Understanding Causes and Comorbidities for Accurate Diagnosis and Patient Selection for Treatment of Adult Growth Hormone Deficiency: An Expert Discussion

Program Highlights

- Understand the underlying causes of growth hormone deficiency (GHD) and recognize key signs and symptoms
- Focus on important risk factors and comorbidities at baseline and beyond
- Highlight the strengths and weaknesses of current testing procedures
- Individualize treatment for each patient
- Recognize patients with GHD who should not receive treatment

For a list of abbreviations and references, click on the right-hand tab.

Optimizing Patient Identification, Treatment & Overall Management of Adult GHD

Presentation Highlights

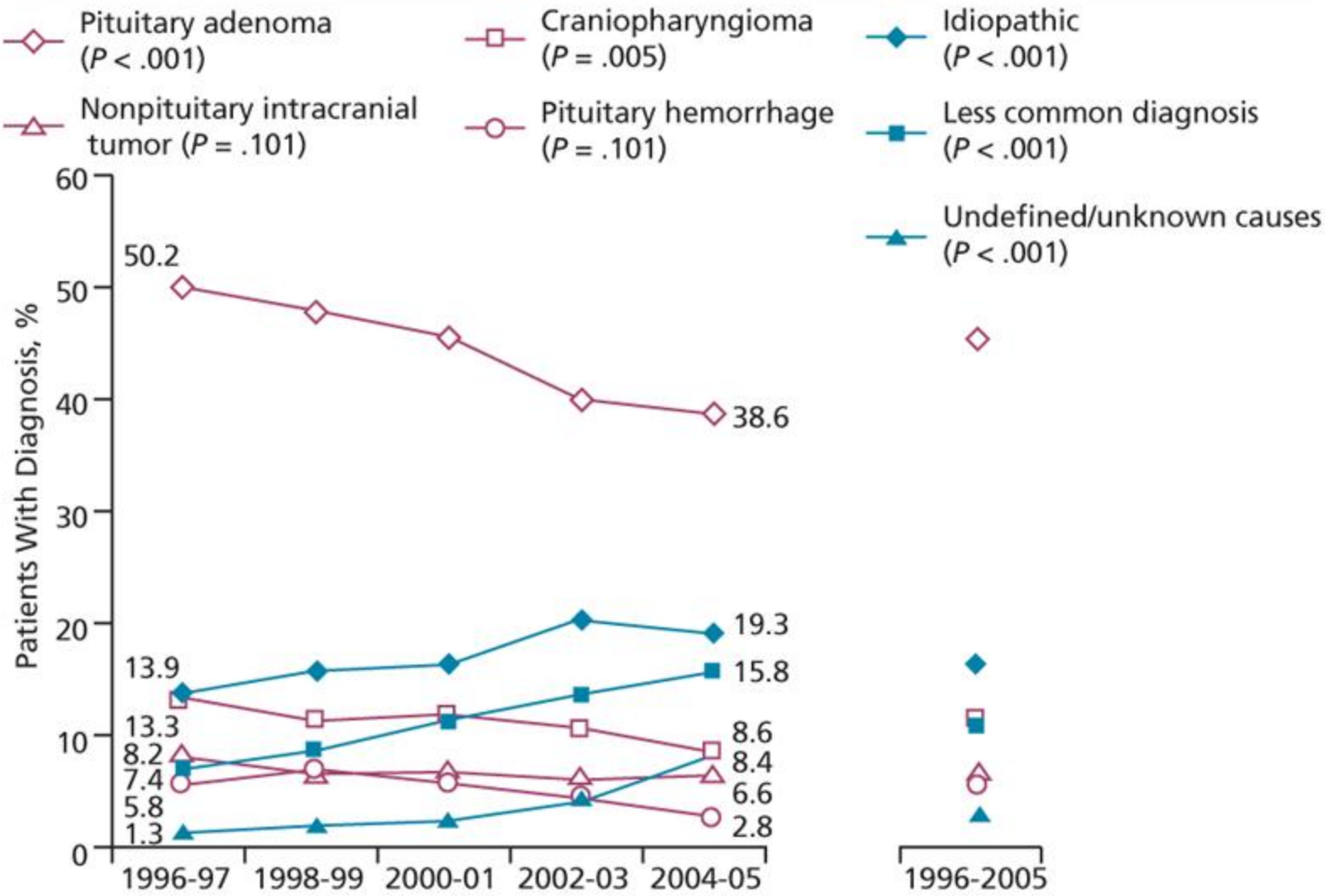
- Understanding the underlying causes of growth hormone deficiency (GHD)
- Recognizing key signs and symptoms of GHD in adults and transitional patients
- Focusing on important risk factors and comorbidities
- Highlighting the strengths and weaknesses of current testing procedures

Epidemiology of Adult Growth Hormone Deficiency

- Limited number of studies outlining incidence of GHD, particularly in the US
  - Estimated to be 12,000 new cases/year

- European studies suggest pituitary tumors to be common
  - In an adult Caucasian population in northwestern Spain, two cross-sectional surveys showed prevalence of 29 and 46 per 100,000 persons, respectively[1]
  - Average incidence: 4.2/100,000 adults
  - Incidence higher among those aged >50 years
  - No differences according to sex observed

Causes of Adult GHD: Trends Over Time



Identifying Undiagnosed Adult Patients

- Patients with adult GHD often present after trauma
  - Making contact with local rehabilitation centers could increase early, appropriate diagnoses of GHD

- Connecting with radiation centers
  - Patients undergoing radiation therapy for pituitary tumors should routinely be referred for GHD testing during treatment

Transition patients: Period of adolescence after growth is completed when the new goals of GH replacement become normalization of metabolism and quality of life

- Discontinued GH treatment when patients reached adult height; now present with cognitive issues

Untreated Adult GHD: Symptoms and Signs

Symptoms	Signs
Decreased psychological well-being • Reduced energy and vitality • Poor general health • Impaired self-control • Disturbed emotional reaction • Lack of positive well-being • Depressed mood • Increased anxiety • Increased social isolation	Truncal obesity
	Increased waist:hip ratio
	Thin, dry skin
	Abnormal body composition • Decreased lean body mass • Increased body fat • Reduced extracellular water
	Decreased psychological well-being
	Reduced exercise performance
	Abnormal cardiac structure and function
	Cardiovascular risk factors • Hyperlipidemia • Decreased fibrinolysis • Increased atherosclerosis
	Decreased bone density
	Disturbed renal function • Reduced glomerular filtration rate • Reduced renal plasma flow
	Lowered basal metabolic rate
	Increased insulin resistance

Adult GHD: Key Health Concerns

Aged 20-40 years[a], primary concern: Bony impact

- Increased risk for developing osteopenia, osteoporosis[1]
- Also at risk for cardiovascular comorbidities
- Quality of life a concern

Aged 41-60 years, primary concern: Cardiovascular risks

- Abnormal cholesterol profile, C-reactive protein increase, visceral fat increase
- Ejection fraction may deteriorate in GH-deficient patients not receiving GH replacement[2]
- Increased intima-media thickness of major arteries[3]
- Higher mortality rate associated with cardiovascular function
- Quality of life a concern

Aged 61+ years, primary concern: Quality of life

[a] Typically the transitional age group.

QOL: Cognition Considerations for All Adults With GHD

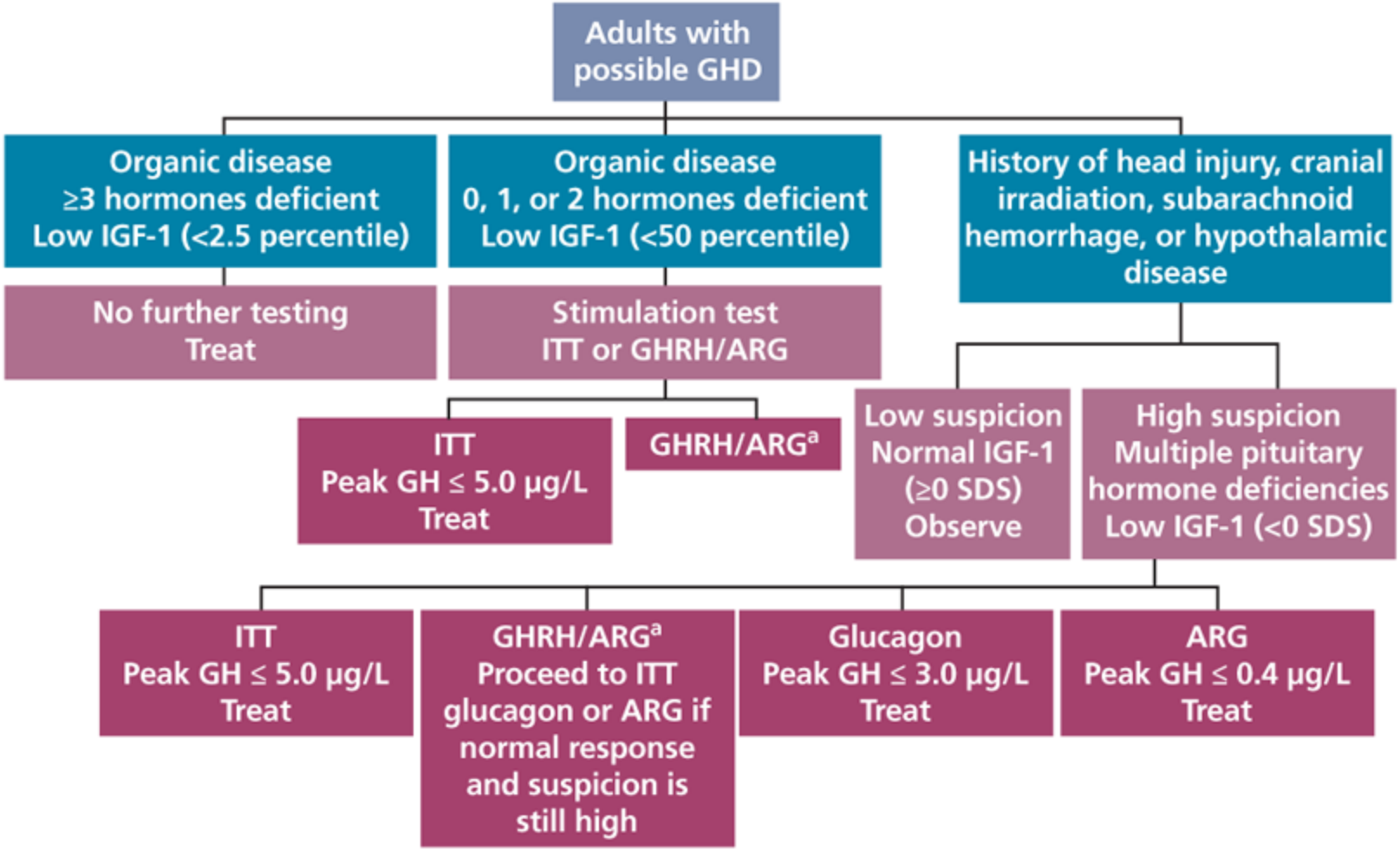
Ask your patients simple, probing questions:

- How are you doing in work/school?

- How is your brain working or functioning?
  - Problems, such as simple calculations, verbal recall, common across age groups

- Meta-analysis has demonstrated the link between GH and cognitive performance[1]
  - Poor performance can be ameliorated with GH treatment

Diagnostic Procedures



[a] Treat if: peak GH ≤ 11.0 µg/L in pts with BMI < 25 kg/m^2; peak GH ≤ 8.0 µg/L in pts with BMI ≥ 25 kg/m^2 and <30 kg/m^2; if peak GH ≤ 4.0 µg/L in pts with BMI ≥ 30 kg/m^2.

Strengths and Weaknesses of Current Testing for Adult GHD

ITT

- Requires physician supervision
  - Patients become hypoglycemic and can pass out
  - Reports of seizures and cardiac events

Glucagon stimulation test

- Alternative to ITT[1]
- Very well-tolerated, safe test
- Can be very useful looking for growth hormone
- Acceptable in the context of hypothalamic disease
- Appropriate for brain injured patients
- BMI may affect test results

Arginine/GHRH

- Can provide a false negative in hypothalamic disease

Arginine alone

- Can provide a false positive for GHD

Abbreviations and References

Epidemiology of Adult Growth Hormone Deficiency

Abbreviation(s): GHD: growth hormone deficiency.

Reference(s): 1. Erfurth EM. *Front Horm Res*. 2005;33:21-32.

Causes of Adult GHD: Trends Over Time

Reference(s): Adapted from: Webb SM et al. *J Clin Endocrine Metab*. 2009;94:392-399.

Identifying Undiagnosed Adult Patients

Abbreviation(s): GH: growth hormone.

Untreated Adult GHD: Symptoms and Signs

Reference(s): Adapted from: Cuneo RC et al. *Clin Endocrinol (Oxf)*. 1992;37:387-397.

Adult GHD: Key Health Concerns

Reference(s): 1. Cook DM et al. *Endrocrine Practice*. 2009;15:1-29. 2. Colao A et al. *J Clin Endocrinol Metab*. 2002;87:1088-1093. 3. Colao A et al. *J Clin Endocrinol Metab*. 2008;93:3416-3424.

QOL: Cognition Considerations for All Adults With GHD

Reference(s): 1. Falleti MG et al. *Psychoneuroendocrinology*. 2006;31:681-91.

Abbreviations and References (Cont'd)

Diagnostic Procedures

Abbreviation(s): ARG: arginine; GHRH: growth hormone–releasing hormone; ITT: insulin tolerance test; SDS: social desirability score.

Reference(s): Adapted from: Cook DM et al. *Endocrine Practice*. 2009;15:1-9.

Strengths and Weaknesses of Current Testing for Adult GHD

Reference(s): 1. Yuen KCJ et al. 92nd Annual Meeting of the Endocrine Society (ENDO 2010). Abstract OR25-2.

Delving Into the Nuanced Treatment of Adult GHD: From Baseline Assessments to Goals of Therapy

Presentation Highlights

- Are there patients with growth hormone deficiency (GHD) who should not receive treatment?
- Addressing consequences of GHD with a detailed baseline assessment
- Establishing an effective treatment strategy for each individual patient
  - Consider dosing and compliance issues

Considerations for Not Treating a Patient With Adult GHD

Consider not treating if the patient has:

- Recent/current malignancy[a] (ie, diagnosis ≤ 5 years)[1]
  - Including neoplasm of the brain
  - Secondary cancers as a result of radiation for a childhood cancer
- Diabetes
  - Lower dose of GH coupled with more aggressive diabetes treatment may be appropriate and effective
- Carpal tunnel syndrome

[a] Do not test or treat.

Address the Consequences of Adult GHD at Baseline

- Patients with benign pituitary tumors not at risk of instigating tumor growth
  - Some centers suggest GH has a protective effect
- Continued monitoring for regrowth recommended
- Conduct baseline evaluation

IGF-1
A1C
Bone density according to DEXA
MRI
Cholesterol/lipid profile

Address the Consequences of Adult GHD at Baseline (Cont'd)

- Changes in body composition; interventions include:
  - Resistance exercise
    - » Can increase skeletal and muscle size, function[1]
  - Dietary interventions
    - » Limit caloric intake, specifically carbohydrates; lower lipids
  - Bisphosphonates can improve bone density

- Assess QOL at baseline, and every 6 months thereafter
  - QOL-specific questionnaire: QLS-H[2]
    - » Includes items related to self confidence, physical stamina, stress tolerability

Factors That May Affect GH Dosing

Starting dose	
Age < 30 years	0.4-0.5 mg/day[a]
Age 30-60 years	0.2-0.3 mg/day
Age > 60 years	0.1-0.2 mg/day

Factors that indicate an increased GH dose[1]

- Young patients, regardless of age of onset
- Low serum IGF-1 levels
- Addition of oral estrogen
- Change from transdermal to oral estrogen
- To induce lipolysis

Factor that may affect dosing for concomitant medication

- Adrenal insufficiency

[a] May be higher for patients transitioning from pediatric treatment.

Factors That May Affect GH Dosing (Cont'd)

Factors that indicate a decreased GH dose

- Age > 60
- High serum IGF-1 levels
- Discontinuation of oral estrogen
- Change from oral to transdermal estrogen
- Addition of testosterone
- Worsening glucose tolerance
- Side effects

AACE Recommendations for GH Replacement

Starting dose	
Age < 30 years	0.4-0.5 mg/day[a]
Age 30-60 years	0.2-0.3 mg/day
Age > 60 years	0.1-0.2 mg/day
Pts with diabetes or pts susceptible to glucose intolerance (any age)	0.1-0.2 mg/day

Dose titration

- At 1- to 2- mo intervals, increase dose in increments of 0.1-0.2 mg/day, based on clinical response, serum IGF-1 levels, side effects, and individual factors
- Longer time intervals and smaller dose increments may be necessary in older patients

Goal

- Aim for serum IGF-1 levels in the mid-normal range appropriate for age and sex, unless side effects are significant
- Consider a trial of high GH doses to determine whether it will provide further benefit, as long as IGF-1 levels remain within normal range and no side effects occur

Monitoring

- 6-mo intervals: Side effects, serum IGF-1, fasting glucose levels, QOL
- 1-year intervals: Lipid profile, QOL (if not assessed at 6 mo)
- 2- to 3-year intervals: DEXA scan
- If pituitary microadenomas or residual tumor present, periodic MRIs recommended
- Pts on concurrent thyroid, glucocorticoid, and gonadal hormone replacement may require dose adjustments after starting GH replacement therapy

[a] May be higher for pts transitioning from pediatric treatment.

Current FDA-Approved GH Delivery Systems

Trade Name	Generic Name	Delivery System	Refrigeration Required
Genotropin MiniQuick®	Somatropin	Prefilled disposable pen[a]	Room temp up to 3 mo
Humatrope HumatroPen®	Somatropin	Refillable pen	Yes
Norditropin NordiFlex®	Somatropin	Prefilled, premixed, disposable pen[a]	Yes
Norditropin FlexPro®	Somatropin	Prefilled disposable pen	Room temp up to 3 wk after first use
Nutropin AQ NuSpin®	Somatropin	Prefilled, premixed injection pen	Yes
Omnitrope®	Somatropin	Refillable pen	Yes
Saizen EasyPod®	Somatropin	Electronic injection device	After reconstitution

Barriers to care

- Inconvenient delivery (ie, injections, required refrigeration)
- Issues with insurance
- Cost

Proposed solutions

- Individualize delivery system to patient needs
- Direct patients to educational resources
  - http://www.hgfound.org
  - http://www.magicfoundation.org

[a] Optional needle guard available.

Conclusions

- GHD largely underdiagnosed
  - Expect greater number of patients to present with GHD in the future
- Universal testing of patients with brain injury could lead to more accurate diagnoses
- Further research required for patients with idiopathic GHD to determine how to pursue treatment
- Treating adult GHD worthwhile
  - Satisfying for physicians and patients
- Barriers often include insurance issues and cost
- Future endeavors focused on more convenient delivery systems

Abbreviations and References

Considerations For Not treating a Patient With Adult GHD

Reference(s): 1. Cook DM et al. *Endocrine Practice*. 2009;15:1-29.

Address the Consequences of Adult GHD at Baseline

Abbreviation(s): DEXA: dual energy x-ray absorptiometry; IGF: insulin-like growth factor.
Reference(s): 1. Cook DM et al. *Endocrine Practice*. 2009;15:1-29.

Address the Consequences of Adult GHD at Baseline (Cont'd)

Abbreviation(s): QLS-H: Questions of Life Satisfaction–Hypopituitarism.
Reference(s): 1. Jørgensen JO et al. *Clin Endocrinol (Oxf)*. 1996;45:681-688.
2. Herschbach P et al. *Eur J Endocrinol*. 2001;145:255-265.

Factors That May Affect GH Dosing

Reference(s): 1. Cook DM et al. *Endocrine Practice*. 2009;15:1-29.

Factors That May Affect GH Dosing (Cont'd)

Reference(s): Based on: Cook DM et al. *Endocrine Practice*. 2009;15:1-29.

AACE Recommendations for GH Replacement

Abbreviation(s): AACE: American Association of Clinical Endocrinologists.
Reference(s): Based on: Cook DM et al. *Endocrine Practice*. 2009;15:1-29.

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