02 - 388 Approach to the Patient with Endocrine Disorders

388 Approach to the Patient with Endocrine Disorders

Section 1 Endocrinology J. Larry Jameson

Approach to the

Patient with Endocrine

Disorders The management of endocrine disorders has applied principles of precision medicine before the term was commonly used (Chap. 5). A general goal is to maintain or restore homeostasis using precise homone measurements to titrate treatment regimens. Effective patient management requires a broad understanding of intermediary metabo lism, reproductive physiology, bone metabolism, and growth. Accord ingly, the practice of endocrinology is intimately linked to a conceptual framework for understanding hormone secretion, hormone action, and principles of feedback control (Chap. 389). The endocrine system is evaluated primarily by measuring hormone concentrations, arming the clinician with valuable diagnostic information. Most disorders of the endocrine system are amenable to effective treatment once the cor rect diagnosis is established. Endocrine deficiency disorders are treated with physiologic hormone replacement; hormone excess conditions, which usually are caused by benign glandular adenomas, are managed by removing tumors surgically or reducing hormone levels medically. SCOPE OF ENDOCRINOLOGY Classically, the specialty of endocrinology encompasses the study of glands and the hormones they produce. Over time, the field has expanded because of the discovery of hormones and growth factors produced by the brain, gastrointestinal (GI) tract, musculoskeletal system, and other nonglandular organs. The term endocrine was coined by Starling to contrast the actions of hormones secreted internally (endocrine) with those secreted externally (exocrine) or into a lumen, such as the GI tract. The term hormone, derived from a Greek phrase meaning “to set in motion,” aptly describes the dynamic actions of hormones as they elicit cellular responses and regulate physiologic processes through feedback mechanisms. Unlike many other specialties in medicine, it is not possible to define endocrinology strictly along anatomic lines. The classic endocrine

glands—pituitary, thyroid, parathyroid, pancreatic islets, adrenals, and gonads—communicate broadly with other organs through the nervous system, hormones, cytokines, and growth factors. In addition to its traditional synaptic functions, the brain produces a vast array of peptide hormones, and this has led to the discipline of neuroendo crinology. Through the production of hypothalamic releasing factors, the central nervous system (CNS) exerts a major regulatory influence over pituitary hormone secretion (Chap. 390). The peripheral nervous system stimulates the adrenal medulla. The immune and endocrine systems are also intimately intertwined. The adrenal hormone cortisol is a powerful immunosuppressant. Cytokines and interleukins (ILs) have profound effects on the functions of the pituitary, adrenal, thy roid, and gonads. Common endocrine diseases such as autoimmune thyroid disease and type 1 diabetes mellitus are caused by dysregulation of immune surveillance and tolerance. Less common diseases such as polyglandular failure, Addison's disease, and lymphocytic hypophysitis also have an immunologic basis. Immune therapies for cancer and vari ous autoimmune diseases can initiate autoimmune endocrine disease as a side effect of treatment. The interdigitation of endocrinology with physiologic processes in other specialties sometimes blurs the role of hormones. For example, hormones play an important role in maintenance of blood pressure,

Endocrinology and Metabolism PART 12 intravascular volume, and peripheral resistance in the cardiovascular system. Vasoactive substances such as catecholamines, angiotensin II, endothelin, and nitric oxide are involved in dynamic changes of vascu lar tone in addition to their multiple roles in other tissues. The heart is the principal source of atrial natriuretic peptide, which acts in classic endocrine fashion to induce natriuresis at a distant target organ (the kidney). Erythropoietin, a traditional circulating hormone, is made in the kidney and stimulates erythropoiesis in bone marrow (Chap. 66). The kidney is also integrally involved in the renin-angiotensin axis (Chap. 398) and is a primary target of several hormones, including parathyroid hormone (PTH), mineralocorticoids, fibroblast growth factor 23 (FGF23), and vasopressin. The GI tract produces a vast array of peptide hormones, such as glucagon-like peptide 1 (GLP1), chole cystokinin, ghrelin, gastrin, secretin, and vasoactive intestinal peptide, among many others. Carcinoid and islet tumors can secrete excessive amounts of these hormones, leading to specific clinical syndromes (Chap. 89). Many of these GI hormones are also produced in the CNS, where their functions are poorly understood. Adipose tissue produces leptin, which acts centrally to control appetite, along with adiponectin, resistin, and other hormones that regulate metabolism. As hormones such as inhibin, ghrelin, and leptin are discovered, they become inte grated into the science and practice of medicine on the basis of their functional roles rather than their tissues of origin. Characterization of hormone receptors frequently reveals unex pected relationships to factors in nonendocrine disciplines. The growth hormone (GH) and leptin receptors, for example, are members of the cytokine receptor family. The G protein–coupled receptors (GPCRs), which mediate the actions of many peptide hormones, are used in numerous physiologic processes, including vision, smell, and neurotransmission. PATHOLOGIC MECHANISMS OF ENDOCRINE DISEASE Endocrine diseases can be divided into three major types of condi tions: (1) hormone excess, (2) hormone deficiency, and (3) hormone resistance (Table 388-1). ■ ■CAUSES OF HORMONE EXCESS Syndromes of hormone excess can be caused by neoplastic growth of endocrine cells, autoimmune disorders, and excess hormone admin istration. Benign endocrine tumors, including parathyroid, pituitary, and adrenal adenomas, often retain the capacity to produce hormones, reflecting the fact that these tumors are relatively well differentiated. Many endocrine tumors exhibit subtle defects in their "set points" for feedback regulation. For example, in Cushing's disease, impaired feed back inhibition of

adrenocorticotropic hormone (ACTH) secretion is associated with autonomous function. However, the tumor cells are less sensitive to feedback inhibition, as evidenced by ACTH suppression at higher doses of dexamethasone (e.g., high-dose dexamethasone test) (Chap. 398). Similar set point defects are also typical of parathyroid adenomas and autonomously functioning thyroid nodules. The molecular basis of some endocrine tumors, such as the multiple endocrine neoplasia (MEN) syndromes (MEN1, 2A, 2B), has provided important insights into tumorigenesis (Chap. 402). MEN1 is char acterized primarily by the triad of parathyroid, pancreatic islet, and pituitary tumors. MEN2 predisposes to medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. The MEN1 gene, located on chromosome 11q13, encodes a tumor-suppressor gene, menin. Analogous to the paradigm first described for retinoblastoma, the affected individual inherits a mutant copy of the MEN1 gene, and tumorigenesis ensues after a somatic “second hit” leads to loss of func tion of the normal MEN1 gene (through deletion or point mutations). In contrast to inactivation of a tumor-suppressor gene, as occurs in MEN1 and most other inherited cancer syndromes, MEN2 is caused by activating mutations in a single allele. In this case, activating mutations of the RET protooncogene, which encodes a receptor tyrosine kinase,

TABLE 388-1 Causes of Endocrine Dysfunction TYPE OF ENDOCRINE DISORDER EXAMPLES Hyperfunction Neoplastic Benign Malignant Ectopic Genetic predisposition Autoimmune Iatrogenic Infectious/inflammatory Activating receptor mutations Pituitary adenomas, hyperparathyroidism, autonomous thyroid or adrenal nodules Adrenal cancer, medullary thyroid cancer, carcinoid Ectopic ACTH, SIADH secretion MEN1, MEN2 Graves’ disease Cushing’s syndrome, hypoglycemia Subacute thyroiditis LH, TSH, Ca2+, PTH receptors, Gsα PART 12 Endocrinology and Metabolism Hypofunction Autoimmune Iatrogenic Infectious/inflammatory Hormone mutations Enzyme defects Developmental defects Nutritional/vitamin deficiency Hemorrhage/infarction Hashimoto’s thyroiditis, type 1 diabetes mellitus, Addison’s disease, polyglandular failure Radiation-induced hypopituitarism, hypothyroidism, surgical Adrenal insufficiency, hypothalamic sarcoidosis GH, LHβ, FSHβ, vasopressin 21-Hydroxylase deficiency Kallmann’s syndrome, Turner’s syndrome, transcription factors Vitamin D deficiency, iodine deficiency Sheehan’s syndrome, adrenal insufficiency Hormone Resistance Receptor mutations Membrane Nuclear Signaling pathway mutations Postreceptor GH, vasopressin, LH, FSH, ACTH, GnRH, GHRH, PTH, leptin, Ca2+ AR, TR, VDR, ER, GR, PPARγ Albright’s hereditary osteodystrophy Type 2 diabetes mellitus, leptin resistance Abbreviations: ACTH, adrenocorticotropic hormone; AR, androgen receptor; ER, estrogen receptor; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; GR, glucocorticoid receptor; LH, luteinizing hormone; MEN, multiple endocrine neoplasia; PPAR, peroxisome proliferator activated receptor; PTH, parathyroid hormone; SIADH, syndrome of inappropriate antidiuretic hormone; TR, thyroid hormone receptor; TSH, thyroidstimulating hormone; VDR, vitamin D receptor. lead to thyroid C-cell hyperplasia in childhood before the develop ment of medullary thyroid carcinoma. Elucidation of this pathogenic mechanism has allowed early genetic screening for RET mutations in individuals at risk for MEN2, permitting identification of those who may benefit from prophylactic thyroidectomy and biochemical screen ing for pheochromocytoma and hyperparathyroidism. Mutations that activate hormone receptor signaling have been identified in several GPCRs. For example, activating mutations of the luteinizing hormone (LH) receptor cause a dominantly transmitted form of male-limited precocious puberty, reflecting premature stimu lation of testosterone synthesis in Leydig cells (Chap. 403). Activating mutations in these GPCRs are located predominantly in the trans membrane domains and induce receptor coupling to Gsα even

in the absence of hormone. Consequently, adenylate cyclase is activated, and cyclic adenosine monophosphate (AMP) levels increase in a manner that mimics hormone action. A similar phenomenon results from acti vating mutations in Gsα. When these mutations occur early in develop ment, they cause McCune-Albright syndrome. When they occur only in somatotropes, the activating Gsα mutations cause GH-secreting tumors and acromegaly (Chap. 392). In autoimmune Graves' disease, antibody interactions with the thyroid-stimulating hormone (TSH) receptor mimic TSH action, lead ing to hormone overproduction (Chap. 394). Analogous to the effects of activating mutations of the TSH receptor, these stimulating auto antibodies induce conformational changes in the TSH receptor that release it from a constrained state, thereby triggering receptor coupling to G proteins, and signaling induces excess thyroid hormone synthesis and secretion. ■ ■CAUSES OF HORMONE DEFICIENCY Most examples of hormone deficiency states can be attributed to glandular destruction caused by autoimmunity, surgery, infection, inflammation, infarction, hemorrhage, or tumor infiltration (Table 388-1). Autoimmune damage to the thyroid gland (Hashimoto's thyroiditis)

and pancreatic islet β cells (type 1 diabetes mellitus) are examples of relatively common endocrine diseases. Mutations in a number of hor mones, hormone receptors, transcription factors, enzymes, and chan nels can also lead to hormone deficiencies. ■ ■HORMONE RESISTANCE Most severe hormone resistance syndromes are due to inherited defects in membrane receptors, nuclear receptors, or the pathways that transduce receptor signals. These disorders are characterized by defective hormone action despite the presence of increased hormone levels. In complete androgen resistance, for example, mutations in the androgen receptor result in a female phenotypic appearance in genetic (XY) males, even though LH and testosterone levels are increased (Chap. 402). In addition to these relatively rare genetic disorders, more common acquired forms of functional hormone resistance include insulin resistance in type 2 diabetes mellitus, leptin resistance in obesity, and GH resistance in catabolic states. The pathogenesis of functional resistance involves receptor downregulation and postrecep tor desensitization of signaling pathways; functional forms of resis tance are generally reversible. ■ ■CLINICAL EVALUATION OF ENDOCRINE DISORDERS Because most glands are relatively inaccessible, the physical exami nation usually focuses on the manifestations of hormone excess or deficiency as well as direct examination of palpable glands, such as the thyroid and gonads. For these reasons, it is important to evaluate patients in the context of their presenting symptoms, review of systems, family and social history, and exposure to medications that may affect the endocrine system. Astute clinical skills are required to detect subtle symptoms and signs suggestive of underlying endocrine disease. For example, a patient with Cushing's syndrome may manifest specific findings, such as central fat redistribution, skin striae, and proximal muscle weakness, in addition to features seen commonly in the general

population, such as obesity, plethora, hypertension, and glucose intol erance. Similarly, the insidious onset of hypothyroidism—with fatigue, mental slowing, dry skin, and other features—can be difficult to dis tinguish from similar, nonspecific findings in the general population. Clinical judgment that is based on knowledge of disease prevalence TABLE 388-2 Examples of Prevalent Endocrine and Metabolic Disorders in the Adult DISORDER APPROXIMATE PREVALENCE IN ADULTSa SCREENING/TESTING RECOMMENDATIONSb CHAPTER(S) Obesity 40% Obese, BMI ≥30 70% Overweight, BMI ≥25 Type 2 diabetes mellitus

> 10% Beginning at age 45, screen every 3 years, or earlier in high-risk groups: FPG >126 mg/dL Random plasma glucose >200 mg/dL An elevated HbA1c Consider comorbid complications Hyperlipidemia 20–25% Cholesterol screening at least every 5 years; more often in high-risk groups Lipoprotein analysis (LDL, HDL) for increased cholesterol, CAD, diabetes Consider secondary causes Metabolic syndrome 35% Measure waist circumference, FPG, BP, lipids

Hypothyroidism 5–10%, women 0.5–2%, men Graves' disease 1–3%, women 0.1%, men Thyroid nodules and neoplasia 2–5% palpable

> 25% by ultrasound Osteoporosis 5–10%, women 2–5%, men Hyperparathyroidism 0.1–0.5%, women > men Serum calcium PTH, if calcium is elevated Assess comorbid conditions Infertility 10%, couples Investigate both members of couple Semen analysis in male Assess ovulatory cycles in female Specific tests as indicated Polycystic ovarian syndrome 5–10%, women Free testosterone, DHEAS Consider comorbid conditions Hirsutism 5–10% Free testosterone, DHEAS Exclude secondary causes Additional tests as indicated Menopause Median age, 51 FSH

Hyperprolactinemia 15% in women with amenorrhea or galactorrhea Erectile dysfunction 10–25% Careful history, PRL, testosterone Consider secondary causes (e.g., diabetes) Hypogonadism, male 1–2% Testosterone, LH

Gynecomastia 15% Often, no tests are indicated Consider Klinefelter's syndrome Consider medications, hypogonadism, liver disease Klinefelter's syndrome 0.2%, men Karyotype Testosterone Vitamin D deficiency 10% Measure serum 25-OH vitamin D Consider secondary causes Turner's syndrome 0.03%, women Karyotype Consider comorbid conditions aThe prevalence of most disorders varies among ethnic groups and with aging. Data based primarily on U.S. population. bSee individual chapters for additional information on evaluation and treatment. Early testing is indicated in patients with signs and symptoms of disease and in those at increased risk. Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; DHEAS, dehydroepiandrosterone; FPG, fasting plasma glucose; FSH, folliclestimulating hormone; HbA1C, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; MRI, magnetic resonance imaging; PRL, prolactin; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

and pathophysiology is required to decide when to embark on more extensive evaluation of these disorders. Laboratory testing plays an essential role in endocrinology by allowing quantitative assessment of hormone levels and dynamics. Radiologic imaging tests such as computed tomography (CT) scan, magnetic resonance imaging (MRI),

Calculate BMI Measure waist circumference Exclude secondary causes Consider comorbid complications

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TSH; confirm with free T4

TSH, free T4

Physical examination or ultrasound of thyroid Fine-needle aspiration biopsy

Bone mineral density measurements in women >65 years or in postmenopausal women or men at risk Exclude secondary causes

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PRL level MRI, if not medication-related

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