

nominally statistically significant for half of the allele pairs, and 17% displayed an expression difference of 2-fold or more for one allele over the other.

Next they searched for DAE in the monozygotic twins utilizing 211 SNPs that were found to be heterozygous in 5 or more twin pairs and did an analysis of variance to determine the significance of twin resemblance. The results revealed much greater similarity between twins than predicted by chance. In a few instances in which more than one informative SNPs mapped to the same gene, the results were concordant. Twin resemblance for DAE was detected not only for genes whose alleles deviated substantially from equal expression, but also for genes whose alleles are expressed at relatively similar levels.

The authors drew 2 conclusions from their results. First, at least 50% of genes expressed in lymphoblastoid B cells show some degree of DAE. The difference is greater than 2-fold for some genes. Second, much of the observed DAE seems to be under genetic control.

Cheung VG, Bruzel A, Burdick JT, Morley M, Devlin JL, Spielman RS. Monozygotic twins reveal germline contribution to allelic expression differences. *Am J Hum Genet.* 2008; 82:1357-60.

Editor's Comment: *This investigation provides another explanation for why monozygotic twins are so similar. A paper was recently reviewed in GGH^{1,2} suggesting that patterns of epigenetic modification diverge in monozygotic twins as they age. Since epigenetic modification influences expression of genes, one wonders if DAE varies with age or correlates at all with such modifications. Similarly, it would be interesting to know the extent to which DAE occurs in cell types other than lymphoblastoid B cells.*

William A. Horton, MD

Reference

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Growth Hormone Therapy Improves Mental and Motor Development in Young Prader-Willi Patients

Prader-Willi syndrome (PWS) is increasingly diagnosed in early infancy because pediatricians and neonatologists are more aware of the clinical picture (muscular hypotonia, feeding difficulties, failure to thrive, and psychomotor delay). The genetic cause of PWS is an alteration in the long arm of paternal chromosome 15 (by deletion, microdeletion, maternal uniparental disomy, mutation of imprinting centre, chromosomal rearrangement). It is well known that methylation analysis is an efficient tool for early and reliable diagnosis of PWS. Children with PWS have an abnormal body composition with a relatively high body fat percentage and a low lean body mass (LBM). Even in PWS infants who are underweight, body fat percentage is high.

Treatment with human growth hormone (hGH) in older children with PWS results not only in an increased growth response but also in an improvement in body composition, with a decline in fat percentage and an increment in LBM, resulting in increased muscle strength and agility. The effects of hGH therapy on psychosocial development in PWS have not been well studied.

Festen and colleagues evaluated psychomotor development in PWS infants and toddlers during hGH treatment compared to controls. Forty-three PWS infants were evaluated at baseline; 29 of them were randomized into a GH group (n=15) receiving 1 mg/m²/day of GH or a non-GH-treated control group (n= 14). At baseline, and after 12 months of GH treatment, an analysis with Bayley Scales of Infant Development II (BSID-II) was performed. Data were converted to percentage of expected development for age, and changes during follow-up were calculated.

Infants in the GH group had a median age of 2.3 years (interquartile range [IQR] 1.7–3.0) and the median age of the control group was 1.5 years (IQR 1.2–2.7) ($p=0.17$). Both mental and motor development improved significantly during the first year of study in the GH group vs the control group: median (IQR) change was +9.3% (–5.3 to 13.3) vs –2.9% (–8.1 to 4.9) ($p<0.05$) in mental development and +11.2% (–4.9 to 22.5) vs –18.5% (–27.9 to 1.8) ($p< 0.05$) in motor development, respectively. Thus, one year of hGH treatment significantly improved mental and motor development in PWS infants compared to controls. Infants with lower developmental age had the greatest improvement in motor development. There was also a normalization of head circumference and a significant increase in height SDS in the GH group, but not in the control group after one year of hGH treatment. The hGH was well tolerated; compared to randomized controls, hGH did not induce disadvantageous effects on sleep-related breathing disorders, carbohydrate metabolism and thyroid hormone levels.

Festen DAM, Wevers M, Lindgren AC, et al. Mental and motor development before and during growth hormone treatment in infants and toddlers with Prader-Willi syndrome. *Clin Endocrinol.* 2008;68:919-25.

Editor's Comment: *The best point of time to initiate hGH therapy for PWS remains unknown. Eiholzer et al' do not recommend starting hGH therapy in PWS in the first year of life because of an increased risk of sudden infant death during this period. Festen and colleagues evaluated whether hGH treatment started at an early age could contribute to an improvement in mental and motor development in a group of PWS patients. They*

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.

Yoshikazu Nishi, MD

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*