PITUITARY DEFICIENCY (HYPOPITUITARISM)

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Definition

- Decrease or absent secretion of anterior pituitary hormones by primitive pituitary lesion or absence of hypothalamic-pituitary stimulatory hormones (hypothalamo-pituitary insufficiency).
  1914 - Simmonds made the first anatomo-clinical description of cachexia in panhypopituitarism. .
  1937 - Sheehan described the multiple/isolated postpartum pituitary insufficiency of the anterior pituitary lobe.

- Nomenclature: anterior pituitary insufficiency, adenohypophyseal insufficiency, hypopituitarism.

- Panhypopituitarism reflects an anterior pituitary insufficiency and diabetes insipidus.

- Frequency: In adults, it is more common in females than in males

Etiology

- A useful mnemonic device is the phrase

"9 I's" (according to Greenspan)

1. Invasive processes: - pituitary tumors, craniopharyngioma, metastatic tumors, CNS tumors – meningioma, optic glioma, epidermoid, carotid aneurism, basal encephalocele

2. Infarction: - postpartum necrosis (Sheehan's syndrome), pituitary apoplexy

- 3. Infiltrative processes: - sarcoidosis, hemochromatosis, histiocytosis X (Hand-Schuller-Christian), eosinophilic granuloma.
- 4. Injury: - head trauma
- 5. Immunologic: - lymphocytic hypophysitis
- 6. Iatrogenic: - surgery or radiotherapy
- 7. Infectious: - mycotic infections, tuberculosis, syphilis
- 8. Idiopathic: - familial
- 9. Isolated: - GH, LH, FSH, TSH, ACTH or PRL deficiency

Clinical features

- Clinical symptoms are related to peripheral glands insufficiency due to the absence of pituitary stimulation.
- Most commonly, growth hormone (GH) is lost first, then gonadotropins, and finally thyroid-stimulating hormone (TSH) and ACTH.
- ADH deficiency is rare in primary pituitary disease but is common with stalk and hypothalamic lesions.
- Function of all target glands decreases when all hormones are deficient (panhypopituitarism).

a) onset: - insidious or - slowly progressive, usually unknown

- pale skin (without anemia)
- deficient or absent hair
- weakness
- cold intolerance
- mental dullness
- decreased libido

Symptoms: *Thyrotropin deficiency (TSH)*

- slowed down metabolism (hypothyroidism) but with
- fine, uninfiltrated skin
- deficient, shedding hair
- absence of axillary perspiration
- cold intolerance

Corticotrope- melanocyte deficiency (ACTH + MSH)

- asthenia, fatigue
- decreased muscle strength
- hypotension
- digestive disturbances
- weight loss
- skin depigmentation

ACTH deficiency results in hypoadrenalism, intolerance to stress and infection.

Gonadotropin deficiency (LH, FSH)

- Lack of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in children leads to delayed puberty.
- Premenopausal women develop amenorrhea, reduced libido, regression of secondary sexual characteristics, and infertility.
- Men develop erectile dysfunction, testicular atrophy, reduced libido, regression of secondary sexual characteristics, and decreased spermatogenesis with consequent infertility.

Gonadotropin deficiency (LH, FSH)

- F. - secondary amenorrhea, silent
  - breast atrophy
  - vulvo-vaginal atrophy
  - frigidity
- M. - testicular atrophy
  - decrease in beard growth
  - impotence

- GH deficiency may contribute to decreased energy but is usually asymptomatic and clinically undetectable in adults. tendency to develop hypoglycemia (accentuated by hypocorticism). Suggestions that GH deficiency accelerates atherosclerosis are unproved.

Prolactin deficiency (PRL)

- failure of postpartum lactation

- Hypothalamic lesions, which can result in hypopituitarism, can also disturb the centers that control appetite, causing a syndrome resembling anorexia nervosa, or sometimes hyperphagia with massive obesity.

Pituitary apoplexy

is a symptom complex caused by hemorrhagic infarction of either a normal pituitary gland or, more commonly, a pituitary tumor. Acute symptoms include severe headache, stiff neck, fever, visual field defects, and oculomotor palsies. The resulting edema may compress the hypothalamus, resulting in somnolence or coma. Varying degrees of hypopituitarism may develop suddenly, and the patient may present with vascular collapse because of deficient ACTH and cortisol. The CSF often contains blood, and MRI documents hemorrhage.

Biology

- *Thyrotrope deficiency:*
  - decreased T4
  - positive Querido test (TSH)
  - decreased or absent TSH
  - negative TRH test
- *Corticotrope deficiency* :
  - decreased cortisol, DHA, DHEA-S levels
  - decreased 11 OHCS, 17 KS, urine free cortisol levels
  - positive Synacthene tests
  - decreased ACTH

- Serum cortisol levels alone are not reliable indicators of ACTH-adrenal axis function. One of several provocative tests should be done. The **short ACTH stimulation test** is a safer and less labor-intensive test for cortisol deficiency than the insulin tolerance test. In the short ACTH stimulation test, synthetic ACTH 250 µg IV or IM (standard test) or 1 µg IV (low-dose test) is given, and the blood cortisol response is measured 30 and 60 min later. Cortisol should rise significantly; a peak of < 20 µg/dL is abnormal. However, the short ACTH stimulation test is abnormal in secondary cortisol deficiency only when done at least 2 to 4 wk after onset of the deficiency; before this time, the adrenal glands have not atrophied and remain responsive to exogenous ACTH.

- The **insulin tolerance test** is considered the most accurate way of evaluating ACTH (as well as GH and prolactin) reserve, but because of its demands, it is probably best reserved for patients who fail the short synacthen test or when a test must be done within 2 to 4 wk of a possible pituitary injury.
- Regular insulin at a dosage of 0.1 units/kg body weight IV is given over 15 to 30 sec, and venous blood samples are obtained to determine GH, cortisol, and glucose levels at baseline (before insulin administration) and 20, 30, 45, 60, and 90 min later. If glucose drops to < 40 mg/dL (< 2.22 mmol/L) or symptoms of hypoglycemia develop, cortisol should increase by > 7 µg/dL or to > 20 µg/dL. (Caution: *This test is hazardous in patients with severe documented panhypopituitarism or diabetes mellitus and in the elderly and is contraindicated in patients with coronary artery disease or epilepsy.* Usually, only transient perspiration, tachycardia, and nervousness occur. If the patient complains of palpitations, loses consciousness, or has a seizure, the test should be stopped promptly by giving 50 mL of 50% glucose solution IV.

- *Gonadotrope deficiency*:

F - atrophic vaginal smear

- plasma: decreased 17 estradiol and progesterone levels

M - oligoasthenospermia – azoospermia

- decreased plasma testosterone

- decreased urine 17 CS

In both sexes: - positive gonadotropin stimulation test

- low LH, FSH

- negative LH-RH test

- *Somatotrope deficiency*:
  - fasting hypoglycemia
  - decreased GH
  - negative GH-RH test
  - IGF-1 decreased
  - stimulatory tests

Prolactin deficiency :

  - decreased PRL
  - negative TRH test

Sheehan syndrome

- pituitary apoplexy of a nontumorous gland
- presumably due to postpartum arterial spasm of arterioles supplying the anterior pituitary and its stalk.
- In 1937, Sheehan reported 11 cases of women who died in the puerperium
- all of whom had necrosis of the anterior pituitary gland (adenohypophysis).
- Nine of the 11 cases had severe hemorrhage at delivery. The other 2 cases had no hemorrhage but were gravely ill prior to delivery

Sheehan syndrome

- Normally, the pituitary gland hypertrophies in pregnancy from diffuse nodular hyperplasia of prolactin secreting cells
- Usually, at least 1-2 liters of blood loss and hypovolemic shock
- 1-2% of women suffering significant postpartum hemorrhage
- inability to lactate after delivery due to prolactin deficiency occurs and amenorrhea due to gonadotrophin deficiency classically develops

Clinical features of Sheehan's syndrome include the following:

A history of postpartum hemorrhage so severe as to cause hypotension and require transfusion of multiple units of blood.

- When the hypopituitarism is severe, development of lethargy, anorexia, weight loss, and inability to lactate during the first days or weeks after delivery.
- When the hypopituitarism is less severe, failure of postpartum lactation and failure to resume menses in the weeks and months after delivery, and loss of sexual hair, as well as milder degrees of fatigue, anorexia, and weight loss.
- When the hypopituitarism is mild, possible delay in recognition for many years after the inciting event.

Loss of all anterior pituitary hormones. In two reports of a total of 48 women with Sheehan's syndrome due to severe postpartum hemorrhage, all patients had GH, prolactin, and gonadotropin deficiency, and the majority had TSH and ACTH deficiency.

- Rare development of overt diabetes insipidus, although subclinical vasopressin deficiency is common.
- Eventual development of a small pituitary within a sella of normal size, sometimes read as an “empty sella” on MRI.

Sheehan syndrome

- after delivery, shaved pubic hair or axillary pubic hair fails to regrow, and waxy skin depigmentation develops
- Signs of hypothyroidism and hypoadrenalism may develop
- posterior pituitary (neurohypophysis) involvement with diabetes insipidus may occur
- clinical presentation of acute pituitary apoplexy has only been reported case

Treatment

Hormone replacement therapy:

- a) *stimulines* - exclusively parenteral administration
- appearance of antistimulin antibodies
- high cost / reasons limiting their indication

Treatment of pituitary dificiency

- b) *peripheral replacement:* - hydrocortisone 10-30 mg/24 h or prednisone 5-15 mg/24 h
  - mineralocorticoid therapy is not required (mineralocorticoid function is preserved)
  - LT4 (L-thyroxine) - 100-200 mcg/24 h

F = estrogens and progesterone - artificial menses

M = long-acting testosterone 250 mg/15 days

Treatment is started with the administration of hydrocortisone because the initial administration of thyroid hormones may cause metabolism normalization and thus favor an acute adrenal insufficiency.

Hormone Replacement

Trophic Hormone Deficit	Hormone Replacement
ACTH	Hydrocortisone (10-20 mg A.M.; 10 mg P.M.) Cortisone acetate (25 mg A.M.; 12.5 mg P.M.) Prednisone (5 mg A.M.; 2.5 mg P.M.)
TSH	L-Thyroxine (0.075-0.15 mg daily)
FSH/LH	**Males** Testosterone enanthate (200 mg IM every 2 wks) Testosterone skin patch (5 mg/d) **Females** Conjugated estrogen (0.65-1.25 mg qd for 25days) Progesterone (5-10 mg qd) on days 16-25 Estradiol skin patch (0.5 mg, every other day) For fertility: Menopausal gonadotropins, human chorionic gonadotropins
GH	Adults: Somatotropin (0.3-1.0 mg SC qd) Children: Somatotropin [0.02-0.05 (mg/kg per day)]
Vasopressin	Intranasal desmopressin (5-20 ug twice daily) Oral 300-600 ug qd

Treatment

- Hormone replacement
- Treatment of cause (eg, tumor)

Adults ≤ 50 yr deficient in GH are now sometimes treated with GH doses of 0.002 to 0.012 mg/kg sc once/day. Benefits of treatment include improved energy and quality of life, increased body muscle mass, and decreased body fat mass. Suggestions that GH replacement can prevent an acceleration of atherosclerosis induced by GH deficiency are unproved.

PITUITARY DWARFISM

Somato-statural underdevelopment due to somatotrope hormone deficit in the child.

Children - normal birth length, height and weight

- gradual decrease in growth velocity = 1-3 cm/year; the deficit is more obvious after the age of 3

- height age is delayed for chronological age

- standard deviations (SD) range between -3 -8 for stature and -2 -4 for other sizes.

- morphogram: normally proportioned = harmonious dwarfism
  In acquired dwarfism - growth curve changes since the diagnosis is made.
  Prevalence: Pituitary dwarfism is rare.
  Frequency: l/3700 (Parkin)

  RO: 1/3000- 6000 deliveries
  It is more common in boys than in girls, ratio 7/1 - 3/1.

Etiopathogenesis

I.Abnormal gene –

- 1. deletion in the GH gene

  2. mutation in the gene regulating GH-RH synthesis with consequent impaired synthesis
  3. gene mutations on more chromosomes, hypothetically chromosome Y, fact explaining the higher frequency in boys

II.Malformations, congenial morphogenetic abnormalities also including malformations of GH-secreting cells and of the entire pituitary gland

Etiopathogenesis

III. Acquired lesion: tumoral, inflammatory, hypoxic

IV. Idiopathic dwarfism = 1/3 of the cases –

- -sensory deficit
- -mental deficit and/or EEG changes
- -low birth weight

V. Hereditary deficit = 1/3 of the cases with neonatal brain damage (Milcu) (breech presentation, coiling of rhe cord around the neck) without other neurological or psycho-intellectual outcomes.

VI. Craniopharyngioma = 60% of the cases develop dwarfism.

Etiopathogenesis

- *IGF-1 deficiency (Laron' s dwarfism)* which is due to a GH receptor gene mutation leading to impaired synthesis of IGF-1 in the liver (*GH resistance syndrome*)
- -*primary IGF-1 deficiency* due to mutations or deletions in the IGF-1 gene
- *-IGF-1 transport deficiency* due to mutations in IGFBP-3 or the acid-labile α-subunit
- *-IGF-1 resistance* due to IGF-1 re-ceptor mutations.

Clinical Manifestations of Pituitary Failure in Children

- *-short stature* (~≥-3SD *versus* children of same age, sex and race) with a final height of 1.10-1.20 m
- –*immature facial appearance* with small nose, micrognatia and retrognatia
- –*immature high-pitched voice*
- –occasionally *obesity*
- –*hypoglycemia*
- –*small internal organs* (liver, kidney, heart *etc.*), according to the height of the patient
- –*normal intelligence*

- ► if *gonadotropin deficiency* is associated → *microphallus* ± *cryptorchidism, sexual infantilism due to delayed/absent puberty*
- ►if *TSH deficiency* is associated → *hypothyroidism*
- ►if *ACTH deficiency* is associated → *hypoglycemia* is usually more severe, even leading to seizures; *hypotension* occurs.

Diagnosis of GH Deficiency in Children

- ►*hormones assays*
- -basal GH measurement is not enough to demonstrate GH deficiency but diagnosis of GH deficiency rests upon demonstration of an inadequate rise of *serum GH after provocative stimuli.* GH inadequate production has to be demonstrated by two independent tests.
- Several tests may be used:

  - GH assessment 2 hours after falling asleep

  - the *insulin tolerance test*, releavs inability of GH to rise above 10 ng/ml after *insulin-induced hypoglycemia*

  - the *GHRH test* - inability of GH to rise above 10 ng/ml after GHRH 1 μ/bw i.v.

  - exercise, ariginin or clonidin stimulation test

- *-low serum IGF-1 and IGFBP-3* (except for IGF-1 resistance where they are high)
- *-tests for diagnosis of gonadotropin, thyrotropin and corticotropin failure*
- ►*radiographs of the left hand and wrist* to assess bone age shows de-layed bone age and opened epiphyses after the age of 20.
- ►*MRI* – if hypotalamo-pituitary tumour is suspected.

Treatment of Pituitary Failure in Children

- Therapy is a complex *hormone replacement therapy* of deficient axes. GH deficiency is substituted with *human biosynthetic GH* produced by recombinant DNA technology. GH replacement therapy should start at the moment of diagnosis and should always precede replacement of sexual hormones – otherwise gonadal steroid replacement may advance bone age and lead to epiphysial fusion and a decrease in ultimate height. Eventually, sexual hormone replacement therapy should be started after the target height is reached.
- o recombinant human GH

  Norditropin®

  Somatropin®

  Genotropin®

  Omnitrope®

  0.02-0.035(0.045)mg/kg/d