Thyroid Function from Birth to Adolescence in Prader-Willi Syndrome

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Objectives To describe the response of thyroid-stimulating hormone (TSH) to thyroid-releasing hormone in children and adolescents with Prader-Willi syndrome (PWS), and to compare TSH and total thyroxine (TT4) concentrations measured on neonatal screening for congenital hypothyroidism in children with PWS and controls.

Study design All participants had genetically confirmed PWS. The TSH responses to thyroid-releasing hormone, free thyroxine (fT4), and free triiodothyronine (fT3) were measured in 21 subjects (14 females and 7 males; mean age, 6.4 years). Capillary TT4 was measured on neonatal screening samples from 23 subjects with PWS (14 females and 9 males), each of whom was matched for birth weight and sex with 4 anonymized controls.

Results One subject with PWS had tertiary hypothyroidism. TSH level increased from 1.37 mU/L at baseline to 39.6 mU/L at 20 minutes, 47.2 mU/L at 40 minutes, 44.5 mU/L at 60 minutes, and 47.2 mU/L at 120 minutes. fT4 concentration was 6.3 pmol/L, and fT3 concentration was 4.6 pmol/L. In the other 20 subjects, mean TSH level was 1.9 mU/L (range, 0.8-4.2 mU/L) at baseline and 21.8 mU/L (range, 10.0-46.7 mU/L) at 20 minutes (peak). Mean fT4 concentration (10.4 pmol/L; range, 8.2-13.5 pmol/L) was in the lower one-third of the normal range in 18 subjects, and mean fT3 concentration (6.1 pmol/L; range, 4.8-8.4 pmol/L) was above the median in 13 subjects. In neonates, mean TSH level was 3.1 mU/L (range, 0.4-10.0 mU/L) in subjects with PWS versus 3.3 mU/L (range, 0.0-7.0 mU/L) in controls, and mean TT4 in subjects with PWS was 111% (range, 17%-203%) that of controls (*P* = not significant).

Conclusion Thyroid function was normal in our newborn subjects. In older children, frank hypothyroidism was found in only 1 of our 21 subjects. Thus, levothyroxine treatment should not be routinely prescribed to youth with PWS. *(J Pediatr 2013;163:800-5)*.

Prader-Willi syndrome (PWS; OMIM #176270) is caused by the loss of expression of paternally transcribed genes in a highly imprinted region of chromosome 15q11-q13. The most common molecular alteration is deletion of the paternal copy of the gene locus (70%), and the remaining cases result from maternal uniparental disomy (28%) and imprinting defects (2%).[1] The clinical phenotype of PWS includes fetal/neonatal hypotonia; poor feeding in the neonatal period, usually followed by marked hyperphagia and obesity starting in childhood; delayed psychomotor development; hypogonadism at puberty; and short adult stature.[2,3]

Abnormalities of the hypothalamo-pituitary axis are present in PWS. Magnetic resonance imaging studies have shown hypothalamic-pituitary abnormalities, including anterior pituitary hypoplasia and an absent, small, or ectopic posterior pituitary gland, in more than 50% of patients with PWS.[4,5] From a functional standpoint, hypothalamic dysfunction is thought to play a role in hyperphagia[6] and in the insufficient secretion of growth hormone, together with the low serum insulin-like growth factor 1 and insulin-like growth factor binding protein 3 concentrations seen in some, but not all, patients with PWS.[7,8] Hypogonadotrophic hypogonadism is not present in infancy,[9] but is seen in virtually all adults with PWS.

Whether hypothyroidism, particularly central hypothyroidism, is present in PWS remains unclear. This question is important, because hypothyroidism could contribute to delayed psychomotor development when present early in life and not treated, and to obesity, increased fat mass, hypotonia, and impaired linear growth when developing during childhood. To date, only a handful of studies have investigated thyroid function in children with PWS.

BMI	Body mass index
CV	Coefficient of variation
fT3	Free triiodothyronine
fT4	Free thyroxine
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LT4	Levothyroxine
PWS	Prader-Willi syndrome
TRH	Thyroid-releasing hormone
TSH	Thyroid-stimulating hormone
TT4	Total thyroxine

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The goal of this study was to clarify the state of the hypothalamo-pituitary-thyroid axis and of the neonatal thyroid function in subjects with PWS. We measured levels of thyroid hormones and examined the thyroid-stimulating hormone (TSH) response to thyroid-releasing hormone (TRH) in children and adolescents with PWS, and compared TSH and total thyroxine (TT4) concentrations measured at neonatal screening for congenital hypothyroidism in neonates with PWS and in controls.

Methods

Thirty-one subjects with PWS were eligible for this study. All had a normal TSH level on neonatal screening for congenital hypothyroidism and participated in the first (hypothalamo-pituitary-thyroid function in children and adolescents), the second (neonatal screening for congenital hypothroidism), or both (n = 13) parts of the study. Written informed consent was provided by the parents of subjects with PWS, and assent was given by the child when appropriate. The study protocol was approved by the Ethics Board of the University of British Columbia. The study was conducted in accordance with the Declaration of Helsinki.

Twenty-one subjects with PWS (14 females and 7 males) followed at British Columbia Children's Hospital in Vancouver participated in the first part of the study. Height or length (in children aged <2 years) and weight were measured in duplicate with the children in light clothing without shoes. Body mass index (BMI; weight in kilograms/height in meters squared) and BMI *z*-score were calculated using the World Health Organization growth charts adapted for Canada.[10] Blood pressure was measured using an automated monitor (Dinamap Pro 300; Critikon, Tampa, Florida) and is expressed as *z*-score.[11]

TSH level was measured before and at 20, 40, 60, and 120 minutes after intravenous injection of TRH (TRH-Thyrel; Ferring, Parsippany, New Jersey), 200 μg given over 90 seconds.[12] Levels of free thyroxine (fT4), free triiodothyronine (fT3), and anti-peroxidase antibodies, as well as fasting blood glucose, insulin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and prolactin, were obtained at baseline. Normative values are provided in **Table I**. An increase in TSH with a peak at 20 or 30 minutes, followed by a decrease toward baseline values, was consistent with a normal TRH test.

An automated chemiluminescent immunoassay was used to measure fT4 (Access; Beckman Coulter, Fullerton, California; intra-assay coefficient of variation [CV], <4.5%; interassay CV, <8.1%), TSH (Access HYPERsensitive hTSH assay; Beckman Coulter; intra-assay CV, <5.9%; interassay CV, <8.9%) and fT3 (Centaur, Siemens Healthcare Diagnostics, Tarrytown, New York; intra-assay CV, <3.1%; total imprecision, <4.1%), as well as insulin, prolactin, and anti-thyroid peroxidase antibodies (Access; Beckman Coulter). Glucose, total cholesterol, HDL cholesterol, and triglycerides were measured with an automated colorimetric/reflectance spectrophotometry assay (Vitros 5600; Ortho-Clinical Diagnostics, Rochester, New York). LDL cholesterol was calculated using the Friedewald equation.[13]

Table I. Laboratory characteristics in the 20 of 21 children and adolescents with PWS who had a normal TRH test

	Values	Reference range
TSH, mU/L	1.9 ± 1.0 (0.8-4.2)	*
Peak TSH, mU/L	21.8 ± 10.2 (10.0-46.7)	NA
fT4, pmol/L	10.4 ± 1.1 (8.2-13.5)	†
fT3, pmol/L	6.1 ± 1.0 (4.8-8.4)	‡
Prolactin, μg/L	10.5 ± 4.6 (5.0-22.4)	2.6-13.1
Fasting blood glucose, mmol/L	4.8 ± 0.5 (3.7-5.7)	3.9-5.9
Fasting insulin, pmol/L	44 ± 27 (10-97)	13-129
Total cholesterol, mmol/L	4.3 ± 0.9 (2.7-6.2)	3.25-5.55
HDL cholesterol, mmol/L	1.3 ± 0.3 (0.8-2.0)	>0.9
LDL cholesterol, mmol/L	2.5 ± 0.8 (1.6-4.3)	1.6-2.8
Triglycerides, mmol/L	1.0 ± 0.5 (0.5-2.3)	0.42-1.47

NA, not applicable.
Data are mean ± SD (range).
Conversion factors: fT4: ng/dL × 12.87 = pmol/L; fT3: pg/dL × 0.0154 = pmol/L; glucose: mg/dL × 0.0555 = mmol/L; cholesterol: mg/dL × 0.0259 = mmol/L; triglycerides: mg/dL × 0.0113 = mmol/L.
*TSH reference range above age 6 mo: 0.3-6 mU/L (from British Columbia Children's Hospital laboratory).
†fT4 reference range (from British Columbia Children's Hospital laboratory):
1 mo-0.99 y: 7.8-18.4 pmol/L
1-4.99 y: 7.9-18.8 pmol/L
5-9.99 y: 7.9-20.3 pmol/L
10-14.99 y: 7.5-17.2 pmol/L
15-17.99 y: 7.6-15.6 pmol/L
Adult: 7.9-14.4 pmol/L.
‡fT3 reference range (pediatric values from Hübner et al,[29] using the same laboratory equipment; adult values from British Columbia Children's Hospital laboratory):
2 mo-0.99 y: 2.72-7.30
1-5.99 y: 3.05-6.93
6-10.99 y: 3.30-6.79
11-14.99 y: 3.46-6.71
15-17.99 y: 3.57-6.65
Adult: 3-6.9.

For the second part of the study, blood samples collected on filter paper for the universal newborn screening for congenital hypothyroidism (referred to herein as "filter papers") were available for 23 subjects with PWS (6 in Quebec and 17 in British Columbia). The filter paper data include date of birth, birth weight, sex, and age at the time of specimen collection.

In Quebec, TSH is measured at the time of screening, and TT4 is subsequently measured on the initial filter paper only when TSH is >15 mU/L. Filter papers are then kept at room temperature for up to 1 year. In the 6 Quebec subjects (2 females and 4 males), filter papers were retrieved from storage and assayed for TT4. The mean duration of filter paper storage before the TT4 assay was 0.56 ± 0.33 year (range, 0.17-1 year).

In British Columbia, only TSH is measured on neonatal screening, and filter papers are stored at room temperature for up to 10 years. The filter papers of the British Columbia participants were sent to the Quebec laboratory for TT4 determination after retrieval from storage. In the 17 British Columbia subjects (12 females and 5 males), mean age at the time of retrieval of the neonatal filter paper for