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High Plasma Neurotensin Levels in Children with Prader–Willi Syndrome

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Abstract

Prader-Willi syndrome (PWS) is an obesity-related genetic condition, most commonly due to a paternal deletion of the chromosome 15q11-q13 region. PWS is characterized by growth hormone deficiency, infantile hypotonia and feeding problems, hypogenitalism/hypogonadism, increased pain threshold and thermal instability, decreased gastric motility, and hyperphagia in childhood leading to severe obesity. Neuro-endocrine peptides are known to influence gastric function and pain sensation which led us to measure a specific peptide that may be involved [i.e., neurotensin (NT)] in PWS and compared with unrelated control siblings. Overnight fasting plasma NT levels were obtained from 23 children with confirmed PWS (age: 8.2 ± 2.0 years; range: 5–11 years) and 18 unaffected, unrelated siblings (age: 8.2 ± 2.3 years; range: 5–11 years) and measured using Multiplex sandwich immunoassays with the Luminex magnetic-bead based platform. Plasma NT levels were natural log-transformed and analyzed by ANOVA with adjustments for age, gender, and body mass index (BMI). No difference was found in plasma NT levels for gender, age or BMI or significant correlations seen with age or BMI. Higher plasma NT levels ($P < 0.001$) were seen in PWS children (mean of 626 ± 238 pg/ ml) compared with unaffected, unrelated siblings (mean of 371 ± 236pg/ml). Plasma levels were also higher in children with maternal disomy 15 (736 ± 182 pg/ml) compared with those having the deletion subtype (548 ± 247 pg/ml, $P < 0.04$). Although no measures for pain threshold, thermal instability or gastric motility were performed in our study participants, higher plasma NT levels were found in PWS children.

Keywords

plasma; neurotensin; Prader-Willi syndrome; gastric motility; analgesia; thermal instability

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INTRODUCTION

Prader-Willi syndrome (PWS) is a rare genomic imprinting disorder with obesity as a major feature. It is caused by loss of expression of paternal genes from the chromosome 15q11-q13 region most often from a deletion (about 70% of cases) but may result from maternal disomy 15 (UPD) having both 15s from the mother (about 25% of cases) or imprinting center defects in the remaining subjects. Decreased fetal activity is noted during preg-nancy followed by severe infantile hypotonia and feeding difficulties with diminished swallowing and sucking reflexes [Butler, 1990; Bittel and Butler, 2005; Cassidy et al., 2011]. These symptoms resolve slowly in early childhood with the development of overeating and hyperphagia, leading to severe obesity and corresponding comorbidities, if not controlled.

Other symptoms of PWS include hypogenitalism/hypogonadism, cognitive impairment (mean IQ of 65), behavioral findings of temper tantrums, OCD, and skin picking, abnormal temperature regulation, increased pain threshold, decreased gastric motility, and growth hormone deficiency with short stature along with small hands and feet. Endocrine disturbances with central adrenal insufficiency and hypothyroidism are also reported in about 10% of cases [Butler et al., 2009]. Disturbed FSH, LH, estrogen, and testosterone levels are found along with an arrested pubertal growth pattern [Butler et al., 2006; Brandau et al., 2008]. Cranio-facial findings in PWS include a narrow forehead with dolichol-cephaly, almond-shaped eyes, a small upturned nose with down-turned corners of the mouth, and a small chin. Enamel hypoplasia and dry, sticky saliva are common. PWS occurs in about 1 in 10,000 live births, with gastric dilatation, necrosis, and rupture as a common cause of death [Butler, 1990; Butler et al., 2006; Stevenson et al., 2007; Butler, 2011; Cassidy et al., 2011]. PWS was first reported and described by Prader et al. [1956], but the mechanism(s) for symptom development and progression have not yet been elucidated. Many protein coding genes and transcripts are localized to the 15q11-q13 region, but definitive genetic disturbances and causative pathophysiology in this rare obesity-related disorder have escaped characterization.

Although neuro-related peptides are thought to contribute to PWS, there is a paucity of laboratory data in humans including neurotensin, a neuropeptide known to be stimulated by food intake. Neurotensin (NT) is a 13 amino acid peptide produced from the NTS gene, located at 12q21.31 [Marondel et al., 1996; Mustain et al., 2011]. It is one of two gene products including neuromedin N (NN), a 5 amino acid peptide and synthesized by ileal mucosa cells. NT induces analgesia, hypothermia, hyperglycemia, and inhibits gastric motility. It is present throughout the CNS [Mai et al., 1987; Kalafatakis and Triantafyllou, 2011; Mustain et al., 2011; Kleczkowska and Lipkowski, 2013] with the highest levels in the hypothalamus, amygdala, and nucleus accumbens but measurable in peripheral blood [Mustain et al., 2011]. The release of NT leads to pancreatic polypeptide and pancreatic bicarbonate secretion with downstream products of NT stimulation being LH, FSH, and ACTH with release of GHRH and CRH from the central nervous system. This release by the brain is stimulated by food intake and bombesin, a peptide that is 14 amino acids in size, with fat intake as the strongest stimulus [Rosell and Rökaeus, 1979]. It plays a role in pain regulation, gastric emptying, and thermal stability, all common findings in PWS [Mai et al., 1987; Ferris, 1989; Bean et al., 1992; DiMario and Burleson, 2002; Mustain et al., 2011;

Kleczkowska and Lipkowski, 2013]. NT levels have not previously been analyzed in patients with PWS with unexplained increases in pain threshold, thermal instability, and decreased gastric motility in addition to abnormal eating behavior. PWS provides an excellent model to study and the basis of our pilot or “proof of principle” investigation to measure fasting plasma NT levels with disturbances predicted in PWS.

MATERIALS AND METHODS

Patients

Forty-one individuals were recruited from a large, ongoing, multi-site rare disease consortium on PWS in the USA carried out with oversight from the Institutional Review Board of the University of Kansas Medical Center and the University of Florida School of Medicine. The investigators at these two sites are experienced in the treatment of PWS. Twenty-three children (13 males, 10 females, age: 8.2 ± 2.0 years, range 5–11 years) were diagnosed clinically and confirmed with PWS using cytogenetic and molecular genetic testing with methylation, chromosomal microarray methylation specific—multiplex ligation probe amplification (MS-MLPA), genotyping, and/or chromosome analyses with fluorescence in situ hybridization (FISH) along with 18 unaffected, unrelated siblings (10 males, eight females; age of 8.2±2.3; range 5–11 years). Fifteen pre-pubertal children with PWS had the 15q11-q13 deletion and eight had maternal disomy 15 or UPD. All children were Caucasian Americans and those with PWS were receiving growth hormone treatment. The PWS and study participants were receiving dietary intervention (60–80% of the caloric intake for age) and engaged in exercise programs (e.g., 30 min of walking per day) to maintain caloric intake and weight control, common in the care and treatment of PWS [Butler, 2006; Butler et al., 2006; Miller et al., 2011]. No child was receiving sex steroids or treated for adrenal insufficiency. Four PWS children had a history of insulin resistance and three were being treated for hypothyroidism. One PWS child was prescribed an atypical anti-psychotic medication. Other parameters including genetic subtype, age, gender weight, height, BMI and BMI-z score, and total body fat percentage in relationship to selected plasma cytokine levels on each child within this cohort have been reported elsewhere [Butler et al., 2014].

Peripheral blood was collected in anti-coagulant EDTA tubes in the morning after an overnight supervised fasting monitored by parents with plasma separated immediately then stored at —80°C until use. Height (cm) and weight (kg) were also routinely obtained on each subject using standing stadiometers and calibrated electronic weight balances in the clinical setting with body mass index (BMI) calculated. Body composition and total body fat percentage were determined using dual-energy X-ray absorptiometry (DXA) and the Lunar DXA Scanner (General Electric, Atlanta, GA).

Neurotensin Assay

Plasma NT levels were analyzed with multiplex sandwich immunoassays from the Milliplex Human Neuropeptide Kit (Millipore; Billerica, MA) and the Luminex 200™ (Luminex Molecular Diagnostic; Toronto, ON) instrument using established protocols following manufacturer’s guidelines [Manzardo et al., 2012]. Plasma (25 μl) from peripheral blood

was collected in EDTA tubes and stored at —80°C until use. Plasma and a Milliplex control standard for quality were combined with pre-mixed antibody-coupled magnetic beads along with an assay buffer for overnight incubation at 4°C. No internal cross-reactivity was observed by the manufacturer when testing individual standards within each neuropeptide. The incubation steps were carried out using a micro-titer plate shaker at 300 RPM and samples washed on the following day then incubated at room temperature with secondary detection antibodies for 1 hr. Another series of washes were carried out followed by adding fluorescent Streptavidin-Phycoerythrin detection solution. The sample mixture was incubated at room temperature for 30 min. Each sample was then run in duplicate. After incubation, the sheath fluid was added to each sample well with the plate read using Luminex 200™ equipment based on magnetic-bead technology and level of magnetic field to separate the beads. Plasma NT levels were analyzed using the Luminex 200™ v2.3 software in both PWS and control specimens and the indicated minimum detectable concentration (pg/ml) levels recorded. NT plasma concentrations were calculated using a standard curve that was derived from the reference neurotensin concentration standards furnished and supplied by the manufacturer of the reagents. The inter-assay coefficient of variation for NT levels ranged from 0–20% while the intra-assay coefficient of variation ranged from 0–10%. Plasma samples were blinded as to gender and control versus PWS diagnosis during each assay run and subsequently analyzed.

Statistical Analysis

Descriptive data were presented as mean ± standard deviation of plasma NT levels by diagnosis (PWS or unaffected, unrelated siblings), gender and PWS genetic subtype. Raw data were natural log-transformed and examined using multiple linear regression to test for differences in NT level by diagnosis and PWS genetic subtype when considering the influence of age, gender, and BMI. Natural log-transformed data met necessary statistical criteria for assumption of normality by showing equal variance and near linear residual plots. Findings with *P*-values of <0.05 were considered significant. Statistical analyses including descriptive statistics were generated using SAS statistical analysis software version 9.4 (SAS Inc., Cary, NC) and R statistics software version 2.14.2 (R Foundation, Vienna, Austria).

RESULTS

No significant differences in age or BMI were found by diagnostic subgroup or PWS subtype and gender did not contribute significantly to changes in NT levels (see Table I). Plasma NT levels for PWS subjects (626 ± 238 pg/ml; range 231–1025 pg/ml) were significantly greater than unaffected, unrelated sibling controls (371 ± 236 pg/ml; range: 80–860 pg/ml; t = 3.49; $P < 0.002$; see Figs.1 and 2). This relationship was independent of age, BMI and gender controls ($F = 0.023$; $P > 0.05$); plasma NT levels for the PWS UPD subtype were significantly higher than what is found for the PWS deletion subtype (t = 1.9; $P = 0.07$). Both PWS deletion and UPD subtypes were significantly greater than unaffected, unrelated sibling controls.

DISCUSSION

There was notable overlap between the symptoms of PWS and the effects of NT. Children with PWS presented with statistically significant elevations in fasting morning plasma NT levels compared to age and gender matched unaffected, unrelated siblings. Overeating or increased food consumption that produces profound obesity is a characteristic symptom of PWS. While hunger is typically managed by the hormones ghrelin and leptin, neuropeptides like NT can also modulate appetite. Work by Luttinger et al. [1982] demonstrated that NT leads to decreased food consumption in food-deprived rats. When NT is administered directly to the CNS, it can yield up to a 40% decrease in baseline food intake. Inhibition of intake was apparently not due to any toxic effects of the peptide, and removal of this compound allowed for recovery of baseline food intake [Luttinger et al., 1982].

In humans, plasma NT levels approximately double following food consumption [Mashford et al., 1978]. This elevation in NT levels is likely homeostatic in nature, preventing overeating. However, in PWS there appears to be no negative feedback on appetite as hunger increases following food consumption as indicated by fMRI brain studies [Holsen et al., 2006]. Even at significantly elevated levels in PWS as seen in our study, NT appears not to produce downstream effects. Thus, if NT is involved in the pathophysiology of PWS, it is clear that NT is unable to function properly in hunger maintenance and its function in the CNS may be disturbed.

Gastric Motility, Necrosis, and Rupture

A rare but serious complication in patients with PWS is gastric dilatation, necrosis, and rupture, the etiology of which is still not completely understood. An explanation posited by Wharton et al. [1997] for this phenomenon is a potential genetic predisposition for acute gastric dilatation in PWS due to abnormal gastric homeostasis. Clearly, if the rate of gastric emptying were severely depressed, gastric dilatation and rupture would be serious risks. While no prior studies have fully elucidated the pathophysiology of the gastric dilatation, the expected effects of NT in the GI system may provide some insight.

When infused intravenously, NT has been shown to inhibit gastric acid and pepsin output as well as delay gastric emptying [Blackburn et al., 1980]. Therefore, if NT were present consistently at high levels in the GI system, sustained gastric immobility could lead to gastric dilatation and possible rupture. Since no explicit quantification of gastric mobility was performed on the patients in this study and since the patients with PWS were on a well-controlled diet, no correlation can be drawn between NT levels and gastric dilatation/rupture status at this time.

Analgesia

The analgesic effects of NT appear to be either facilitatory or inhibitory, depending on NT levels [Smith et al., 1997; Kleczkowska and Lipkowski, 2013]. When NT is administered intracisternally to mice and rats at high levels, hot plate reactivity and writhing response to acetic acid were decreased, indicating an antinociceptive response; the minimum effective dose was 25 ng and the maximum effect dose was 250 ng [Clineschmidt et al., 1979]. In

contrast, low (picomolar) doses of NT that were injected into the rostroventral medial medulla yielded hyperalgesia [Smith et al., 1997]. Intravenous administration of 2,500 ng of NT did not yield an analgesic effect [Clineschmidt et al., 1979].

NT signaling occurs through one of three receptors: NTS1, NTS2, and NTS3/sortilin [Luttinger et al., 1982]. Both NTS1 and NTS2 belong to the G protein-coupled receptor superfamily and can be distinguished by their affinities for NT [Vincent et al., 1999]. NTS2 has a lower affinity for NT, but this receptor is strongly associated with the nociceptive properties of NT. Inhibition of NTS1 using a selective antagonist SR48692 at low doses had no effect on NT-induced analgesia [Dubuc et al., 1994], whereas levocabastine, an NTS2 agonist, induced an antinoci-ceptive effect [Dubuc et al., 1999]. However, more recent studies have shown that NTS1 is involved in the analgesic effect of NT, at least modestly [Sarret et al., 2005]; both NTS1 and NTS2 are expressed in the PAG and raphe nuclei [Sarret et al., 2003; Buhler et al., 2005; Katsanos et al., 2008].

In children with PWS in our study, plasma levels of NT appear to be persistently elevated. If NT is able to act on its receptors in the CNS and if replicated, this could partially explain the analgesic effects seen in PWS although no recording of pain threshold measures were obtained in our study participants. Alternatively, NT may not function properly in the CNS, meaning elevated levels of other neuropeptides such as beta-endorphin may explain the antinociception common in PWS; this idea should be explored further in other studies. Since there is no humane and reliable way to measure NT levels in the CNS in living patients with PWS, it is difficult to explore its function directly.

Genetic abnormalities coupled with complex environmental pressures modify specific complications in PWS such as gastric dilatation and rupture, increased pain threshold and thermal instability. It is unlikely that a single neuropeptide would explain the complete pathophysiology of PWS, but NT may provide insight into some complications and symptoms of this disorder.

Based on the expected effects of NT, it appears that this neuropeptide is functioning locally to decrease gastric motility (and perhaps to increase gastric enzymes) but not yielding downstream effects in the CNS. In the GI system, an elevation in NT levels in patients with PWS could be related to reduce gastric mobility, thereby increasing the risk for gastric dilatation and rupture. In the CNS, elevation of NT levels should produce decreased appetite and antinociception, only one of which is seen in PWS. To reconcile this disparity in function, one may suggest that an abnormality in NT receptors or production is present in the CNS of patients with PWS. Since NT levels in the CNS are not readily or humanely quantifiable, and since NT is produced in both the GI and central nervous systems, it is possible to merely speculate on the role of NT in the GI symptoms and other features seen in PWS. Although a limitation of our study was the lack of measures to assess thermal instability, delayed gastric motility and increased pain threshold, all impacted by neurotensin, NT levels found in this patient group support involvement of NT. The authors would encourage further exploration to replicate the NT findings in this pilot study and undertake a more thorough investigation and data collection on gastric motility, thermal stability, and pain threshold patterns in PWS and correlation with NT levels.

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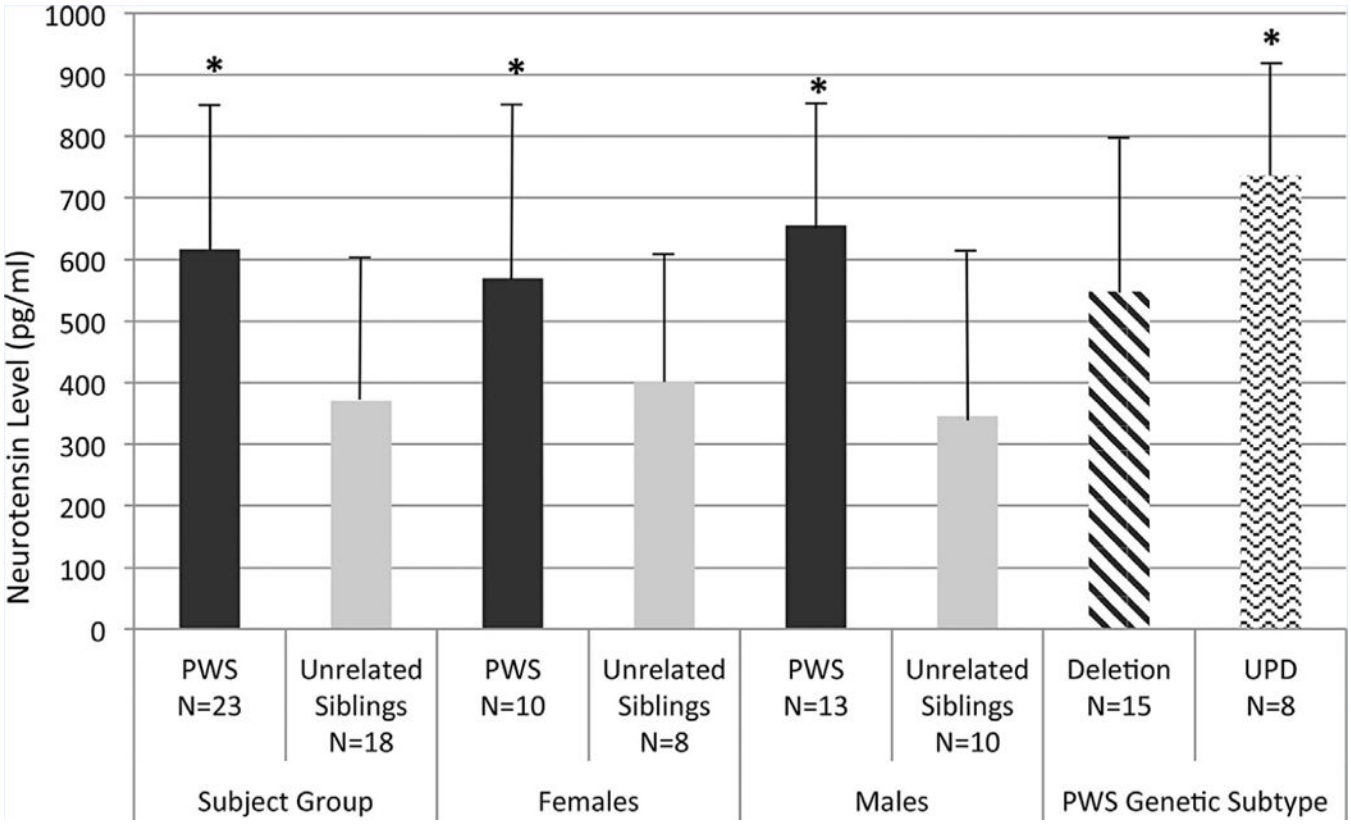

FIG. 1.

Plasma neurotensin levels grouped by gender, diagnosis and PWS genetic subtype. *P<0.05.

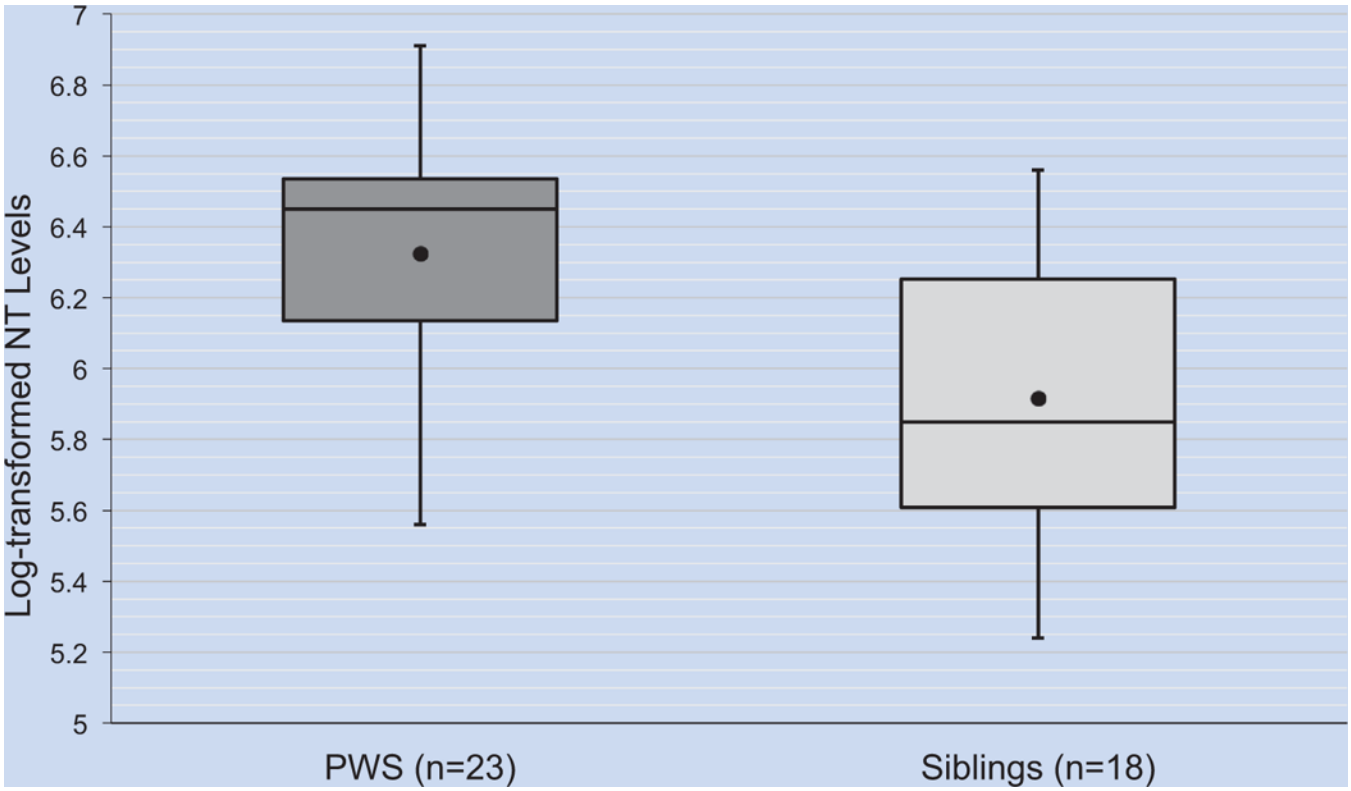

FIG. 2.

Box and whisker plot of log-transformed NT levels. Box plots representing the 25th and 75th quartile ranges. Bars represent maximum and minimum natural log-transformed values.

TABLE I.

Descriptive Summary Data for Prader–Willi Syndrome and Control Subjects

Subject group comparison				
	Prader-Willi syndrome (N = 23)	**Unrelated siblings (N = 18)**	***F*-value**	***P*-value**
Age (yrs)	8.2 ± 2.0	8.2 ± 2.3	0.01	0.92
BMI (kg/m^2)	20.7 ± 5.0	18.2 ± 3.3	3.1	0.08
BMI-z score	0.96 ± 1.40	0.52 ± 1.35	1.1	0.31
Total body fat (%)	33.1 ± 13.1	24.0 ± 10.1	5.5	0.03
Neurotensin (pg/ml)[a]	626 ± 238	371 ± 236	13.4	0.001
Gender comparison				
	Male (N = 23)	Female (N = 18)		
Neurotensin (pg/ml)[a]	529 ± 277	495 ± 261	0	0.97
PWS genetic subtype comparison				
	Deletion (N = 15)	UPD (N = 8)		
Neurotensin (pg/ml)[a]	548 ± 247	736 ± 182	4.9	0.04

Analysis carried out using uncontrolled analysis of variance by diagnostic subgroup, gender or PWS genetic subtype.

[a]Statistical analysis utilized natural log-transformed values for neurotensin levels.