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Cortisol Levels in Prader-Willi Syndrome Support Changes in Routine Care

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Prader-Willi syndrome (PWS) is a complex genetic disorder due to loss of paternally expressed genes from the 15q11–q13 region [Bittel and Butler, 2005; Cassidy and Driscoll, 2008] and recognized as the most common genetic cause of life-threatening obesity [Butler, 1990]. The natural history and clinical course in PWS indicates two major stages: (1) infantile hypotonia, a poor suck, feeding difficulties, and failure to thrive; and (2) hyperphagia with subsequent obesity during early childhood and learning/behavioral problems [Butler et al., 2006; Goldstone et al., 2008]. Hyperphagia, central obesity, short stature, decreased muscle mass, cryptorchidism, and hypogonadism are consistent with endocrine and/or metabolic abnormalities involving the hypothalamus in PWS [Burman et al., 2001; Eiholzer and Lee, 2006]. Additionally, small adrenal size has been reported in autopsies of PWS children [Stevenson et al., 2004].

Several unexplained deaths have been reported in children with PWS including some individuals on growth hormone (GH) treatment [Schrandt-Stumpel et al., 2004; Stevenson et al., 2004; Tauber et al., 2008]. Additionally, no difference was reported in gender ratio or prevalence of sleep apnea between 28 children with PWS treated with GH and 36 untreated subjects in a recent review of 64 deaths in children with PWS [Tauber et al., 2008]. Most deaths occurred during the first 9 months after initiation of GH treatment with respiratory problems (respiratory insufficiency or infections) being the most common cause of death [Tauber et al., 2008].

Because of an annual death rate of 3% in PWS and with most deaths occurring at times of moderate infections along with various recognized hypothalamic insufficiencies, de Lind van Wijngaarden et al. [2008] studied 25 randomly selected PWS children (median age of 9.7 years) and found that 60% showed central adrenal insufficiency (CAI) following overnight metyrapone testing. However, morning salivary cortisol levels and diurnal profiles were normal suggesting that CAI becomes apparent only during stressful conditions, de Lind van Wijngaarden et al. [2008] suggested that this high percentage of CAI in PWS could explain the high rate of sudden death particularly during times of stress in this syndrome.

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Similarly, related to this issue, our group studied morning (8–11 am) plasma cortisol levels in 63 genetically confirmed PWS subjects (30 males, 33 females) with a mean age of 20.8 years (range: 2.5 months to 50 years) and 30 individuals with simple obesity at comparable ages (15 males, 15 females) with a mean age of 23.2 years (range: 12 months to 50 years), as a preliminary measure of adrenal status during regular health surveillance. We used a solid phase, competitive chemi-luminescent enzyme immunoassay kit following manufacturer's instructions (Siemens, Los Angeles, CA) and the normative reference range (5–25 µg/dl) provided with the kit. All subjects were healthy, and mostly Caucasian.

The majority of PWS subjects were not on GH and none were using insulin, thyroid or sex hormones, or steroids. Age, BMI, gender, and PWS genetic subtypes were also recorded (see Table I). Two subjects had levels below the normative range (one control adult female with a cortisol of 4.6 µg/dl and one of four PWS infants studied with repeated measures had a level of 1.9 µg/dl). No significant differences were found for age (23.2 ± 15.6 years; 20.8 ± 10.7 years), BMI (33.1 ± 12.0 kg/m²; 34.1 ± 10.9 kg/m²), or cortisol concentration (14.6 ± 6.5 µg/dl; 13.5 ± 6.1 µg/dl) between the obese and PWS groups, respectively, or among the PWS genetic subtypes (deletion, maternal disomy, imprinting defect) using univariate analysis with age correction. Age correction was required as cortisol levels were positively correlated with age for the PWS subjects ($r = 0.34$; $P = 0.007$), but not for obese controls ($r = 0.08$; $P = 0.69$). Two-sided *t*-tests showed a significant difference in cortisol levels between young (< 3 years) and older (>3 years) PWS subjects (mean 7.6 and 13.9 µg/dl, respectively; $P = 0.045$).

Several factors can influence cortisol levels, but this observation of difference in age groups suggests that a transition from the hypotonic failure-to-thrive stage during infancy in PWS to the hyperphagic obesity stage involves changes in cortisol production related to changes in hypothalamic activity overtime.

Conclusions cannot be reached regarding health-care management based on morning cortisol samples alone and our study of only four PWS infants. However, combined with the data reported by de Lind van Wijngaarden et al. [2008] of CAI in PWS children, it is recommended that PWS infants and children undergo endocrine evaluation to monitor cortisol levels including low-dose ACTH stimulation testing to determine if adrenal insufficiency is present before GH treatment or other interventions considered to be stressors. Of note, de Lind van Wijngaarden et al. [2008] suggested that hydrocortisone should be used during acute illness in individuals with PWS unless CAI has been excluded previously.

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TABLE I.

Subject Groups, Age, BMI, and Morning Plasma Cortisol Data

Groups (N)	Age (years), mean $\pm$ SD	BMI (kg/m ²), mean $\pm$ SD	Cortisol (μ g/dl), mean $\pm$ SD
Control (30)	23.2 $\pm$ 15.6	33.1 $\pm$ 12.0	14.6 $\pm$ 6.5
Prader—Willi syndrome (63)	20.8 $\pm$ 10.7	34.1 $\pm$ 10.9	13.5 $\pm$ 6.1
<i>P</i> -value	0.393 ^a	0.691 ^a	0.512 ^b
PWS deletion type I (15)	27.1 $\pm$ 10.1	37.0 $\pm$ 10.5	14.4 $\pm$ 5.0
PWS deletion type II (19)	20.5 $\pm$ 9.8	34.0 $\pm$ 8.4	15.4 $\pm$ 7.4
PWS uniparental disomy (24)	18.3 $\pm$ 10.8	31.1 $\pm$ 11.0	11.8 $\pm$ 5.6
PWS imprinting center defect (5)	15.2 $\pm$ 9.9	40.6 $\pm$ 17.1	11.6 $\pm$ 3.7
<i>P</i> -value	0.047 ^c	0.193 ^c	0.329 ^b
Control 3 years old (4)	—	—	19.4 $\pm$ 11.8
Control >3 years old (26)	—	—	13.8 $\pm$ 5.3
<i>P</i> -value	—	—	0.113 ^a
PWS 3 years old (4)	—	—	7.6 $\pm$ 3.8
PWS >3 years old (59)	—	—	13.9 $\pm$ 6.0
<i>P</i> -value	—	—	0.045 ^a

^aIndependent samples Student's *t*-test.^bUnivariate analysis of variance (ANOVA) correcting for age.^cOne-way ANOVA.