Hypopituitarism

Chapter 391 | Harrison's 22e | Part 12 – Endocrinology & Metabolism | DETAILED EDITION

KEY CLINICAL POINTS

1. See source text for full details

FIGURES IN THIS CHAPTER

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PART

12

Endocrinology

and

Metabolism

TABLE 391-1 Etiology of Hypopituitarisma

391 Hypopituitarism

Development/structural

Midline cerebral defect syndromes

Shlomo Melmed, J. Larry Jameson

Pituitary dysplasia/aplasia

Primary empty sella

Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi

Deficient production of anterior pituitary hormones leads to features syndrome, Bardet-Biedl syndrome, Kallmann syndrome)

of hypopituitarism. Impaired production of one or more of the anterior Congenital central nervous system mass, encephalocele

pituitary trophic hormones can result from inherited disorders; more Genetic

commonly, adult hypopituitarism is acquired and reflects the com-

Combined pituitary hormone deficiencies

pressive mass effects of tumors or the consequences of local pituitary

Isolated primary hormone deficiencies

or hypothalamic traumatic, autoimmune, inflammatory, or vascular

Traumatic

damage. These processes also may impair synthesis or secretion of

Surgical resection

hypothalamic hormones, with resultant pituitary failure (Table 391-1).

Radiotherapy damage

DEVELOPMENTAL CAUSES OF HYPOPITUITARISM Head injuries

Pituitary dysplasia may result in aplastic, hypoplastic, or ectopic Neoplastic

pituitary gland development. Because pituitary development follows Pituitary adenoma

midline cell migration from the nasopharyngeal Rathke's pouch, mid- Parasellar mass (germinoma, ependymoma, glioma)

line craniofacial disorders may be associated with pituitary dysplasia.

Rathke's cyst

Acquired pituitary failure in the newborn also can be caused by birth

Craniopharyngioma

trauma, including cranial hemorrhage, asphyxia, and breech delivery. Hypothalamic hamartoma, gangliocytoma

A large number (>50) of transcription factors and growth factors are

Pituitary metastases (breast, lung, colon carcinoma)

critical for the development of the hypothalamus and pituitary gland

Lymphoma and leukemia

and the function of differentiated anterior pituitary cell lineages. Muta-

tions have been described in the HESX1, SOX2, SOX3, LHX3, LHX4, Meningioma

OTX, GLI2, PAX6, BMP4, ARNT2, FGF8, FGFR1, SHH, PROKR2, Infiltrative/inflammatory

GPR161, IGSF1, PITX2, and CHD7 genes, among others. Heterozygous Lymphocytic hypophysitis

loss-of-function or autosomal recessive mutations disrupt hypothalamic Hemochromatosis

and pituitary development at different developmental stages, causing a Sarcoidosis

wide array of phenotypes ranging from severe syndromic midline and Histiocytosis X

other defects to combined pituitary hormone defects or isolated hor- Granulomatous hypophysitis

mone deficiencies. Depending on the gene involved, the pituitary may

Transcription factor antibodies

be hypoplastic, hyperplastic, or ectopic. Midline defects include variable

Immunotherapy

combinations of abnormal development of the eyes, corpus collosum,

Vascular

vertebrae, and genital systems. Pituitary dysfunction ranges from iso-

Pituitary apoplexy

lated hormone deficiency to combined pituitary hormone deficiency

Pregnancy-related (infarction with diabetes; postpartum necrosis)

(CPHD) and arginine vasopressin deficiency (AVP-D).

In addition to these syndromic developmental disorders, some Subarachnoid hemorrhage

mutations affect specific pituitary cell lineages. For example, Pit-1 Sickle cell disease

mutations cause combined growth hormone (GH), prolactin (PRL), Arteritis

and thyroid-stimulating hormone (TSH) deficiencies. These patients Snake bite venom

usually present with growth failure and varying degrees of hypothy- Infections

roidism. The pituitary may appear hypoplastic on magnetic resonance Fungal (histoplasmosis)

imaging (MRI). Prop-1 is expressed early in pituitary development Parasitic (toxoplasmosis)

and appears to be required for Pit-1 function. Familial and sporadic

Tuberculosis

PROP1 mutations result in combined GH, PRL, TSH, and gonado-

Pneumocystis jirovecii

tropin deficiency. Over 80% of these patients have growth retarda-

Drug-induced

tion; by adulthood, all are deficient in TSH and gonadotropins, and

CTLA-4 inhibitors

a small minority later develop adrenocorticotropic hormone (ACTH)

PD-1/PD-L1 inhibitors

deficiency. Because of gonadotropin deficiency, these individuals do

not enter puberty spontaneously. In some cases, the pituitary gland aTrophic hormone failure associated with pituitary compression or destruction

appears enlarged on MRI. TPIT mutations result in ACTH deficiency usually occurs sequentially: growth hormone > follicle-stimulating hormone >

luteinizing hormone > thyroid-stimulating hormone > adrenocorticotropic hormone.

associated with hypocortisolism. Mutations in NR5A1 (also known as

During childhood, growth retardation is often the presenting feature, and in adults,

steroidogenic factor 1 [SF1]) impair development of gonadotropes, as hypogonadism is the earliest symptom.

well as adrenal/gonadal development. Abbreviations: CTLA-4, cytotoxic T lymphocyte antigen 4; PD-1, programmed cell

death protein 1; PD-L1, programmed cell death protein ligand 1.

HYPOTHALAMIC ENDOCRINE DYSFUNCTION

Hypothalamic disorders can affect temperature regulation, appetite,

such as mirror movements. The initial genetic cause was the X-linked

sleep-wake cycles, autonomic systems, behavior, and memory, as well

KAL gene, mutations of which impair embryonic migration of GnRH

as multiple endocrine systems. Selected examples of hypothalamic dis-

neurons from the hypothalamic olfactory placode to the hypothala-

orders that affect the endocrine system are described below.

mus. Since then, more than a dozen additional genetic abnormalities,

Kallmann Syndrome Kallmann syndrome results from defective in addition to KAL mutations, have been found to cause isolated

hypothalamic gonadotropin-releasing hormone (GnRH) synthesis and GnRH deficiency. Autosomal recessive (i.e., GPR54, KISS1) and

is associated with anosmia or hyposmia due to olfactory bulb agenesis dominant (i.e., FGFR1) modes of transmission have been described,

or hypoplasia (Chap. 403). Classically, the syndrome may also be asso- and there is a growing list of genes associated with GnRH deficiency

ciated with color blindness, optic atrophy, nerve deafness, cleft palate, (including GNRH1, PROK2, PROKR2, CHD7, PCSK1, FGF8, NELF,

renal abnormalities, cryptorchidism, and neurologic abnormalities WDR11, TAC3, TACR3, and SEMA3E). Some patients have oligogenic

[TABLE]

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syndrome, Bardet-Biedl syndrome, Kallmann syndrome)

Congenital central nervous system mass, encephalocele

Genetic

Combined pituitary hormone deficiencies

Isolated primary hormone deficiencies

Traumatic

Surgical resection

Radiotherapy damage

Head injuries

Neoplastic

Pituitary adenoma

Parasellar mass (germinoma, ependymoma, glioma)

Rathke’s cyst

Craniopharyngioma

Hypothalamic hamartoma, gangliocytoma

Pituitary metastases (breast, lung, colon carcinoma)

Lymphoma and leukemia

Meningioma

Infiltrative/inflammatory

Lymphocytic hypophysitis

Hemochromatosis

Sarcoidosis

Histiocytosis X

Granulomatous hypophysitis

Transcription factor antibodies

Immunotherapy

Vascular

Pituitary apoplexy

Pregnancy-related (infarction with diabetes; postpartum necrosis)

Subarachnoid hemorrhage

Sickle cell disease

Arteritis

Snake bite venom

Infections

Fungal (histoplasmosis)

Parasitic (toxoplasmosis)

Tuberculosis

Pneumocystis jirovecii

Drug-induced

CTLA-4 inhibitors

PD-1/PD-L1 inhibitors

[/TABLE]

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CHAPTER

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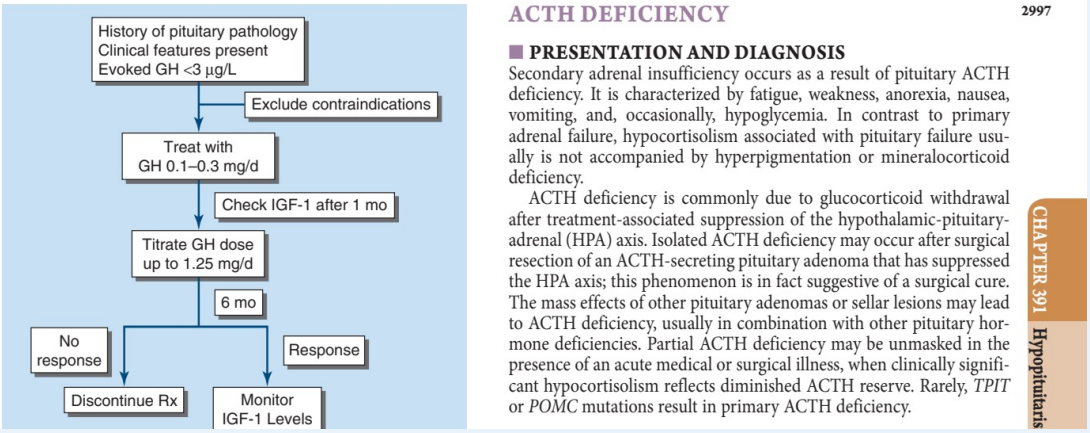
Hypopituitarism

mutations in which mutations in a combination of different genes lead hypothalamic and pituitary neuronal and neurochemical tracts. Con-

to the phenotype. Associated clinical features, in addition to GnRH sequently, AVP-D is a common presentation, reported in half of

deficiency, vary depending on the genetic cause. GnRH deficiency patient

FLOWCHARTS & ALGORITHMS — FROM HARRISON'S



Harrison's 22e · Flowchart 1

FIGURE 391-1 Management of adult growth hormone (GH) deficiency. IGF, insulin- like growth factor; Rx, treatment.