

found a significant improvement of both mental and motor development in the hGH group compared to the control group. Children with lower developmental age had the greatest improvement in motor development, suggesting that hGH treatment might be considered at an early developmental age to optimize the hGH effects on motor development. They also found that hGH did not induce disadvantageous effects on sleep-related breathing disorders.

In their study, insulin-like growth factor (IGF)-I levels increased rapidly during hGH treatment from below the normal range to the high-normal range. IGF-I receptors have been localized in several areas in the human brain, indicating that IGF-I may have a neuroregulatory role in the central nervous system. Theoretically, IGF-I may directly influence the central nervous system or hGH might induce local IGF-I expression in brain tissue,

thereby improving psychomotor development. Another possible explanation for the improvement in mental development during hGH treatment might be that, because of the improved motor development, children are able to sit, stand and walk independently, enabling them to explore and interact with the environment and resulting in a subsequent improvement in mental development. The results of this study suggest that early start with hGH might be beneficial in PWS. However, long-term double-blind studies are needed to evaluate the efficacy and safety of the early treatment with hGH on cognition in childhood and adulthood.

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References

1. Eiholzer U, l'Allemand D, Schlumpf M, Rousson V, Gasser T, Fusch C. Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome. *J Pediatr* 2004 ;144:753-8.

Central Adrenal Insufficiency, Pituitary and Neuroradiological Alterations in Prader-Willi

Prader-Willi syndrome (PWS; OMIM 176270) is a genetic disorder caused by an alteration in the long arm of paternal chromosome 15 (by deletion, microdeletion, maternal uniparental disomy, mutation of imprinting centre, chromosomal rearrangement). PWS is characterized by a complex clinical picture (short stature, uncontrollable hyperphagia, obesity, hypogonadism) and growth hormone deficiency that seem to be a central hypothalamic/pituitary dysfunction.

The annual death rate of PWS patients is very high (3%). Many of these deaths are sudden and unexplained. Because most deaths occur during infections and PWS patients suffer from various hypothalamic insufficiencies, de Lind van Wijngaarden and colleagues investigated whether PWS patients suffer from central adrenal insufficiency (CAI) during stressful conditions. Twenty-five children genetically confirmed PWS were randomly selected. Twelve patients had paternal deletion (63%), 6 had maternal disomy (32%), and one an imprinting center mutation (5%). Median age of patients with PWS was 9.7 years (range 3.7 to 18.6 years). All were treated with recombinant human growth hormone (rhGH). Overnight single-dose metyrapone tests were performed. Metyrapone (30 mg/kg) was administered at 2330 h. At 0400, 0600, and 0730 h, ACTH, 11-deoxycortisol, cortisol, and glucose levels were measured. Diurnal salivary cortisol profiles were also assessed on a different day at wake-up, 30 minutes after wake-up, at 1400 h, and at 2000 h. Fifteen patients (60%) showed an insufficient ACTH response at the metyrapone test. There was no significant difference in age, gender, genotype, and BMI SD score between patients with CAI and those without. Morning salivary cortisol levels and diurnal profiles were normal in all children, suggesting that CAI becomes apparent only during stressful conditions.

Moreover, lughetti and colleagues retrospectively analyzed 91 patients with PWS (42 females, 49 males; age range 0.7 to 16.8 years) by cerebral MRI to determine whether there was any diminution in the anterior pituitary gland or other neuroradiological alterations. All subjects were genetically confirmed as PWS (58 microdeletions, 8 deletions, 28 maternal uniparental disomy). Of these 91 patients, MRI analysis showed a reduction in pituitary height (height <1 SD) in 45 patients (49.4%: 23 cases <2 SD; 20 males, 25 females) with 4 cases of empty sella, a complete absence of the posterior pituitary bright spot in 6 patients (6.6%) and other neuroradiological alterations in 10 patients (11%: 8 cases of ventricular enlargement, 2 cases of thin corpus callosum). Altogether, neuroradiological alterations were present in 61 of the 91 (67%) patients. No genotype-phenotype relationship was shown. These results of both de Lind van Wijngaarden and lughetti indicate that CAI and neuroradiological alterations are more frequent in PWS patients than has been reported to date.

de Lind van Wijngaarden RF, Otten BJ, Festen DAM, et al. High prevalence of central adrenal insufficiency in patients with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2008;93:1649-54.

lughetti L, Bosio L, Corrias A, et al. Pituitary height and neuroradiological alterations in patients with Prader-Labhart-Willi syndrome. *Eur J Pediatr*. 2008;167:701-2.

Editor's Comment: *These are very interesting observational studies, which provide important information for physicians who care for those with PWS. Strikingly, de Lind van Wijngaarden and colleagues reported 60% of PWS patients had CAI; the high percentage of CAI in PWS patients might explain the high rate of sudden death in these patients, particularly during infection-related stress. Because metyrapone blocks cortisol synthesis, it causes a sudden increased demand for ACTH production, a*

situation mimicking stress. Patients with an insufficient ACTH response during the metyrapone test are therefore considered as having CAI during stressful conditions such as infection and surgery. In view of the importance of an adequate function of the hypothalamus-pituitary-adrenal axis for survival, the high prevalence of CAI may be an explanation for the high death rate in PWS patients. In addition to CAI, the condition of acutely ill PWS patients is further compromised by an increase in those with sleep apnea and sudden death during upper respiratory infection. Therefore, de Lind van Wijngaarden and colleagues stated that PWS patients

should be considered to have CAI during stress until proven otherwise with a metyrapone test and they recommended hydrocortisone treatment for PWS patients during stressful conditions including mild upper respiratory infections.

From these results, both neuroradiological alterations and CAI may relate mutually and may be important risk factors for a tendency of sudden, unexpected death in PWS patients. Further studies, including functional and longitudinal neuroradiological investigation, are needed to clarify these problems in PWS patients.

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Genital Function and Sensitivity Following Feminizing Surgery

Like other disorders of sex development (DSD), congenital adrenal hyperplasia (CAH) in 46,XX can be associated with ambiguous genitalia at birth. Clinical management commonly involves surgery performed during infancy and childhood to feminize the appearance of genitals. However, it has been suggested that surgery to the clitoris potentially disrupts neurological pathways and compromises erotic sensation and pleasure. In a cross-sectional investigation, Crouch and colleagues investigated the genital sensitivity of women with CAH and 10 healthy controls (23 to 38 years old). Sensitivity thresholds for the clitoris and upper vagina were measured using a GenitoSensory Analyzer and sexual function by standardized self-report questionnaire including 7 subscales assessing sexual anorgasmia, satisfaction, sensuality, communication, vaginal penetration difficulties, frequency of intercourse and avoidance. Thirty-two of 56 eligible women with CAH (17 to 39 years of age) agreed to participate: 25 with classic CAH, 4 with non-salt losing CAH, and 3 with late-diagnosed CAH. A total of 28 of 32 women participated in sensory testing, including 4 who had not undergone prior genital surgery. The sample is heterogeneous with regard to the type of genital surgery (clitoridectomy versus clitoral reduction and with or without surgery to the lower vagina), age at surgical

procedures, and number of surgical procedures.

Clitoral sensation (temperature) testing indicated relative impairment for those who underwent clitoridectomy. As anticipated, clitoral sensation was not impaired in those with CAH who had not undergone surgery. In comparison with control group participants, women who had undergone clitoral reduction had a higher median threshold for warmth detection and a lower median threshold for cold. Vaginal sensitivity (vibratory) testing could not be assessed in some participants due to introital vaginal stenosis which prevented insertion of the vaginal probe. In addition, some control group participants chose not to undergo vaginal testing. For those who did, no difference was observed in vaginal sensation between the CAH group and control group participants (regardless of prior vaginal surgery).

Assessment of sexual function also proved to be challenging in this study; only 19 of 32 CAH participants adequately completed the questionnaire because of

GRISS sexual function scores in women with CAH divided into those with and without surgery compared to normal controls

	Median CAH (range)		Median Normal (range)	P Value (Kruskal-Wallis test)
	Surgery	No Surgery		
No. pts	15*	4	10	
Global score	5 (1-9)	4 (1-5)	2 (1-8)	0.029
Infrequent intercourse	8 (1-9)	6 (3-8)	5 (1-7)	0.030
Non communication	4 (1-9)	5 (2-6)	5 (3-9)	0.884
Dissatisfaction	4 (1-9)	3 (2-5)	3 (1-6)	0.195
Avoidance	6 (1-9)	5 (4-7)	2 (1-7)	0.043
Non sensuality	5 (1-8)	3 (2-6)	2 (1-9)	0.331
Vaginal penetration difficulties	6 (1-9)	1 (1-2)	1 (1-2)	0.006
anorgasmia	6 (3-9)	4 (3-6)	3 (2-9)	0.065

Score range 1 to 9 with 5 or greater indicating difficulty.

*One respondent excluded since she did not indicate a history of surgery.

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