Tips and Tricks in Endocrine Surgery

John C. Watkinson
David M. Scott-Coombes
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ISBN 978-0-85729-982-6 ISBN 978-1-4471-2146-6 (eBook)
DOI 10.1007/978-1-4471-2146-6
Springer London Heidelberg New York Dordrecht

Library of Congress Control Number: 2013950912

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

In spite of a somewhat protracted and tortuous development, endocrine surgery has now come of age with its recognition and acceptance as a true surgical speciality in its own right.

It is difficult to determine at which point exactly this event occurred, but it was probably sometime in the 1960s and 1970s when surgeons began to regard the endocrine system as a whole, appreciated the need to work closely with other disciplines (endocrinologists, biochemists, radiologists, pathologists, nuclear medicine specialists, basic scientists, etc.), and also began to publish books and journals devoted to the subject. Postgraduate courses in endocrine surgery started to appear and very soon national and international associations were born.

Dramatic progress in the basic science underlying the speciality, particularly in the areas of biochemistry, molecular biology, and genetics, has placed unique demands upon the endocrine surgeon and emphasized the imperative to continually keep abreast of the latest information and knowledge. A veritable explosion of endoscopic and minimally invasive surgical advances has placed additional pressures upon the endocrine surgeon to keep up-to-date and remain at the forefront of his speciality.

The standard textbook has always fulfilled an important function in the communication of new knowledge, but with the arrival of the digital age and the ever-expanding role of the Internet and rapid electronic information transfer, some might consider the place of the traditional textbook to be under threat.

However, I believe that there is still an important role for the concise focused text which can provide the reader with instant, easily accessible advice and guidance.

This book, *Tips and Tricks in Endocrine Surgery*, is such a text and will certainly fill a vacant niche in the literature. Its publication will add to the legitimacy of the debate regarding the ideal educational medium. It is always difficult to decide upon the precise type of audience to which such a text should be directed. This book will be of particular value to the higher surgical trainee in endocrine surgery as well as the established consultant.

The contributors have been handpicked across the breadth of the speciality, including otorhinolaryngologists with expertise in thyroid and parathyroid surgery.

Indeed the professional credentials of the two extremely experienced coeditors testify to this cross-speciality cooperation. There is an excellent balance of contributions from surgeons and medical endocrinologists, including a rare finding in such a book of chapters addressing disorders of the pituitary.

It might be thought invidious to single out any particular chapter for comment, but there are several scholarly highlights, particularly in the sections describing surgical techniques for open and minimally invasive adrenalectomy, which are worthy of mention. These chapters provide exceptional detail and are full of tips, tricks, and pearls of wisdom completely in keeping with both the title and ethos of the book.

In a multiauthor book it is challenging to establish a uniform style and format throughout. However, in *Tips and Tricks in Endocrine Surgery*, the contributors and editors have succeeded in producing an academically credible text which is extremely readable, comprehensive and detailed, and full of sound practical advice which will undoubtedly have the potential to contribute to the provision of better and safer clinical care.

Throughout the book there are many references to the importance of team work and a multidisciplinary approach to difficult and complex endocrine problems. It is worth remembering that this is not a new concept in surgery. The famous Dr. Charles H. Mayo, a veritable doyen of thyroid surgery at the Mayo Clinic, wisely said, "The keynote of progress in the twentieth century is system and organization – in other words, 'team work.'" Few would today disagree with this sentiment.

I hope that Scott-Coombes and Watkinson's book will join the standard texts in the quest for provision of a continuum of information and opinion in the speciality. I enthusiastically recommend it to all endocrine surgeons.

Wales, UK Malcolm H. Wheeler, MD, FRCS

Preface

This book was conceived from discussions between us about surgical teaching and multidisciplinary working. We believe there is still a place in the modern era for a text that simplifies a subject with a series of learning points, generated from the expert contribution of a number of specialities. This book aims to do just that. An international multidisciplinary faculty has combined to bring together the relevant endocrine topics, and the algebraic generic sum of their wisdom, learning, and experience means that anyone reading this text can do so in the confidence of knowing that the subject essentials will be both up-to-date and comprehensive.

Have a good read and spread the word!

Birmingham, UK — John C. Watkinson
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Part I
Adrenal

Chapter 1
Adrenal and Paraganglioma: Presentation, Assessment, and Diagnosis

Andrew Lansdown and Aled Rees

- The adrenal cortex represents 90 % of the gland and is divided into three zones:
  - Zona glomerulosa (outer), aldosterone-secreting
  - Zona fasciculata (intermediate), cortisol-secreting
  - Zona reticularis (inner), androgen-secreting
- The medulla is the inner core of the gland and secretes around 20 % noradrenaline and 80 % adrenaline.

Cushing's Syndrome

Presentation

- Typically affects women (4:1) at a young age (30–40 years).
- A high index of suspicion is required for early diagnosis and treatment.
- Left untreated, Cushing's syndrome is associated with a high mortality (up to 50 % within 5 years), principally from cardio-/cerebrovascular disease.
- Clinical features include:
  - Central weight gain, buffalo hump, plethoric "moon" face 70–80 %
  - Hypertension 70–80 %
  - Skin thinning, purple striae, easy bruising, facial plethora 60–70 %
  - Psychological symptoms, depression, irritability 60–70 %

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J.C. Watkinson, D.M. Scott-Coombes (eds.), *Tips and Tricks in Endocrine Surgery*,
DOI 10.1007/978-1-4471-2146-6_1,

  - Proximal myopathy 50–60 %
  - Oligomenorrhea/impotence 50–60 %
  - Hirsutism and acne 40–70 %

- Consider the diagnosis particularly if osteoporosis and/or hypertension is present in a young person.
- "Subclinical" Cushing's syndrome refers to the presence of mild, autonomous hypercortisolism without specific clinical signs of cortisol excess; this typically occurs in the context of incidentally discovered adrenal adenomas (adrenal "incidentalomas").
- Subclinical Cushing's syndrome may be associated with an increased prevalence of hypertension and impaired glucose tolerance, but the natural history and optimal management is presently unclear.
- Cushing's syndrome from ectopic ACTH secretion is usually due to malignancy and presents with weight loss, metabolic disturbances (hypokalemic alkalosis), and severe myopathy.

Assessment

- Features which best discriminate Cushing's syndrome from simple, generalized obesity include proximal myopathy and thinning of the skin/easy bruising.
- Full assessment of metabolic and cardiovascular status should be undertaken.
- Blood pressure should be measured and controlled appropriately.
- Patients should be screened and treated for diabetes mellitus and any underlying infection.

Diagnosis

1. Is hypercortisolism present?

   Screening tests:

   - Overnight dexamethasone suppression test. Give 1 mg oral dexamethasone at 11 p.m. and measure serum cortisol at 9 a.m. the following morning. Normal response is complete cortisol suppression (<50 nmol/l). High sensitivity (95 %) and moderate specificity (85 %); false positive with oral contraceptive, hormone replacement therapy and liver enzyme inducers.
   - Late night salivary cortisol. Convenient, measured at 11 p.m. or midnight. High sensitivity but low specificity.
   - Urinary free cortisol – at least two collections needed to avoid missing mild disease. False negative with renal failure. Low specificity: false positive in alcoholism, depression, and polycystic ovary syndrome.
   - A combination of tests is usually required to make the diagnosis.

Confirmatory tests:

- Low-dose dexamethasone suppression. Administer 0.5 mg dexamethasone 6 hourly for 48 h. Normal response is complete cortisol suppression (<50 nmol/l). High sensitivity and specificity (98 %) when interpreted at this cortisol cutoff.

2. What is the cause of hypercortisolism?

Tests to confirm source:

- Tests to confirm the source should only be undertaken when a diagnosis of hypercortisolism is established.
- First step is to measure plasma ACTH. Levels <5 pg/ml on several occasions indicate ACTH-independent disease; levels >15 pg/ml indicate likely ACTH-dependent source.
- In cases where ACTH independence is confirmed, CT is indicated to establish an adrenal lesion.
- In ACTH-dependent Cushing's syndrome, MRI pituitary may demonstrate a pituitary adenoma.
- Bilateral inferior petrosal sinus sampling (BIPSS) can be used to differentiate between a pituitary and ectopic ACTH source. High sensitivity and specificity (95 %).
- Chest X-ray may localize an ectopic source (mandatory in all smokers).
- CT/MRI chest and abdomen is recommended to search for tumors associated with ectopic ACTH production when pituitary source excluded.

Medical Management

- In severe Cushing's syndrome, or where complications such as refractory hypertension or poorly controlled diabetes are present, medical treatment should be considered prior to surgery.
- Metyrapone (11-β-hydroxylase inhibitor), ketoconazole (imidazole antifungal), or etomidate alone or in combination can be used in these situations. Etomidate infusion requires ventilation on ICU.
- Liaison with endocrinologist is essential.

Conn's Syndrome

Presentation

- Moderate to severe hypertension, often refractory to treatment (three or more drugs) (systolic blood pressure 140–160 or diastolic blood pressure 90–99 mmHg) in a relatively young patient.

Table 1.1 Medications that may interfere with PAC: PRA ratio

Amiloride
Estrogen (combined oral contraceptive pill, hormone replacement therapy)
Diuretics
ACE inhibitors
Angiotensin II receptor blockers
Dihydropyridine calcium channel blockers
Heparin
Lithium
Nonsteroidal anti-inflammatory drugs (NSAIDs)

- Hypokalemia (serum K^+ <3.5 mmol/l) (50 %), with symptoms including fatigue, muscle cramps, thirst, polyuria, and nocturia, although commonly asymptomatic.
- 50 % are normokalemic.
- Increased risk of cardio-/cerebrovascular disease compared to essential hypertension.

Assessment

- Check blood pressure.
- U+E (hypokalemia, sodium upper end of normal or mildly elevated) with alkalosis.
- Indications for screening include adrenal incidentaloma with hypertension, refractory hypertension (on three or more drugs), severe hypertension (≥160 mmHg systolic and/or ≥100 mmHg diastolic), hypertension in a young adult (less than 40 years or strong family history), and hypokalemic alkalosis.

Diagnosis

- Liaise with endocrinologists.

  Screening tests:

  - Correct hypokalemia before collecting blood for aldosterone and renin.
  - Measure plasma aldosterone to plasma renin ratio (ARR).
  - Discontinue beta-blockers (2 weeks) and spironolactone (6 weeks) beforehand.
  - Other drugs may also affect interpretation but alpha-blockers do not (Table 1.1).
  - Plasma renin activity will typically be suppressed (<0.5 pmol/ml/h; normal 0.5–3.5) with a raised plasma aldosterone concentration >250 pmol/l. An ARR of >2,000 makes a diagnosis of Conn's syndrome very likely.

  Confirmatory tests:

  - These include the fludrocortisone suppression test and saline suppression test depending on local policy. Aldosterone fails to suppress in patients with primary hyperaldosteronism.

- High-resolution CT of the adrenal glands is required in patients with biochemically confirmed primary hyperaldosteronism. This may show a unilateral hypodense adenoma, bilateral hyperplasia/nodularity, unilateral adrenal thickening, or normal appearances.
- Other than in young (<40 years) patients with a typical presentation and confirmed (>1 cm) adenoma, all patients require lateralization of aldosterone secretion prior to surgery, principally because incidentalomas are common (4–7 % of the population), and there is a risk of misattributing the aldosterone excess to the adrenal adenoma.
- Adrenal venous sampling for primary hyperaldosteronism:
  - Samples are collected from the left and right adrenal veins, inferior vena cava, and peripheral blood pre- and post-synacthen stimulation.
  - An aldosterone to cortisol ratio of one adrenal vein versus the other of >4:1 is indicative of unilateral secretion, whereas a ratio of <3:1 is indicative of bilateral secretion.
- ^{11}C-metomidate PET-CT scanning may be a sensitive and specific noninvasive alternative to adrenal venous sampling for lateralizing aldosterone secretion by Conn's adenomas, but is not widely available.
- Testing for rare genetic causes (e.g., familial hyperaldosteronism type I or type II) may be necessary in certain circumstances (very early onset or family history of stroke or hypertension at a young age).

Medical Management

- Aldosterone receptor antagonists, such as spironolactone and eplerenone, can be used.
- Spironolactone can cause gynecomastia and reduced libido in men and menstrual disturbance in women.
- Eplerenone has a lower affinity for sex hormone receptors, hence is a useful alternative to spironolactone for men who develop gynecomastia, but has marginally inferior antihypertensive effects.
- Patients with Conn's syndrome may have coexisting essential hypertension and often need other antihypertensive treatment even after successful surgery.

Pheochromocytoma/Paraganglioma

Presentation

- Patients may be symptomatic or asymptomatic.
- Typical symptoms include sweating (60–70 %), sustained or episodic hypertension (>90 %), and headache (90 %).

- Other symptoms include pallor or flushing, palpitations, anxiety, panic attacks, and postural hypotension (due to decreased plasma volume).
- The presentation depends on the predominant catecholamine secreted by the tumor together with the pattern of release. Noradrenaline-secreting tumors tend to cause sustained hypertension, whereas tumors secreting adrenaline and noradrenaline often cause episodic hypertension. Rarely, dopamine-secreting tumors can cause hypotension.
- About 10 % of tumors are discovered incidentally on abdominal imaging undertaken for other reasons.
- Clinical signs are usually absent.

Assessment

- Assessment of blood pressure and cardiovascular status (including evidence of arrhythmias or left ventricular failure).
- Check for evidence of hypercalcemia and glucose intolerance.
- Screening for pheochromocytomas should be considered in:
  - Patients of a young age with hypertension
  - Patients with unexplained heart failure
  - Patients with classic episodic symptoms
  - Those with adrenal incidentalomas
  - Patients with a family history of von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia (MEN) 2A or 2B, type 1 neurofibromatosis (NF1), or inherited paraganglioma syndrome (due to mutation in one of the succinate dehydrogenase (*SDH*) genes)

Diagnosis

- Biochemical confirmation of elevated catecholamines and/or their metabolites is required.
- Measurement of plasma or urinary metanephrines (99 and 97 % sensitive) and plasma or urinary catecholamines (86 and 84 % sensitive) have superseded urinary vanillylmandelic acid (72 % sensitive).
- More than one measurement may be required because of intermittent tumor secretion.
- False positive results can occur with sympathomimetics, phenoxybenzamine, tricyclic antidepressants, and other drugs (Table 1.2).
- The initial imaging test of choice is CT or MRI of the abdomen/adrenals.
- If a tumor is not localized, ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scanning and/or whole body imaging with CT or MRI is indicated.
- Ultrasound scanning is useful for surveillance of the neck in patients with inherited paraganglioma syndromes (due to mutations in the *SDHC* and *SDHD* genes).
- In special circumstances positron emission tomography may be indicated (see Chap. 4).

Table 1.2 Drugs known to increase catecholamine and metanephrine concentrations

Levodopa
Adrenergic receptor agonists, e.g., decongestants such as phenylephrine and ephedrine
Tricyclic antidepressants
Amphetamines
Buspirone and most psychoactive drugs
Prochlorperazine
Reserpine
Withdrawal from clonidine
Ethanol
Paracetamol (may interfere with plasma metanephrine assays)

- Up to 30 % of patients with pheochromocytoma/paraganglioma have a genetic cause for their disease (see Chap. 4). This is more likely in young patients (<50 years) or those presenting with malignant, bilateral, or extra-adrenal disease. Such patients should be referred for genetic testing.

Adrenal Incidentaloma

Presentation

- Defined as an adrenal tumor not suspected prior to the imaging procedure that led to its discovery.
- Overall 4 % prevalence, increasing to 7 % over the age of 70 years.
- At the time of diagnosis, up to 20 % of all incidentalomas may be endocrinologically active.

Assessment

- Larger tumors are more likely to be malignant, especially >6 cm diameter.
- The likelihood of endocrine overactivity increases with increasing size of the mass, except for aldosterone-producing adenomas with hypertension (typically <1 cm).
- Assessment should include examination for symptoms and signs of hormone excess and extra-adrenal malignancy.
- Questions for consideration are:
  - Is this an adrenal or extra-adrenal mass?
  - Is the adrenal mass a metastasis of a primary tumor?
  - Is the mass hormonally active?
  - Is there evidence of adrenocortical carcinoma (ACC)? The incidence of ACC at presentation is very low as is development with follow-up.

Diagnosis

- Biochemical evaluation should include:
  - Overnight dexamethasone suppression test
  - Measurement of renal function and electrolytes
  - ARR if hypertensive
  - Plasma or urinary metanephrines/catecholamines
- Urine steroid metabolomics may offer a novel, highly sensitive, and specific biomarker for distinguishing benign from malignant adrenal tumors but is not yet widely available.
- Measurement of Hounsfield units (HU) in an unenhanced CT is helpful in distinguishing benign from malignant disease. A threshold value of 10 HU has sensitivity and specificity for characterizing a lesion as benign of 71 and 98 %, respectively. Incidentalomas with >10 HU attenuation on unenhanced CT require more detailed review.
- Patients with a nonfunctioning adrenal mass should undergo follow-up CT or MRI at 6 months.
- Endocrinologically active tumors, tumors >4 cm, tumors showing imaging characteristics of malignancy (e.g., vascular invasion, lack of well-demarcated margins), and tumors showing significant growth should be removed.
- Patients with mild glucocorticoid autonomy ("subclinical Cushing's") should be assessed for possible complications related to cortisol excess (e.g., hypertension, type 2 diabetes, osteoporosis), and a decision on the need for surgery should be made on a case-by-case basis, in the absence of a robust evidence base with which to inform management.

Adrenocortical Carcinoma (ACC) (See Chap. 5)

Presentation

- Bimodal age distribution – children under 5 and adults 30–40 years old.
- In children most tumors are functional and may present with symptoms and signs of virilization, Cushing's syndrome, and precocious puberty.
- In adults, the most common presentation is rapidly progressing Cushing's syndrome, with or without virilization.
- In women, androgen-secreting ACCs may cause hirsutism, virilization, male-pattern baldness, and deepening of the voice.
- In males, rare estrogen-secreting adrenal tumors are invariably malignant and present with gynecomastia/testicular atrophy.
- Nonfunctional ACCs may present with abdominal/flank pain from local invasion or rarely may be detected incidentally.
- Occasionally patients may present with weight loss and fever.

Assessment

- Assess for signs and symptoms of Cushing's syndrome, virilization in women, Conn's syndrome (rare), or feminization in men (rare).

Diagnosis

- Biochemical assessment for evidence of glucocorticoid (see section on Cushing's syndrome), mineralocorticoid (see section on Conn's syndrome), or sex steroid excess, as well as metanephrine/catecholamine measurement.
- Measure sex steroids and steroid precursors including dehydroepiandrosterone-sulfate (DHEAS), 17-hydroxyprogesterone, androstenedione, testosterone, and 17-beta estradiol (latter only in men and postmenopausal women).
- CT or MRI: ACCs are typically >6 cm in size, heterogeneous with necrosis and calcification, and show evidence of local invasion. However, appearances are often nonspecific and may not discriminate from pheochromocytoma or extra-adrenal malignancy.
- ^{18}F-FDG PET scanning may provide additional information to define malignant potential, but this is not specific.
- High-resolution CT of the chest should also be performed prior to surgery to assess for the presence of metastases.
- Biopsy is rarely required and should never be undertaken without prior exclusion of a pheochromocytoma. A biopsy is not indicated in patients with an isolated adrenal mass due to the risks of needle-track metastasis and the difficulty in distinguishing benign from malignant pathology. A diagnostic biopsy may be required if the presence of extensive metastases precludes surgery or if malignant disease elsewhere raises the possibility of a non-adrenal primary tumor.
- Pathological assessment should be performed by an experienced pathologist.

Pearls and Pitfalls
Pearls

- Liaise closely with endocrinologists when assessing and diagnosing adrenal disease
- Beware of false-positive test results when investigating adrenal disorders
- A combination of biochemical and radiological investigations is usually required to make an accurate diagnosis of an adrenal lesion
- Do not presume that an adrenal adenoma is the cause of primary hyperaldosteronism without undertaking lateralization studies
- Cushing's syndrome should be approached with two questions: Is hypercortisolism present? What is the cause of hypercortisolism?

- Never proceed to surgery or biopsy of an adrenal mass without prior exclusion of a pheochromocytoma
- PET scanning using new tracers and urinary steroid metabolomics are emerging as novel tools in assessing the nature of adrenal lesions

Pitfalls

- All patients with paraganglioma and young patients (<50 years) with pheochromocytoma should undergo genetic testing for mutations in relevant susceptibility genes
- Preoperative medical preparation is often required in advance of adrenal surgery and is mandatory in patients with paraganglioma or pheochromocytoma

Further Reading

Burton TJ, Mackenzie IS, Balan K, Koo B, Bird N, Soloviev DV, Azizan EA, Aigbirhio F, Gurnell M, Brown MJ. Evaluation of the sensitivity and specificity of (11)C-metomidate positron emission tomography (PET)-CT for lateralizing aldosterone secretion by Conn's adenomas. J Clin Endocrinol Metab. 2012;97(1):100–9.

Lacroix A. Approach to the patient with adrenocortical carcinoma. J Clin Endocrinol Metab. 2010;95:4812–22.

Mulatero P, Monticone S, Bertello C, Tizzani D, Iannaccone A, Crudo V, Veglio F. Evaluation of primary aldosteronism. Curr Opin Endocrinol Diabetes Obes. 2010;17(3):188–93.

Nieman LK. Approach to the patient with an adrenal incidentaloma. J Clin Endocrinol Metab. 2010;95(9):4106–13.

Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93(5):1526–40.

Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D, Fishman E, Kharlip J, American Association of Clinical Endocrinologists, American Association of Endocrine Surgeons. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract. 2009;15 Suppl 1:1–20.

Chapter 2
Cushing's Disease and Syndrome

Thomas W.J. Lennard

Definition

Cushing's is characterized by increased levels of circulating glucocorticoids. There are two types:

- ACTH dependent due to either pituitary or ectopic ACTH secretion
- ACTH independent due to an autonomous adrenal excess production of corticosteroids from the zona fasciculata
  - 50 % benign adenoma
  - 50 % adrenocortical carcinoma (ACC)

The majority of patients (80 %) have ACTH (pituitary driven) dependent Cushing's disease.

Epidemiology

- A rare entity with a prevalence of ten cases per million of the population per year
- Peak presentation at 20–40 years
- More common in women

Clinical features of the disease include:

- Truncal obesity and limb muscle wasting ("lemon on sticks").
- Facial plethora.
- Hirsutism.

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J.C. Watkinson, D.M. Scott-Coombes (eds.), *Tips and Tricks in Endocrine Surgery*,
DOI 10.1007/978-1-4471-2146-6_2,