

Baillargeon JP, Carpentier AC. Brothers of women with polycystic ovary syndrome are characterized by impaired glucose tolerance, reduced insulin sensitivity and related metabolic defects. *Diabetologia*. 2007;50:2424-32.

Editor's Comment: *Over the past several years pediatric endocrinologists have been evaluating an increasing number of adolescents with PCOS. It is not uncommon for these teenagers to be accompanied by mothers and sisters who also have obvious signs suggestive of PCOS. It is uncommon, at least in this editor's experience, for brothers of these teenagers to accompany them to the clinic visit. Thus, there is a potentially large group of teenagers and young adults*

with significant metabolic abnormalities who are not being evaluated and counseled. With the growing epidemic of obesity one is hesitant to suggest that pediatric endocrinologists actively recruit additional overweight adolescents to their clinics. However, the information presented above by Baillargeon and Carpentier suggests that to exclude the discussion of brothers' health status during the evaluation of girls with PCOS may be a significant omission. It would be of interest to obtain additional clinical information on brothers of adolescents with PCOS. This would appear to be an area for further clinical research.

William A. Clarke, MD

Consensus Guidelines for Adult Growth Hormone Deficiency 2007

Ten years after the Growth Hormone (GH) Research Society drafted its "Consensus Guidelines for the Diagnosis and Treatment of Adults with Growth Hormone Deficiency (GHD)", a second international workshop was convened (Sydney, Australia) with 30 delegates to create an updated set of guidelines in 2007. Diagnosis of adult GHD was expanded in patient scope since the first document. Testing should be reserved for patients with evidence of hypothalamic-pituitary disease and with intention to treat. This includes patients with signs and symptoms of hypothalamic-pituitary disease (endocrine, structural, or genetic causes), patients who had received cranial irradiation or tumor treatment, and a new group, patients who had sustained traumatic brain injury or subarachnoid hemorrhage. Of note, the degree of pituitary dysfunction does not correlate with the severity of brain injury, and GH testing should be deferred for at least 12 months after injury due to the rate of endogenous GH axis recovery.

Another new patient group discussed is the GHD patient during the transition period, that newly recognized life stage between cessation of statural growth (ie, epiphyseal closure) and acquisition of complete somatic maturation (ie, full development of lean body mass and bone mineralization). Apart from patients with known genetic causes of GHD/hypopituitarism and patients with multiple pituitary hormone deficiencies (who should continue GH treatment without the need for further testing), patients with childhood onset GHD should undergo reevaluation of their GH function after at least one month off GH treatment for assessment of potential treatment during the transition period. A second reevaluation may be considered at the end of the transition period (about age 25) for those with isolated idiopathic GHD or discordant testing (low insulin-like growth factor [IGF]-I but normal stimulated GH peak) at the start of transition. Adult GH treatment is not indicated for patients with non-GHD pediatric indications, such as those born small for gestational age or Turner syndrome.

Adult GH treatment aims to "...correct the metabolic,

functional, and psychological abnormalities associated with adult GHD." Dosing should be based on age and gender, not body weight, and escalated to response in a gradual and individualized fashion. Recommended monitoring of response includes:

1. Anthropometry (including weight, height, BMI and waist circumference): at least yearly
2. Quantified body composition and bone mineral density (DEXA): at baseline and every 2 years thereafter
3. Serum marker for GH dose titration (serum IGF-I): at least yearly and no sooner than 6 weeks after a dose change
4. Cardiovascular risk factors (blood pressure, fat mass, cholesterol panel): yearly, with similar goals as the general population
5. Fasting serum glucose: yearly
6. Quality of life (careful history, not disease-specific quality of life questionnaires)

Although GH treatment is indicated for adult patients with proven GHD, GH supplementation is not recommended for the physiologic age-related decline in GH/IGF secretion. Lower doses are called for in the elderly, to reduce the incidence of side effects and maintain age-dependent normal levels of IGF-I.

Ho KKY on behalf of the 2007 GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol*. 2007;157:695-700.

First Editor's Comment: *The reader is encouraged to go through the entire original document, as the guidelines were too extensive to summarize here; this abstract highlights the newer recommendations. Also covered are the dosing recommendations, interactions with other hormone deficiencies, and treatment safety issues.*

More than the advances, what struck me were the

persistent unknowns of the field. Ten years after the first set of guidelines, we remain prey to suboptimal diagnostic testing. The lack of standardization of the GH and IGF-I assays was lamented in the consensus statement, as was the need for better age- and gender-related normative data. There was an entire section devoted to the various GH stimulation tests, their respective indications and limitations, and the multiple cut-off levels which also need better substantiating normative data. It is not surprising that the authors concluded, "...partial GHD is not adequately defined." Unless we can accurately distinguish normal from abnormal hormone levels, how can clinical care and research in the growth field advance effectively?

Adda Grimberg, MD

Second Editor's Comment: *The reader is encouraged to review the article in its entirety. However it may be worth noting a few more pertinent points in addition to those elaborated above. The consensus of experts stated that one stimulation test was sufficient for the diagnosis of adult GHD. They endorsed the use of*

an insulin or a glucagon tolerance test, and did not recommend clonidine, L-DOPA or arginine. GH releasing hormone (GHRH) + arginine or GHRH + GH-releasing peptide (GHRP) have also been validated, though GHD of hypothalamic origin may be missed, particularly in patients treated with cranial irradiation, then insulin or glucagon tolerance test may be necessary. The peak GH level for diagnosis was <3 mcg/L after insulin, higher levels may be acceptable following GHRH in individuals with a BMI of <25 kg/m². Measurements of circulating IGF-I levels constitute a good screen, though a normal level may not rule out GHD. Sex steroid, glucocorticosteroid and thyroid replacement should be optimized before testing or initiating GH treatment. The efficacy of treatment should be monitored and objective parameters determined, ie, body composition. Where available, DEXA should be utilized to quantitate body composition changes. IGF-I levels are indicted for titration of the GH dosages. Disease-specific quality of life questionnaires that assess the problems need to be validated.

Fima Lifshitz, MD

Genetics of Stature

Variation in adult height is a classic polygenic trait, ie, it is determined by many genes each having a small effect. The identity of these genes has been elusive despite delineating many genes that have a major impact on height based on detection of mutations that cause severe growth deficiency. Although linkage studies have pointed to several genomic regions that influence height, there have not been any examples of gene variants that are reproducibly associated with height variation in the general population. However, from analysis of genome-wide association data, Weedon et al now showed that common variants in the *HMG2A* oncogene are associated with height.

The investigators began by analyzing data from 4,921 individuals including 1,896 UK individuals with type 2 diabetes from the Wellcome Trust Case Control Consortium and 3,025 Swedish or Finnish participants from the Diabetes Genetics Initiative. More specifically, they performed a meta-analysis of sex- and age-adjusted height z-scores for 364,301 autosomal single nucleotide polymorphisms (SNPs) common across data sets. These SNPs provide 64% coverage of the Utah-based Haplotype Map.

Two SNPs most associated with height were mapped in and 12 kb downstream of the 3' UTR (3' untranslated region) of the high mobility group-A2 (*HMG2A*) gene. *HMG2A* is a strong biological candidate for influencing height because its homozygous deletion produces the dwarf *Pygmy* mutant in mice. In replication studies of adults sampled from across the height distribution, each copy of the C allele of the SNP was associated with an increase of 0.07 in the adult height z-score, which is equivalent to ~0.4 cm in height.

To determine the age at which the association appears, longitudinal data from the Avon Longitudinal Study of Parents and Children were analyzed. There was no evidence of association at birth, but strong association with height was observed at age 7 years, suggesting that the effect was on longitudinal skeletal growth. Since the *Pygmy* mice also displayed greatly reduced fat mass, the investigators sought evidence that the association affects BMI, but none was observed.

The authors discussed the fact that HMG proteins are DNA-binding proteins and often serve an architectural function with regard to chromatin structure and modeling, but they did not suggest possible mechanisms through which the polymorphism might alter bone growth.

Weedon MN, Lettre G, Freathy RM, et al. A common variant of *HMG2A* is associated with adult and childhood height in the general population. *Nat Genet.* 2007;39:1245-50.

First Editor's Comment: *It is ironic that although normal height is probably one of the most studied polygenic traits in humans, the first gene to show a strong effect in the general population is only now coming to the fore. It will be interesting to see how this story unfolds and what other genes are identified with new genomics analysis technology. The genetics of height variation assessed by linkage studies were reviewed in GGH.¹ These identified proteins, whose genes map to chromosomes 2q21 and 6q21 with locus interacting on an epistatic model, account for approximately 20% of height variation. These gene loci contain *RUNX2* transcription factors with known functions on linear skeletal growth.*

William A. Horton, MD