Hypopituitarism: Diagnosis and management

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Definition of Hypopituitarism

- Failure of one or more pituitary hormones to be produced or secreted from the anterior or posterior pituitary
- Failure can be the result of any step in production, stimulation, secretion, regulation

Epidemiology of hypopituitarism

• First described in 1914
• Often chronic and progressive
• 4 out of 100,000 people per year are diagnosed
• Overall, 46 per 100,000 people are affected
• Often delayed diagnosis as initial clinical expression of hypopituitarism is often mild and nonspecific
• Significant health burden, especially from cardiovascular disease
Causes of hypopituitarism

• Masses
  o Pituitary adenoma
  o Meningiomas
  o Craniopharyngiomas
  o Cysts

• Treatment effect
  o Surgery
  o Radiotherapy
  o Radiosurgery

• Infiltrative/autoimmune
  o Sarcoidosis
  o Hypophysitis
  o Genetic Causes
  o Empty Sella
  o Developmental

• Functional Causes
  o Endogenous or exogenous hormonal excess
  o Systemic Disease
    ▪ Obesity
    ▪ Anorexia nervosa
    ▪ Chronic Illness
  o Medications

• Infectious

• Traumatic/Vascular
  o Aneurysm
  o Apoplexy
  o Subarachnoid hemorrhage
  o Traumatic brain injury

• Idiopathic

60% of cases are from pituitary or peripituitary tumors and their treatment by surgery or radiotherapy.

<table>
<thead>
<tr>
<th>Symptoms of hypopituitarism</th>
<th>Adrenal insufficiency</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue</td>
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</tr>
<tr>
<td>• Loss of appetite</td>
<td>• Colder than other people</td>
<td></td>
</tr>
<tr>
<td>• Weight loss</td>
<td>• Constipation</td>
<td>• Hair loss</td>
</tr>
<tr>
<td>• Low blood sugar</td>
<td>• Dry skin</td>
<td>• Dry skin</td>
</tr>
<tr>
<td>• Low blood pressure</td>
<td>• Hoarseness</td>
<td>• Hoarseness</td>
</tr>
<tr>
<td>• Low blood sodium level</td>
<td>• Slower thought processes</td>
<td>• Slower thought processes</td>
</tr>
<tr>
<td>• Weakness</td>
<td>• Weight gain</td>
<td>• Weight gain</td>
</tr>
<tr>
<td>• Nausea/vomiting</td>
<td>• Low heart rate</td>
<td>• Low heart rate</td>
</tr>
<tr>
<td>• Dizziness</td>
<td>• Low blood pressure</td>
<td>• Low blood pressure</td>
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</tbody>
</table>
Symptoms of hypopituitarism

Gonadal deficiency

- Women:
  - Irregular or absence of menstrual cycles
  - Low libido
  - Infertility
  - Osteoporosis

- Men:
  - Low libido
  - Impaired sexual function
  - Mood changes
  - Loss of facial, scrotal, body hair
  - Low muscle mass
  - Osteoporosis
  - Anemia

- Growth hormone deficiency
  - Low muscle mass and strength
  - Obesity
  - Fatigue
  - Impaired attention and memory

- Diabetes insipidus (ADH deficiency)
  - Frequent urination
  - Excessive thirst

- Prolactin deficiency
  - Inability to lactate
Principles of diagnostic testing for hypopituitarism

• Basal (non-dynamic) testing sufficient for some pituitary hormones
• Dynamic testing may be required
• Different assays for the hormones affect the cutoff points in the assessment of normal function
• Many tests used in the past are unavailable or not performed today
• Role of pituitary imaging
  o Once confirm biochemical hypopituitarism
  o To rule out sellar/parasellar mass
  o Traumatic damage may present with stalk deviation, change in signal intensity indicative of hemorrhage or infarct, empty sella

Assessment of the corticotrophs

- ACTH and cortisol have a diurnal, pulsatile secretory pattern
- Random measurements of ACTH and cortisol are generally not helpful
- Basal (8AM) serum cortisol
  - If above 18 µg/dl adrenal insufficiency is ruled out
  - Level below 3 µg/dl highly suggestive of adrenal insufficiency
- Dynamic testing usually required
- Perform ACTH (cosyntropin) stimulation test
  - Injection of ACTH
  - Measure cortisol at baseline and then 30 and 60 minutes after
  - Look for rise of cortisol above 18 mcg/dL
  - May not be accurate in 1st 2 months after acute injury
  - Need to hold hydrocortisone medication for 24 hours prior to test

Veldhuis JD, et al. JCEM 1990; 71:452
Assessment of the thyrotrophs

- Measure serum TSH and thyroxine (T4)
- Serum TSH
  - Normal in 84%
  - Elevated in 8%
  - Low in 8%
- T4 levels are low
- T3 levels are usually normal and not routinely measured
- exclude other illnesses which give similar results

Persani et al. JCEM (2000); 85 (10) 3631-3635.
### Assessment of the gonadotrophs

<table>
<thead>
<tr>
<th>Gender</th>
<th>Test</th>
<th>Normal Results</th>
<th>Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Male</td>
<td>Basal Measurement (Morning 7:00 – 9:00AM) Total Testosterone, LH, FSH</td>
<td>Normal age adjusted testosterone. LH and FSH may be normal or low.</td>
<td>Low testosterone with low or normal LH/FSH</td>
</tr>
<tr>
<td>Premenopausal Female</td>
<td>Menstrual History</td>
<td>Normal, regular menses</td>
<td>If no menses: low estradiol with low-normal LH/FSH</td>
</tr>
<tr>
<td>Postmenopausal Female</td>
<td>Estradiol, LH, FSH</td>
<td>Low estradiol, high LH, FSH</td>
<td>Low estradiol with low-normal LH/FSH</td>
</tr>
</tbody>
</table>

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Assessment of the somatotrophs

• Important to test in the right clinical picture
  o Known structural hypothalamic-pituitary disease, surgery
  o History of cranial irradiation
  o History of childhood onset GHD
  o Traumatic brain injury
  o Subarachnoid hemorrhage
  o Evidence of other hormonal deficits
• Basal IGF-1 may be normal in hypopituitarism
• Need dynamic testing
  o Insulin tolerance test—rarely performed
  o Arginine-GHRH test—GHRH no longer available
  o Glucagon stimulation test—currently performed
    ▪ Inject 1 mg in the muscle
    ▪ Measure glucose and growth hormone level every 30 minutes for 3-4 hours
    ▪ Cutoff for GHD is peak GH of less than 3 ng/mL (may be <1 ng/mL in overweight patients)
Assessment of posterior pituitary deficiency—Diabetes Insipidus

- Urine and blood tests
- High-normal serum sodium (>145 meq/L) with dilute urine
- Water deprivation test if picture is unclear
Therapy: Adrenal replacement

- Glucocorticoid replacement dose of 15-25 mg a day
- Prefer hydrocortisone twice to three times a day
- Prednisone once a day is an option
- When start on growth hormone, may need increased dose of hydrocortisone
- Dual release hydrocortisone in trials for primary adrenal insufficiency
  - Once a day
  - Has intermediate release coating surrounding extended release core
  - Provides high cortisol in morning followed by gradual decrease during day

Veldhuis JD, et al. JCEM 1990; 71:452
Weitzman ED, et al. JCEM 1971; 33:14
Adrenal replacement—Monitoring

- No consensus
- Serum cortisol in morning and afternoon after taking hydrocortisone doses may be useful if levels are too low
- Best tool is clinical evaluation:
  - Look for signs of over-replacement: weight gain, central obesity, high blood pressure, hyperglycemia, osteoporosis
  - Look for signs of under-replacement: afternoon headache, loss of appetite, muscle aches
  - Medic-alert bracelet is vital
- Sick day rules
  - Doubling or tripling oral medication for febrile illness for 2-3 days
  - Injection of steroids if unable to take oral meds
- Stress dosing for procedures, surgery
  - Have your surgeon contact your endocrinologist before surgery to discuss
Thyroid hormone replacement

- Recommend synthetic T4 therapy based on body weight (1.6 mcg/kg/day)
- T3 therapy generally not needed
- Prefer taking in morning, empty stomach, 30-60 minutes before breakfast
- Avoid iron and calcium supplements within 4-6 hours of taking T4
- Treat adrenal insufficiency first
- Start low dose in elderly patients, especially with known heart disease
- Younger patients may need higher doses than elderly
- Estrogen and GH therapy may increase T4 dose requirements
- Monitor with free T4 levels drawn before morning dose
  - Target middle-upper half of normal range
- Pregnancy
  - Dosing adjustments required early in pregnancy
  - Increase in 30% dose expected during pregnancy
  - Monitor dose monthly
  - May need to adjust dose when start on estrogen therapy

Persani L. J Clin Endocrinol Metab. 2012 Sep;97(9):3068-7
ATA/AACE Guidelines for Hypothyroidism in adults, Endocr Pract 2012; 18: 988-1028
Gonadal replacement

**Women**

- Premenopausal:
  - Oral contraceptive therapy or transdermal estrogen
  - Progesterone if intact uterus
- Stop replacement once reach typical age of menopause

**Men**

- Testosterone therapy sufficient if fertility is not desired
- Injection
  - Testosterone cypionate or enanthate 200mg IM every 2 weeks or 100 mg weekly
- Transdermal gel applied daily
  - Caution regarding transfer of gel to others (wife/children)
  - Newer formulations with higher potency, less volume of gel required
- Transdermal Patch daily
  - Caution regarding skin irritation, rash

Monitoring on testosterone replacement

- Target is to raise serum testosterone levels into a range that is mid-normal for healthy, young men
- In men receiving testosterone enanthate or cypionate, aim for levels between 400 and 700 ng/dl midway between injections
- If on transdermal patch, measure levels 3-12 hours after application
- For gel preparation, measure level anytime, at least 1 week after starting on therapy
- Monitor for side effects
  - Complete blood count
  - PSA, prostate exam
  - Bone mineral density

Fertility

• Women
  - FSH or pulsatile GnRH

• Men
  - Assess semen analysis
  - Gonadotropins or GnRH analogs
  - HCG (LH analog)
    - Stimulates Leydig cells to produce and secrete testosterone in testis
    - Usually sufficient alone to initiate spermatogenesis
    - Occasionally add recombinant FSH

• Spermatogenesis usually obtained within 6-9 months
Benefits of testosterone therapy

Benefits

- Body Composition
  - Increased fat-free mass
  - Decreased fat mass
- Strength, exercise performance
- Cardiovascular risk profile
- Improves mood, sense of well being
- Improved sexual function
- Increases spine and hip bone mineral density by up to 8%
- May improve insulin sensitivity

Contraindications

- Prostate cancer
- Breast cancer
- Nodules on prostate exam
- PSA >4 mcg/L or >3 mcg/L in high risk men
- Severe lower urinary tract symptoms
- Hematocrit >50%
- Untreated severe sleep apnea
- Uncontrolled congestive heart failure
Cardiovascular outcomes and testosterone

• FDA and Endocrine Society issued statements alerting physicians on possible increase of risk of cardiovascular outcomes in older men on testosterone
• FDA is investigating the data but have not concluded that testosterone therapy increases risk of stroke, heart attack, or mortality
• Call for more large-scale trials to determine true risks and benefits of testosterone therapy in older men
• Bottom line: use testosterone in appropriate candidates
  - Man who is hypogonadal
    - Has clinical symptoms and signs consistent with low testosterone state
      - Low libido, decreased morning erections, loss of body hair, low BMD, gynecomastia, small testes
    - And low morning serum testosterone concentration on 3 separate occasions
  - Not necessarily for age related drop in levels without symptoms

http://www.fda.gov/drugs/drugsafety/ucm383904.htm
Growth hormone therapy in adults

• Formerly dosed by weight—increased side effects
• Recommend individualized regimen starting with low doses and titrating according to clinical response, side effects, and IGF-1 levels
• Usual starting dose of 0.2 mg/day in men, 0.3 mg/day in women, 0.1 mg/day in elderly
  o Women on oral estrogen may need higher doses
• Tend to administer in the evening to mimic normal secretion
• Contraindications
  o Absolute
    ▪ Active malignancy
    ▪ Intracranial hypertension
    ▪ Proliferative diabetic nephropathy
  o Relative
    ▪ Uncontrolled diabetes
    ▪ Untreated thyroid dysfunction

Benefits of GH replacement

**Figure 2 | Main effects of GH replacement therapy in adult GH deficiency.**

- **Brain**
  - Quality of life
  - Psychological well-being
  - Cognitive function

- **Cardiovascular system**
  - Myocardial function
  - Endothelial function
  - LDL cholesterol
  - IMT
  - Aerobic capacity

- **Liver**
  - Gluconeogenesis

- **Adipose tissue**
  - Lipolysis

- **Skeletal muscle**
  - Protein synthesis
  - Strength

- **Bone**
  - BMD

Kargi, A. Y. & Merriam, G. R. Nat. Rev. Endocrinol. 9, 335–345 (2013);
Side effects of GH replacement

• Usually temporary
  o Joint pains
  o Swelling
  o Carpal tunnel syndrome
  o Hyperglycemia

• Brain tumors in GH treated survivors of cranial radiation therapy
  o 5% GH treated developed neoplasms (meningioma, glioma) compared to 2% without GH treatment
Monitoring GH therapy

• Daily dose titrated by 0.1-0.2 mg/day every 6 weeks based on IGF-I level, side effects, clinical response
• Monitor at 1-2 month intervals during titration and then semiannually
• Give at least 3 months for effects
• Monitoring can be done every 6-12 months
• Goal IGF-I is upper mid normal range
• Clinical trials often did not show clinical benefit until after 9 months
• If no benefit from treatment, could consider discontinuing therapy after 1 year
• Monitor:
  o lipid profile
  o glucose
  o DEXA scan if abnormal at baseline
• Re-evaluate thyroid and adrenal replacement after initiating GH therapy

Diabetes insipidus

• Acute setting (in the hospital)
  ○ Drink to thirst
  ○ If unable to drink → use IV fluids
  ○ Vasopressin analog desmopressin subcutaneous injection
    ▪ 1 mcg-4 mcg given 1-2x a day

• Chronic management
  ○ Limit fluid intake to satisfy thirst when on therapy
  ○ Maintain adequate urine output (not less than 15-30 mL/kg/day)
  ○ Formulations of desmopressin
    ▪ Nasal spray—10-20 mcg, duration from 4-24 hours
    ▪ Oral—0.1-0.4 mg, duration variable, may need three times a day
      ○ Absorption reduced by food within 90 minutes of eating

Let’s test you on a case

• 70 year old woman presented with right visual field loss
• Short term memory loss and word finding difficulty
• MRI showed a meningioma in the sellar area
• Over course of 5 years:
  o Had craniotomy
  o Had radiation therapy
  o Had 2nd surgery—transsphenoidal
  o Stereotactic radiotherapy
• Complaining of nausea, constipation, feeling cold

Should we suspect hypopituitarism in this patient? What are her risk factors?

Normal pituitary

Patient’s MRI
Case—screening for hypopituitarism

• How test for cortisol deficiency?
  o ACTH stimulation test
  o Peak cortisol was 15.3 mcg/dL

• How test for hypothyroidism?
  o TSH and free T4
  o TSH is 0.28 mIU/L (0.4-4.5)
  o Free T4 was 0.5 ng/dL (0.8-1.8)

• How test for gonadal deficiency?
  o LH/FSH and estradiol
  o Estradiol <5 pg/mL, LH <0.5 mIU/mL, FSH 0.9 mIU/mL

• How test for growth hormone deficiency?
  o IGF-1 and stimulation test
  o Stimulation may not be necessary
  o IGF-1 of 70 ng/mL (34-245)
Case—how will we treat her?

• 1<sup>st</sup> step
  o Replace with hydrocortisone 10 mg in morning, 5 mg in afternoon
  o Education on sick day rules, medic-alert bracelet
  o Reassess at each visit how she feels, look at weight, blood pressure, glucose

• 2<sup>nd</sup> step
  o Start on levothyroxine 50 mcg in morning
  o Monitor free T4 levels

• 3<sup>rd</sup> step
  o Do not recommend estrogen therapy given age of patient
  o Do not recommend growth hormone replacement given recurrent, active tumor
Take home points

• Multiple causes for pituitary failure
• Diagnosis of pituitary deficiencies requires rigorous testing
• Treatment of pituitary deficiencies includes replacement of target hormones or direct substitution of pituitary hormones
• Long-term monitoring for side effects and adequacy of replacement