

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

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Suppression of Aging

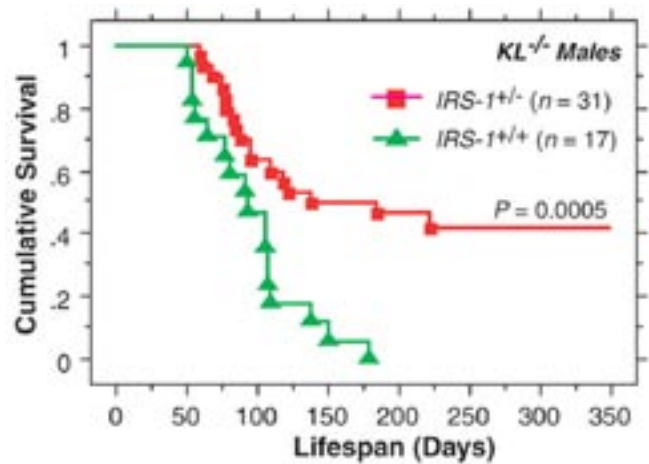
A spontaneous homozygous loss-of-function mutation in *KLOTHO* (*KL*) gene (OMIM 604824, chromosome 13q12) was initially described in a strain of mice with accelerated aging and premature death.¹ Its human homolog was later identified. *KL* encodes a transmembrane protein expressed in renal distal convoluted 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

and suppressed aging by antagonizing the cellular effects of insulin and IGF-I.

Kurosu H, Yamamoto M, Clark JD, et al. Suppression of aging in mice by the hormone Klotho. *Science*. 2005;309:1829–1833.

Editor's Comment: *Klotho* may be the long sought after elixir from the “fountain of youth.” *KLOTHO* is named after the mythological Greek Fate who spun the “thread of life.” By alternative RNA splicing, *KL* generates 2 transcripts: a 1012 amino acid protein with extracellular, transmembrane, and intracellular domains and a 549 amino acid peptide, the amino terminal sequence of the extracellular domain that is secreted and is the predominant form produced. In man, single-nucleotide polymorphisms in *KL* have been associated with altered life span and risk for atherosclerosis and osteoporosis.² That increased generation of Klotho extended life span without impairing growth emphasizes the distinctive difference between the effects of this gene and that related to caloric deprivation, another experimental mechanism to prolong life. Although both processes act by impeding insulin and IGF-I action, Klotho apparently enhances their production but antagonizes their function, while caloric deprivation depresses their production and impairs growth and fertility. These studies reinforce the concept that decreased secretion of growth hormone, insulin, and IGF-I extends life and suppresses aging,³ a concept that is the opposite of that voiced by many lay “anti-aging authorities.” Although excess Klotho decreased fecundity between like-breeding pairs of mice, the effect of this protein on the fertility of a mouse with a high level of Klotho when mated with a WT animal remains to be explored. Conceptually, there appears to



Rescue of aging-like phenotypes in *KL*^{-/-} mice by genetic intervention in insulin and IGF-1 signaling.

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be a “trade-off” between life span and reproduction. It will be of great interest to measure serum concentrations of Klotho at various stages of life and in various hormonal and metabolic disorders, particularly those involving energy utilization, as well as to determine its physiologic (and potentially therapeutic and anti-aging) effects in humans of all ages.

Allen W. Root, MD

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Motivations for GH/GnRHa Treatment and Psychosocial Functioning

Visser-van Balen et al reported (in the first paper) on the psychological consequences of combined growth hormone (GH)/gonadotropin-releasing hormone agonist (GnRHa) treatment in a multicenter, randomized-controlled study conducted in early pubertal youths (ages 11 to 13 years; Tanner breast stage 2 or 3 for girls, Tanner genital stage 2 or 3 for boys) with a diagnosis of either idiopathic short stature (ISS; 17 girls, 9 boys) or born small for gestational age (SGA; 8 girls, 4 boys). The authors explained the unusual predominance of girls as reflective of the combination of SS and relatively early puberty is more common in girls than boys. Participants had a height SDS below –2, or between –1 and –2 with a predicted adult height SDS below –2. In the second paper, the authors examined patients’ and parents’ motivations in choosing to participate in this study.

Adolescents in the treatment group were administered GH (4 IU [1.33mg]/m² BSA, SQ, daily) and GnRHa (3.75 mg, IM depot, every 4 weeks). At baseline, 1, 2, and 3 years

after beginning treatment, adolescents and their parents (mostly mothers) in both groups completed questionnaires to assess the psychosocial functioning of the adolescents by completing a standardized assessment evaluating adolescents’ health-related development, current height-related stressors, and parental concerns about their child’s future behavioral and emotional functioning; perceived current and expected adult height; global intelligence; perceived competence, psychological distress, and personality characteristics.

At baseline, a minority of parents (28%) reported their child experienced teasing or juvenilization by peers; however, a higher proportion (44.5%) anticipated their child would face challenges in the labor market as an adult (39% of boys, 48% of girls) and 39% expected their child to have lower prospects of finding a spouse (77% of boys, 17% of girls, $p < 0.01$). Parent reports of behavioral and emotional functioning suggested a statistically significant excess of problems. In contrast, adolescents’