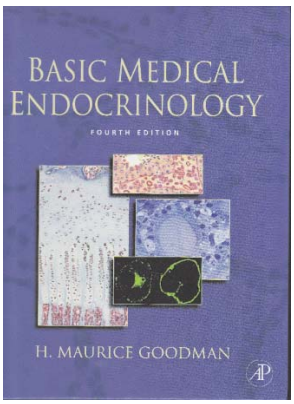

BASIC MEDICAL ENDOCRINOLOGY
Fourth Edition
Editor: H. Maurice Goodman
Publisher: Elsevier –Academic Press
ISBN: 978-0-12-373975-9
No. pages: 309
Year: 2009

This basic endocrinology textbook is centered on the integrative and regulatory roles of the endocrine system in humans, with an emphasis on cellular and molecular mechanisms. Maurice Goodman, the editor, has forty-five years of experience teaching endocrinology and physiology to medical students at Harvard Medical School and at the University of Massachusetts Medical School. The fourth edition of this book captured the major progress of molecular biology in understanding the cellular and molecular bases of hormonal actions.

The text is organized into 14 chapters. In the introduction, we find the essential features of the physiology of hormones, feedback regulation, essentials of the competitive binding assays. 4 of the chapters present individual endocrine glands and some basic information about their morphology and physiological functions. The chapter "Principles of Hormonal Integration" shows some of the general principles of endocrine integration at the cellular and the whole body level. In subsequent chapters we find integrated hormonal actions that govern homeostatic regulation, growth and development and reproduction. In response to the increasing epidemic of obesity and diabetes, 3 chapters are dedicated to the physiology of the hormones of the gastrointestinal tract, the largest and the most complex endocrine organ, with the neuroendocrine regulation of the gastrointestinal tract and the roles of the gastrointestinal hormones in nutrient assimilation and the regulation of food intake.

In this forth edition, the old figures have been redrawn in color and more than 75 new figures have been added. This book has also a web link to the companion website, with all figures available as Powerpoint slides which can be used by the professors in their teaching needs at the http:/textbooks.elsevier.com/companions/9780123739759.

All these recommend "Basic Medical Endocrinology " as a valuable resource for medical students and their professors, and also for young or experimented endocrinologists.

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Book Review:
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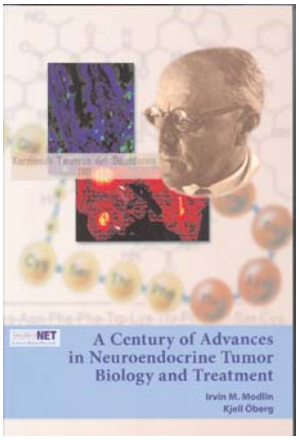
A CENTURY OF ADVANCES IN NEUROENDOCRINE TUMOR BIOLOGY AND TREATMENT



Editors: Irvin M. Modlin & Kjell Öberg

Publisher: Felsenstein C.C.C.P
ISBN: 978-3-00-023638-9
No. pages: 463 year: 2007

This text, memorializes the centenary of the discovery of carcinoid tumors by Siegfried Oberndorfer.

This book produced by an internationally recognized group of authorities from the USA and Europe, is a compendium of current information on a wide range of clinical and scientific aspects of neuroendocrine tumor disease.

The book has seven chapters: tumor disease overview, neuroendocrine cell biology, pathobiology, neuroendocrine pathology, diagnostic strategy, medical therapy, interventional therapy. Substantial advances have been made not only in the elucidation of the pathobiology of the tumors, but also in the management of the disease itself. The relationship of the symptomatology and pathological behavior of neuroendocrine tumors to the diverse cell types and bioactive agents produced by the lesions has been dramatically expanded recently by advances in cell biology, peptide chemistry and molecular biology.

The text details the development and regulation of neuroendocrine cell secretion, proliferation and neoplasia as well as the biology of the naive cells and tumors. In addition, it describes the genetic aspects of neuroendocrine disease as well as the diverse lesions, their clinical manifestations, diagnosis and management. The diagnostic role of radiology, isotope scintigraphy, functional PET scanning, and endoscopy are all critically assessed. In addition a detailed assessment of current therapeutic agents, novel isotopic therapy and surgical as well as radiological interventional therapy is provided. The identification of somatostatin receptors and the development of the somatostatin class of agents have provided a substantial advance in diagnosis and therapy.

The editors suggest that in the years to come it is necessary to develop the centers of excellence and neuroendocrine tumors clinical teams to coordinate multicenter studies. We anticipate that this book is useful for: endocrinologists, gastroenterologists, oncologists, interventional radiologists and surgeons.

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Primary hyperparathyroidism is usually caused by a tumor within the parathyroid gland. The symptoms of the condition relate to the elevated calcium levels, which can cause digestive symptoms, kidney stones, psychiatric abnormalities, and bone disease. The diagnosis is initially made on blood tests; an elevated level of calcium together with a raised level of parathyroid hormone are typically found. To identify the source of the excessive hormone secretion, medical imaging may be performed he surgical treatment of primary hyperparathyroidism (pHPT) has undergone extensive change in the past 2 decades. The presentation, diagnosis, and medical management have been previously addressed by an international workshop.1-4 To meet the need for a detailed focus on operative management, the American Association of Endocrine Surgeons (AAES) developed evidence-based guidelines to delineate the safe and effective practice of parathyroidectomy to achieve definitive treatment.Â A multidisciplinary panel of endocrinologists, pathologists, surgeons, and radiologists established PubMed search parameters for the worldwide medical literature from January 1, 1985, to July 1, 2015, using the National Library of Medicine Medical Subject Headings We reviewed the surgical management of primary hyperparathyroidism through a retrospective chart review of 200 parathyroidectomy procedures performed over a 12 year period. Epidemiological data and accuracy of radiological investigations used in identifying pathological parathyroid tissue location were assessed. We determined how often simultaneous removal of thyroid tissue was required during parathyroidectomy and the associated pathology. Radiology reports were screened to determine if confirmed thyroid pathology from histological specimens were referenced pre-operatively.Â A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. N Khorasani, A Mohammadi. Otolaryngol Head Neck Surg. 2014.