Published in final edited form as:

Am J Med Genet A. 2007 March 01; 143A(5): 488–492. doi:10.1002/ajmg.a.31683.

Thyroid Function Studies in Prader–Willi Syndrome

Merlin G. Butler^{*}, Mariana Theodoro, Jennifer D. Skouse

Section of Medical Genetics and Molecular Medicine, Children's Mercy Hospitals and Clinics and University of Missouri-Kansas City School of Medicine, Kansas City, Missouri

To the Editor: Prader–Willi syndrome (PWS) is a complex genomic imprinting disorder in which afflicted individuals experience physical and behavioral abnormalities. Most diagnosed subjects have abnormalities of chromosome 15 generally due to a typical paternal deletion of chromosome 15q11–q13 (about 70% of subjects) followed by maternal disomy 15 (about 25%) with the remaining subjects having imprinting defects or chromosome 15 rearrangements [Cassidy, 1984; Butler, 1990; Bittel and Butler, 2005; Butler et al., 2006]. The typical deletion is further divided into type I and type II deletions depending on chromosome breakpoint assignments. Individuals with PWS have a recognized phenotype consisting of minor facial anomalies, short stature, small hands and feet, hyperphagia, infantile hypotonia, hypogonadism, early childhood obesity, and behavioral/learning problems. Many of the characteristic features such as short stature, central obesity, hyperphagia, decreased lean mass, cryptorchidism, and hypogonadism are consistent with an underlying endocrine or metabolic abnormality including the hypothalamic-pituitary axis while short stature and obesity can be seen in hypothyroidism. However, there is a lack of data describing thyroid hormone levels in PWS [Tze et al., 1981; Bray et al., 1983; Butler, 1990; Ritzen et al., 1992; Butler et al., 2006].

The primary function of the thyroid gland is to produce the hormones, thyroxine (T₄) and triiodothyronine (T₃). Thyroxine is converted into T₃ in the thyroid gland and various organs of the body. T₃ is the more active hormone produced by the thyroid. When thyroid-stimulating hormone (TSH) produced by the anterior pituitary stimulates the thyroid gland, the thyroid follicular cells reabsorb thyroglobulin and attached iodinated tyrosines are cleaved, forming T₄ and T₃. Free T₄ (not bound to protein) is the preferred measurement in diagnostic studies. The thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and affect carbohydrate, lipid and vitamin metabolism [LaFranchi, 2004]. The production of TSH can be inhibited by increased levels of sex hormones, glucocorticoids and by somatostatin [Refetoff et al., 2001].

Primary hypothyroidism occurs when the thyroid gland does not respond appropriately to TSH released by the brain while secondary (central) hypothyroidism occurs when there is a lack of TSH production. Hypothyroidism is seen more often in advancing age and in more females than males. Approximately 1.5–2% of women and 0.2% of men in the general population have hypothyroidism [Ferri, 2003]. Of those diagnosed with hypothyroidism,

^{*}Correspondence to: Merlin G. Butler, M.D., Ph.D., Section of Medical Genetics and Molecular Medicine, Children's Mercy Hospitals and Clinics, 2401 Gillham Road, Kansas City, MO 64108. mgbutler@cmh.edu.

90% have primary hypothyroidism in which the defect or deficiency originates from the thyroid gland itself [Vanderpump and Tunbridge, 1996; Wang and Crapo, 1997]. Thus, secondary hypothyroidism which originates from abnormalities of the hypothalamic-pituitary axis is less common. However, secondary hypothyroidism may be more common in the PWS population due to brain dysfunction known to be associated with this disorder.

The majority of subjects with PWS develop obesity, but this can be prevented or controlled with close supervision, strict dietary management and regularly scheduled exercise. Obesity can lead to multiple physiological changes or result from hormone disturbances such as hypothyroidism. Body composition differences have been reported in PWS and obese subjects. PWS have significantly decreased lean body mass and an increased percentage of body fat compared with obese controls [Bray et al., 1983; Meaney and Butler, 1989; Ritzen et al., 1992; Butler et al., 2006; Theodoro et al., 2006]. In addition, body fat distribution by dual energy X-ray absorptiometry (DEXA) measurements show more peripheral fat in subjects with PWS; whereas, visceral and central adiposity is more common in subjects with simple obesity [Meaney and Butler, 1989; Burman et al., 2001; Theodoro et al., 2006].

Most children with PWS also have growth hormone deficiency with reduced serum IGF-I levels while obese children generally have normal or elevated IGF-I levels [Burman et al., 2001; Butler et al., 2006]. While obesity seen in PWS can lead to the development of type 2 diabetes mellitus, glucose tolerance, and insulin sensitivity testing in PWS subjects show more insulin sensitivity than seen in obese controls [Tze et al., 1981; Bray et al., 1983; Ritzen et al., 1992; Burman et al., 2001; Talebizadeh and Butler, 2005].

Previous reports have shown thyroid hormones and TSH to be normal or slightly elevated in PWS while disturbances in other hormone levels (e.g., growth hormone) are present [Jeffcoate et al., 1980; Tze et al., 1981; Burman et al., 2001]. Yet, in one study of 28 children with PWS, in which 23 had been genetically confirmed to have PWS, 32% presented with hypothyroidism (either with low T4 and/or elevated TSH levels) [Tauber et al., 2000]. Similarly, a child with PWS and congenital hypothyroidism has also been reported [Sher et al., 2002]. Subjects with PWS have been given thyrotropin-releasing hormone (TRH) and an increase was found in TSH response as compared with obese controls. An increased response to TRH injection may support a disruption in the hypothalamic-pituitary system in PWS [Tze et al., 1981; Bray et al., 1983; Ritzen et al., 1992; Butler et al., 2006]. Most of the previous thyroid hormone studies were reported prior to the advancement of diagnostic genetic testing and/or determination of the genetic subtype in PWS. Variations in laboratory assays, reference ranges and the age of subjects could also contribute to the variation reported in thyroid hormone studies in PWS. Hence, we report the results of thyroid function tests in individuals with PWS ranging from 10 to 44 years of age with the typical 15q11-q13 deletion subdivided into type I and type II deletions or with maternal disomy 15.

Our study to determine the frequency of hypothyroidism in a relatively large cohort comprised of 47 individuals with PWS recruited from a genotype-phenotype study and examined by one of us (M.G.B.). This study was reviewed and approved by the local institutional review board. Experimental protocols were explained to all participants and/or

their legal guardians and informed consent and assent were obtained following approved guidelines. Of these subjects, 26 had a deletion of the 15q11-q13 region detected by fluorescence in situ hybridization using 15q11-q13 probes (e.g., SNRPN) and 21 individuals had UPD. The deletion subtype (type I or type II) was determined using specific polymorphic DNA microsatellites from the 15q11-q13 region and genomic DNA from the parents and the individual with PWS. The genetic status (UPD, type I or type II deletion) was identified by polymerase chain reaction (PCR). Furthermore, abnormal methylation testing with PCR analysis was consistent with the diagnosis in all individuals with PWS. The overall male to female ratio in the PWS group was 21:26 and their age range was 10–44 years with a mean of 22 ± 8 years.

The PWS deletion group consisted of 11 males (10 Caucasian, 1 African-American) and 15 females (14 Caucasian, 1 African-American) with a mean age of 22 years while the PWS UPD group encompassed 10 males (9 Caucasian, 1 Hispanic) and 11 females (10 Caucasian, 1 Hispanic) with a mean age of 24 years. None of the PWS subjects were on growth, thyroid or sex hormone treatment. Eight of the 47 individuals with PWS (5 deletion and 3 UPD) had a history of diabetes mellitus, nonetheless, only 3 PWS individuals were being treated with insulin at the time of study.

Height to the nearest 0.1 cm and weight to the nearest 0.1 kg were obtained at baseline for each subject in the clinical setting. Waist circumference was measured to the nearest 0.1 cm with a steel tape measure at the umbilicus level in standing position. Likewise, the hip circumference was obtained to the nearest 0.1 cm at the greater trochanter level. Body mass index (BMI) was calculated (kg/m^2) for each subject and obesity was defined as BMI ≥ 30 for adults (≥ 18 years of age) and a BMI $> 95\%$ using published standards for sex for subjects less than 18 years old [Kuczmarski et al., 2000].

Blood samples were obtained (between 7 and 9 am) after a 12 hr overnight fast for basal plasma concentrations of total thyroxine (T4), free thyroxine (fT4), triiodothyronine (T3), and TSH and measured routinely with standard laboratory methods and established normative data used for reference ranges [Robertson and Shilkofski, 2005]. All participants were consuming a weight-maintaining diet for 2 days before blood sampling.

Data generated in this study were analyzed by univariate analysis of variance correcting for age and gender, one-way ANOVA and Pearsonian correlation coefficients. Statistical significance was set at the 5% level for all tests. The results were presented as mean $\pm$ SD. Statistical analyses were performed using SPSS version 12.0 for Windows (SPSS, Inc., Chicago, IL).

Because hypothyroidism is associated with an increased weight gain and obesity, PWS subjects may be expected to have an increased risk compared to the general population. There were no significant differences in age, BMI, tissue % fat or waist to hip ratios between the PWS genetic subtypes. We then measured total thyroxine (T4), free thyroxine (fT4), triiodothyronine (T3), and TSH levels in 47 PWS individuals (26 deletion, 21 UPD; 21 males, 26 females; mean age $\pm$ SD = 22.5 ± 8.1 years). Significant differences were seen using univariate analysis of variance for total thyroxine levels between PWS deletion type I

and type II individuals with the type I deletion group having a lower level of thyroxine (6.3 ± 0.6 and 8.6 ± 0.5 $\mu\text{g/dl}$; $P < 0.05$) when adjusted for age and gender. T4 levels also showed significant differences between all three PWS genetic subtypes when analyzed with a one-way ANOVA test ($P < 0.01$, see Table I). No significant differences were seen for any of the thyroid hormones analyzed between deletion and UPD, and male and female PWS individuals. The individual thyroid hormone levels are illustrated in Figure 1. However, we found one (or 2.1%) of our 47 PWS subjects had hypothyroidism which compares with about 2% in the general population. This individual with PWS was a 30-year-old female with a type I deletion and thyroid hormone levels consistent with secondary hypothyroidism, that is, low T4, fT4 and T3 levels and normal TSH level (see Fig. 1).

There appeared to be a possible correlation between body fat distribution, measured by waist to hip measurement ratios, and total thyroxine and free thyroxine levels with the male and female PWS subjects showing opposite findings. PWS females showed a significant positive correlation ($r = 0.51$; $P = 0.02$) with waist to hip ratio and total thyroxine levels but with no significant correlation with free thyroxine levels. However, PWS males had a significant negative correlation ($r = -0.56$; $P = 0.02$) with waist to hip ratio and free thyroxine levels but with no significant correlation with total thyroxine levels. The level of obesity and fat patterns are also known to be reversed in males and females, that is, males have more obesity than seen in females with PWS [Meaney and Butler, 1989; Theodoro et al., 2006]. The correlation observations seen in our subjects could also be explained by sex differences in binding proteins or other factors such as differing medication use in males versus females. However, no significant differences were observed when comparing those PWS males or females with or without sex hormone replacement or use of selective serotonin reuptake inhibitors (SSRIs). Two subjects with a history of diabetes (a 28-year-old male on insulin and a 29-year-old male on an oral hypoglycemic agent) had TSH levels above the normal range.

In summary, we found a similar frequency of hypothyroidism in our PWS subjects compared to the general population. The expected frequency of hypothyroidism in the general population is about 2% and one (or 2.1%) of our 47 PWS subjects had hypothyroidism. If a general disturbance of the hypothalamic-pituitary axis exists in PWS, we would have anticipated a frequency greater than 2% for hypothyroidism in our subject cohort; thus, our data may reflect a selective hypothalamic-pituitary dysfunction in PWS.

ACKNOWLEDGMENTS

We thank the subjects with PWS and their families for participating in the study. This study was partially funded by the National Institute of Child Health and Human Development (P01HD30329), by The Hall Foundation, and by a Physician Scientist Award (Children's Mercy Hospital and Clinics).

Grant sponsor: National Institute of Child Health and Human Development; Grant number: P01HD30329; Grant sponsor: The Hall Foundation.

REFERENCES

- Bray GA, Dahms WT, Swerdloff RS, Fiser RH, Atkinson RL, Carrel RE. 1983 The Prader-Willi syndrome: A study of 40 patients and a review of the literature. *Medicine* 62:59–80. [PubMed: 6338343]

- Bittel DC, Butler MG. 2005 Prader-Willi syndrome: Clinical genetics, cytogenetics and molecular biology. *Expert Rev Mol Med* 7:1–20.
- Burman P, Ritzen EM, Lindgren AC. 2001 Endocrine dysfunction in Prader-Willi syndrome: A review with special reference to growth hormone. *Endocrin Rev* 22:787–799.
- Butler MG. 1990 Prader-Willi syndrome: Current understanding of cause and diagnosis. *Am J Med Genet* 35:319–332. [PubMed: 2309779]
- Butler MG, Hanchett JM, Thompson T. 2006 Clinical findings and natural history of Prader-Willi syndrome In: Butler MG, Lee P, Whitman B, editors. *Management of Prader-Willi Syndrome*. 3rd edition. New York, NY: Springer p 3–48.
- Cassidy SB. 1984 Prader-Willi syndrome. *Curr Prob Pediatr* 14:1–63.
- Ferri FF. 2003 Hypothyroidism In: Ferri's clinical advisor instant diagnosis and treatment. St. Louis, MO: Mosby p 455.
- Jeffcoate WJ, Laurance BM, Edwards CRW, Besser GM. 1980 Endocrine function in the Prader-Willi syndrome. *Clin Endocrin* 12:81–89.
- Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. 2000 CDC Growth Charts: United States. *Adv Data* 8:1–27.
- LaFranchi S. 2004 Disorders of the thyroid gland In: Behrman RE, Kliegman RM, Jenson HB, editors. *Nelson textbook of pediatrics*. 17th edition. Philadelphia, PA: Saunders p 1870–1879.
- Meaney FJ, Butler MG. 1989 Characterization of obesity in the Prader-Labhart-Willi syndrome: Fatness patterning. *Med Anthropol Q* 3:294–305. [PubMed: 27695159]
- Refetoff S, Dumont J, Vassart G. 2001 Thyroid disorders In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. *The metabolic & molecular bases of inherited disease*. 8th edition. New York, NY: McGraw-Hill p 4029–4064.
- Ritzen EM, Bolme P, Hall K. 1992 Endocrine physiology and therapy in Prader-Willi syndrome. *NATO ASI Series H61*:153–169.
- Robertson J, Shilkofski N. 2005 *The Johns Hopkins Hospital Harriet Lane Handbook*. 17th edition. Philadelphia, PA: Mosby p 274–281.
- Sher C, Bistrizter T, Reisler G, Reish O. 2002 Congenital hypothyroidism with Prader-Willi syndrome. *J Ped Endo Metab* 15:105–107.
- Talebizadeh Z, Butler MG. 2005 Insulin resistance and obesity related factors in Prader-Willi syndrome: Comparison with obese subjects. *Clin Genet* 67:230–239. [PubMed: 15691361]
- Tauber M, Barbeau C, Jouret B, Pienkowski C, Malzac P, Moncla A, Rochiccioli P. 2000 Auxological and endocrine evolution of 28 children with Prader-Willi syndrome: Effect of growth hormone therapy in 14 children. *Hormone Res* 53: 279–287. [PubMed: 11146368]
- Theodoro MF, Talebizadeh Z, Butler MG. 2006 Body composition and fatness patterns in Prader-Willi syndrome: Comparison with simple obesity. *Obesity* 14: 1685–1690. [PubMed: 17062796]
- Tze WJ, Dunn HG, Rothstein RL. 1981 Endocrine profiles and metabolic aspects of Prader-Willi syndrome In: Holm VA, Sulzbacher S, Pipes PL, editors. *The Prader-Willi Syndrome*. Baltimore, MD: University Park Press p 281–291.
- Vanderpump MP, Tunbridge WM. 1996 The epidemiology of thyroid disease In: Braverman LE, Uriger RD, editors. *Werner and Ingbar's the thyroid*. 7th edition. Philadelphia, PA: Lippincott-Raven p 474–482.
- Wang C, Crapo LM. 1997 The epidemiology of thyroid disease and implications for screening. *Endocrinol Metab Clin North America* 26:189–218.

Fig. 1. Histograms of T3, T4, fT4, and TSH levels for each subject with Prader–Willi syndrome. * Designates below and ** designates above normal range.

TABLE I.
Demographic, Body Measurements, and Thyroid Hormone Levels in Prader–Willi Subjects

Variables	PWS (total)		PWS deletion type I		PWS deletion type II		PWS UPD		P-value*
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
Age (years)	47	22.5 $\pm$ 8.1	11	24.6 $\pm$ 7.6	15	19.4 $\pm$ 6.3	21	23.6 $\pm$ 9.2	0.200
Body mass index (Kg/m ²)	47	34.3 $\pm$ 9.1	11	35.6 $\pm$ 11.7	15	34.0 $\pm$ 7.3	21	33.8 $\pm$ 9.1	0.857
Tissue % fat	47	51.2 $\pm$ 7.7	11	52.4 $\pm$ 7.7	15	52.7 $\pm$ 7.6	21	49.5 $\pm$ 7.7	0.404
Waist to hip ratio	38	1.0 $\pm$ 0.1	10	0.9 $\pm$ 0.1	14	1.0 $\pm$ 0.1	14	1.0 $\pm$ 0.1	0.078
Total thyroxine (T4) (μ g/dl)	38	8.1 $\pm$ 2.0	10	6.3 $\pm$ 0.6	13	8.6 $\pm$ 0.5	15	8.8 $\pm$ 0.5	0.008
Free thyroxine (fT4) (ng/dl)	43	1.1 $\pm$ 0.2	10	1.0 $\pm$ 0.1	13	1.2 $\pm$ 0.1	20	1.1 $\pm$ 0.1	0.235
Triiodothyronine (T3) (ng/dl)	41	137 $\pm$ 38	10	125 $\pm$ 14	12	145 $\pm$ 12	19	140 $\pm$ 9	0.568
Thyroid-stimulating hormone (TSH) (μ U/ml)	47	2.2 $\pm$ 1.3	11	2.6 $\pm$ 0.5	15	2.3 $\pm$ 0.4	21	2.0 $\pm$ 0.3	0.504

* P-values calculated using one-way ANOVA among all three groups (deletion type I, deletion type II, and UPD).