

CONGENITAL ADRENAL HYPERPLASIA

The presence of testicular adrenal rest tumors in congenital adrenal hyperplasia (CAH) patients is known to cause Leydig cell failure and impaired spermatogenesis. These rest tumors are often unresponsive to intensified corticoid therapy. Bachelot et al (OR 14-142) from Paris reported treatment of 3 adult patients with mitotane, an adrenolytic agent, for 2 to 3 years and obtained a reduction in the testicular rest tumor volume with an improved sperm count. This may represent a potent tool to improve fertility of some poorly controlled CAH patients.

OVARIAN FAILURE

The causes of premature ovarian failure (POF) are rarely identified in adults. However Conway (S9-38)

from London approached this issue with data related to optimization of the substitutive estrogenic therapy in adolescents. Age at onset of this treatment was critical for adult carotid intima media thickness, predictive of vascular complications, and was inversely correlated with the estrogen dosage. Appropriate uterine thickness for future pregnancy was obtained if treatment was not delayed. Finally, better results in assisted conception with donated oocytes were also obtained in women with early ovarian failure who received treatment before the age of 14. These data may also be relevant to patients with gonadal dysgenesis and those with ovarian failure secondary to cancer therapy in pediatric practice.

Raphaël Rappaport, MD

Measured versus Reported Parental Height

Cizmecioglu and colleagues interviewed 200 parents (100 males, 100 females), mean age 37.8 years and ascertained their reported height. Their actual height was then measured by a single observer using a Harpenden stadiometer. On average, males overestimated their height, while females reported their height relatively accurately. However, there was a wide spread of discrepancies for both sexes. Overall there was a small positive correlation between age and the difference between reported and measured height. Of interest, subjects who had been measured previously were less accurate at reporting their height than those who guessed their height. The mean difference in reported versus measured height was 1.09 cm for men (range -3.3 to 5.2) and -0.09 for females (range -6.2 to 6.4). The authors pointed out that there was considerable individual variation among both sexes in over or under estimating their exact height and state that their data reinforces the need for accurate height measurement and recording of both mother and father at the earliest possible opportunity.

Cizmecioglu F, Doherty A, Paterson WF, Young D, Donaldson MD. Measured versus reported parental height. Arch Dis Child. 2005;90:941-942.

Editor's Comment: *This is a very short paper which represents some interesting and very important information. It is a relatively common practice in pediatric endocrine clinics to calculate the mid-parental height as a target height for the child being evaluated. Clearly it is important that this target height is calculated correctly. It is not uncommon for parents to state that they are unaware of their precise height or to report their height with obvious discrepancy from observation. In addition it is not uncommon for children to come the clinic with either one or more non-biological parents, or for information regarding the "no longer present" parent's height to be estimated with little precision. The recommendations of the authors of this study should be taken seriously: parental height should be measured at the earliest possible time and become part of the child's permanent medical record. Such information could be exceedingly helpful in guiding the evaluation and treatment of children with growth failure at a later date. At the very least, pediatricians and pediatric endocrinologists should be encouraged to actually measure parents who accompany their child for evaluation of growth failure.*

William L. Clarke, MD

Apnea in Prader-Willi Syndrome Patients on Growth Hormone Therapy

Case reports of sudden fatalities, primarily respiratory, in children with Prader-Willi Syndrome (PWS) receiving growth hormone (GH) therapy caused alarm and prompted a voluntary label change to include a new warning. Benefits of GH treatment in these patients include improved linear growth, increased muscle mass and amelioration of hypotonia, and decreased total body fat. Sleep-disordered breathing is common in PWS, both obstructive (from pharyngeal narrowing, respiratory muscle hypotonia, and later compounded

by obesity) and central (hypothalamic dysfunction with abnormal arousal and response to hypercarbia which can be further blunted by obesity).

Miller and colleagues performed a prospective study of the respiratory effects of 6 weeks of GH treatment in 25 patients with genetically confirmed PWS. All patients underwent standard overnight polysomnography (PS) at baseline (either GH-naïve or voluntarily withdrawn from GH treatment for 3 months) and after 6 weeks of GH (0.24 mg/kg/wk for children and 0.0006 mg/kg/day for adults,

based on ideal body weight); two of the patients were also retested after 6 months. Subjects ranged in age from 5 months to 39 years. All had sleep-disordered breathing during the baseline PS, with both obstructive and central apneic events. After 6 weeks of treatment, 19 of the patients (76%) had improvement of the apnea/hypoxia index (AHI); the frequency of central events decreased by a median of 1.7 events/hr, while the frequency of obstructive events did not change significantly. However, 6 patients (24%) had worsening of obstructive sleep apnea/hypopnea, related to upper respiratory tract infections (URIs) and tonsillar hypertrophy. Two of these patients had high insulin-like growth factor (IGF)-I levels for bone age (z scores of +1 and +2; the others had IGF-I z scores of 0). After GH dose reduction and normalization of IGF-I level, one patient had an improved AHI on repeat PS while the other had increased AHI and a URI at the time of the repeat study. Body-mass index was not related to PS results.

The authors concluded that PS should be performed in all PWS patients at baseline, after 6 weeks of treatment with GH, and with otorhinolaryngologic evaluation whenever symptoms of sleep apnea or snoring develop. Adenotonsillectomy and titrating GH dose to achieve an IGF-I z score of 0 were also recommended as needed. Finally, they supported the warning of GH manufacturers contraindicating GH use in PWS patients with CRI or lung infections.

Miller J, Silverstein J, Shuster J, Driscoll DJ, Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi Syndrome. *J Clin Endocrinol Metab.* 2006;91:413–417.

First Editor's Comment: *I applaud the authors for performing a prospective study to directly address the question of GH effects on respiratory function in PWS patients, and I agree with the proposed pathophysiologic mechanisms. However, the finding of sudden death*

in individuals with hypothalamic dysfunction and the recurrent theme of exacerbation by intercurrent infections make me wonder about central adrenal insufficiency, which was not mentioned. Indeed, a PubMed search of adrenal insufficiency and PWS produced only one paper.¹ In this retrospective series report of 8 children and 2 adults with unexpected death or critical illness, 3 of the children had below-average sized adrenal glands on autopsy; childhood illnesses in general under the age of 2 years were associated with high fever and rapid demise or near-demise. Increased mortality among individuals with GH deficiency (GHD) despite GH treatment has been attributed to under-diagnosed and under-treated central adrenal insufficiency, and recent papers highlighted the increased risk for central adrenal insufficiency even in patients with idiopathic GHD or familial isolated GHD.^{2,3} Thus, in addition to the recommendations by Miller et al, I would encourage monitoring of adrenal function in PWS patients.

Adda Grimberg, MD

Second Editor's Comment: *Excellent points made by the authors of the paper and the editorial comment of Dr. Grimberg. I urge caution and continuous monitoring of PWS patients throughout their life, not just after initiating GH therapy, and particularly when ill.*

Fima Lifshitz, MD

References

1. Stevenson DA, Anaya TM, Clayton-Smith J, et al. *Am J Med Genet A.* 2004;124:158–164.
2. Lange M, Feldt-Rasmussen U, Svendsen OL, Kastrup KW, Juul A, Muller J. *J Clin Endocrinol Metab.* 2003;88:5784–5789.
3. Mullis PE, Robinson IC, Salemi S, et al. *J Clin Endocrinol Metab.* 2005;90:2089–2096.

Suppression of Aging

A spontaneous homozygous loss-of-function mutation in *KLOTHO* (*KL*) gene (OMIM 604824, chromosome 13q12) was initially described in a strain of mice with accelerated aging and premature death.¹ Its human homolog was later identified. *KL* encodes a transmembrane protein expressed in renal distal convoluted tubules and neural choroid plexus. Kurosu et al developed 2 strains of transgenic mice that **overexpressed** *Kl* under the control of the promoter of human elongation factor 1 α . Both male and female animals overexpressing *Kl* lived 20% to 30% longer than did wild-type (WT) control mice. They did so without restricting caloric intake or impeding somatic growth; however, fecundity was reduced in like-breeding pairs. Mice overexpressing *Kl* were euglycemic, but males had higher serum insulin concentrations than did WT controls, and both genders had attenuated hypoglycemic responses to exogenous insulin and/or

insulin-like growth factor (IGF)-I. The serum concentration of the extracellular domain of Klotho was twice as high in transgenic as in WT mice. Intraperitoneal administration of Klotho protein increased blood glucose concentrations and depressed the hypoglycemic effect of co-injected insulin. *In vitro* in cultured cells, Klotho peptide did not inhibit binding of insulin or IGF-I to their specific receptors, but specifically suppressed autophosphorylation of these receptors and impaired insulin-stimulated glucose uptake. Furthermore, Klotho down-regulated intracellular signaling transmitted through insulin receptor substrate (IRS)-1 and -2 and phosphoinositide 3-kinase p85. In *Kl*^{-/-} mice who die prematurely, life could be substantially prolonged and signs of aging halted (ie, arteriosclerosis, renal calcification, testicular atrophy) by decreasing a generation of IRS-1. The authors concluded that Klotho was a secreted protein (ie, a hormone) that extended life