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Oxytocin alterations and neurocognitive domains in patients with hypopituitarism

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Abstract

Purpose Oxytocin is a hypothalamus derived, posterior pituitary stored nonapeptide which has gained recent interest as an important neuropsychiatric and metabolic hormone beyond its classic role in lactation and parturition. Hypopituitarism is a heterogenous disorder of derangement in one or more anterior or posterior pituitary hormones. Diagnosis of deficiency and hormone replacement exists to address all relevant axes except for oxytocin. Our study aims to define derangements in oxytocin in a unique population of patients with hypopituitarism and correlate levels with measures of emotional health and quality of life.

Methods A cross-sectional, single day study was completed to measure plasma oxytocin levels in a diverse population of patients with hypopituitarism compared to controls. Subjects also completed depression, quality of life and stress-related questionnaires, and emotion recognition tasks.

Results Thirty-eight subjects completed the study, 18 with hypopituitarism (9 with diabetes insipidus) and 20 controls. After controlling for differences in age, weight and gender, plasma oxytocin levels were highest in subjects with diabetes insipidus compared to control [mean, IQR: 44.3 pg/ml (29.8–78.2) vs. 20.6 (17–31.3), $p = 0.032$]. Amongst hypopituitary subjects, those with duration of disease greater than 1 year had higher oxytocin levels. No significant differences were observed for psychosocial measures including emotion recognition tasks.

Conclusions Plasma oxytocin levels were found higher in patients with hypopituitarism compared to controls and highest in those with diabetes insipidus. Longer duration of hypopituitarism was also associated with higher plasma levels of oxytocin. Further study is needed to better define oxytocin deficiency and investigate response to treatment.

Keywords Oxytocin · Hypopituitarism · Diabetes Insipidus · Neurocognition

Introduction

Oxytocin (OXT) is a nine amino acid peptide synthesized primarily in the supraoptic and paraventricular nuclei of the hypothalamus and stored within the posterior pituitary [1]. OXT plays a clear and critical role in postpartum lactation as well as uterine contracture during labor [1]. Although this has been OXT's traditional role, recent literature supports substantially broader potential impact for OXT. For example, oxytocin plays a role in metabolic function and feeding behavior [2]. In animal models (diet induced obese mice, nonhuman primates), OXT administration resulted in weight loss from reduced food intake, increased energy expenditure and possibly even increase lipolysis [3]. Human studies are limited but administration of intranasal oxytocin resulted in,

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reduced caloric intake as well as weight loss after 4–8 weeks of therapy [4, 5].

In the realm of neuroscience, OXT is believed to support pro-social behavior [6]. OXT administration has produced favorable responses in paradigms of trust and generosity [7]. Additionally, visual attention to the eye region ("eye contact") as well as proper interpretation of facial affect (both important components of positive social interaction) appear to be influenced by the oxytocinergic system [8]. OXT has also been suggested to have a role in the pathophysiology of a variety of neuropsychiatric conditions that affect social functioning. OXT alterations are described in patients with schizophrenia, autism, depression and ADHD [9, 10]. While intranasal oxytocin is also being actively investigated here, conflicting results are being reported [11, 12].

While most OXT research has focused on derangements in a variety of neuropsychiatric diseases, an obvious but sparsely investigated population are those with pituitary injury or disease. Hypopituitarism (HP) is a heterogeneous condition of deficiency in one or more of the anterior pituitary derived (GH, FSH, LH, TSH, ACTH, Prolactin) or posterior pituitary stored (ADH, OXT), hormones. Patients with HP experience excess morbidity and mortality which improves but do not normalize with hormone replacement. Morbidity consists of abnormal body composition (decreased bone and muscle mass, increased body fat), reduced exercise capacity and muscle strength, insulin resistance, altered lipid profiles and reduced quality of life. Although some of this has been attributed to growth hormone deficiency, attempts at replacement improve but do not normalize excess morbidity [13]. Estimated mortality increase varies from non-significant up to 13–42%, even in those patients receiving growth hormone replacement therapy [14–16].

There have been only a few studies investigating oxytocin derangements in patients with hypopituitarism [17–20]. Most have focused on patients with craniopharyngioma and have examined saliva samples exclusively. We present the first study assessing plasma oxytocin levels in patients with hypopituitarism, and examining for differences in quality of life measures and psych-social health.

Materials and methods

The study was approved by the University of Illinois at Chicago (UIC) Institutional Review Board- Protocol # 2016-1206.

Subjects

Subjects participated in research protocol between 3/2017 and 4/2018. Most patients with hypopituitarism were recruited from the UIC Endocrinology clinic during routine clinical follow-up care. Additionally, electronic medical record search identified potential subjects by diagnoses (e.g. hypopituitarism, diabetes insipidus, etc). Finally, subjects were recruited through university mass emails and fliers. Inclusion criteria for the population of interest included men and women age 18–85 years with hypopituitarism. Hypopituitarism was defined as at least one hypothalamic/pituitary/end organ dysfunction: secondary hypogonadism, secondary hypothyroidism, secondary adrenal insufficiency, growth hormone deficiency or diabetes insipidus. Participants were excluded if they were under 18 years old or over 85 years old, breast feeding or pregnant, or unable to participate in emotion recognition tasks due to vision impairment or language barrier. Participants were also excluded if they were currently on antipsychotic medications or had any documented psychiatric conditions known to impact emotional processing like bipolar disorder, schizophrenia, schizoaffective disorder, or autism. Participants were placed into one of three groups: Hypopituitarism with DI group (HP + DI), Hypopituitarism without DI (HP − DI) group, and control group. The diagnosis of DI and anterior hypopituitarism was established clinically and biochemically as part of their regular care with basal and dynamic testing as appropriate. Subjects with hypopituitarism were on replacement hormonal therapy as determined by their primary clinical endocrinologist. All participants provided written informed consent and were financially compensated for their participation.

Facial affect recognition tests

The Penn emotion recognition 40 task (PennER)

The PennER 40 task was used to measure affect recognition. In this task, participants view images representing facial expressions. There are equal numbers of female and male faces, and four races are represented (Caucasian, African-American, Asian, and Hispanic). One face at a time is shown and participants have to choose the emotion that is represented from a list of five possibilities (anger, fear, neutral, happiness and sadness), shown on the right of the screen. The total score ranges from 0 to 40, and the individual sub-scores for happy, sad, angry, fearful, and neutral facial expressions. The percentage of accurate responses was calculated and the time to response was recorded [21].

The dynamic affect recognition evaluation task (DARE)

The DARE task was used to measure affect recognition. Participants view videos of male and female faces from Cohn-Kanade Action Unit-Coded Facial Expression Database [22] starting with a neutral expression which slowly transitions

into one of the six target emotions (sadness, fear, surprise, disgust, anger, happiness). Participants were instructed to choose the emotion being expressed as quickly as possible. The percentage of accurate responses was calculated and the time to response was recorded [23].

Questionnaires

The Center for Epidemiologic Studies Depression Scale (CESD) is a self-reported 20-item scale which measures an individual's depressive feelings and behaviors in the past week. It utilizes 9 symptom groups as defined by the DSM-V: sadness, anhedonia, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, poor concentration, psychomotor retardation, loss of appetite, sleep disturbance, and suicidal ideation. A score of >16 is clinically significant for depression [24].

The Perceived Stress Scale (PSS) is the most widely used psychological instrument for measuring the perception of stress. It is a 10-item questionnaire developed for measuring the degree to which situations in one's life are perceived as stressful. Items were chosen to determine how unpredictable, uncontrollable, and overloaded respondents find their lives to be and are rated on a 5-point Likert scale ranging from "0 = never" to "4 = very often" [25].

The PTSD Checklist-Civilian version (PCL-C) is a 17-item self-report inventory to measure how often individuals experience problems related to previous "stressful experiences". These are rated on a 5-point Likert scale ranging from "1 = not at all" to "5 = extremely". The total severity score is calculated with a suggested cut off of 30–35 considered positive for PTSD in a civilian primary care setting [26].

The European Quality of life 5-D (EQ-5D) is a standardized well-validated tool to measure health outcomes. It is applicable to a wide range of health conditions and provides a simple descriptive profile and a single value for an individual's health status. The questionnaire consists of five items (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each with five potential responses (no problems up to extreme/unable). Subjects then respond to "how good or bad is your health today" on a visual analog scale from 0 (worst health imaginable) to 100 (best health imaginable). Scoring for the 5 response items dichotomizes those with no problems (response 1) compared to all other responses (2–5) [27].

The Questions on Life Satisfaction-Hypopituitarism (QLS-H) is a self-administered questionnaire which aims to measure disease-specific quality of life in patients with hypopituitarism. First, patients must indicate how important a certain quality of life aspect is to them and then their degree of satisfaction with that aspect. Examples of questions include ability to tolerate stress, body shape, self-confidence, ability to become sexually aroused, ability to concentrate, physical endurance, initiative/drive, ability to deal with anger, and ability to withstand the disturbances and noise of daily life. These 9 items (18 total responses) are rated on a 5-point Likert scale form "1 = not important" to "5 = extremely important" and from "1 = dissatisfied" to "5 = very satisfied" for importance and satisfaction sections respectively [16].

Study procedure

On the study day the protocol was re-reviewed and informed consent forms were signed. Participants were instructed to abstain from food, alcohol and tobacco use for 12 h prior to testing. Subjects routine medications were not restricted from administration due to safety concerns (e.g. hydrocortisone, desmopressin etc). All testing was carried out between 8:00 and 10:00 a.m. to control for hormonal circadian rhythm. All subjects had weight and height measured according to standardized techniques, and body mass index (BMI) was calculated as weight per height squared (kilograms per square meter).

All participants were asked a brief history including presence or absence of diabetes, hypertension, hyperlipidemia, osteoporosis, and osteopenia. Hypopituitary patients had their history of prior treatment reviewed and confirmed from electronic medical record. Data collected on subjects with hypopituitarism included age at diagnosis of hypopituitarism, duration of hypopituitarism, hormonal deficiency (ies) (secondary hypogonadism, secondary hypothyroidism, secondary adrenal insufficiency, growth hormone deficiency or diabetes insipidus), cause of hypopituitarism (e.g. surgery, radiation, congenital), and if relevant, dates of any parasellar surgery and date and type of radiation therapy.

An active medication list on the study day was collected. For hypopituitary subjects, doses of hormone replacements were obtained as applicable (corticosteroid dose/form, thyroid hormone, estrogen/progestin or testosterone dose/form, growth hormone dose, desmopressin dose).

Participants submitted to venipuncture and blood, processed to separate plasma and was immediately frozen in −80 °C freezer. Then participants completed both the DARE and PennER tasks and the five self-administered web-based questionnaires.

Oxytocin measurement

To measure OXT levels, plasma samples were thawed and the OXT extracted with solid phase extraction (SPE) columns, which removed possible contaminates [28]. The samples were assayed with Assay Design ELISA kits (Enzo Life Sciences, Ann Arbor, MI) per kit instructions as described in Seltzer et al. [28].

Statistical methods

Prior to analysis, variables were inspected for normality of distributions, and log transformed where necessary. We denoted statistical significance using an alpha p-value of $p < 0.05$. To explore associations between controls, patients with hypopituitarism (DI+), and patients with hypopituitarism (DI−), we used linear regression, adjusting for age, sex and BMI, the K-sample equality-of-medians test, multiple linear regression for continuous outcomes, and logistic regression for categorical outcomes. All statistical analyses were performed using STATA (V.13) statistical software (STATA Corp., College Station, TX).

Results

Participant characteristics

Thirty-eight subjects completed the study protocol, 18 with hypopituitarism (9 HP + DI, 9 HP − DI) and 20 controls. Baseline characteristics revealed hypopituitary subjects were significantly older ($p < 0.01$), heavier ($p = 0.05$) and more were male ($p = 0.05$) compared to controls (Table 1). Body mass index was highest in HP + DI group [32.0 (29.4–38.7), median (interquartile range (IQR))], followed by HP − DI [27.1 (25.0-29.7)] and then controls [25.4 (21.7–30.4)]. Therefore, additional statistical analysis, adjusted for age, sex and BMI. There were no differences between groups regarding other chronic medical diseases (Type 2 diabetes, hypertension, hyperlipidemia, osteoporosis/osteopenia, anxiety or depression).

Overall, oxytocin levels were significantly higher in hypopituitary patients compared to controls ($p < 0.01$, Fig. 1). Highest levels of OXT were observed in the HP + DI group compared to controls [44.3 pg/ml (29.8–78.2) vs. 20.6 (17-31.3), $p = 0.032$], when adjusted for age, sex and BMI. The differences between HP − DI group trended towards being lower than HP + DI but did not reach significance.

Amongst the hypopituitary subjects, differences were observed between those with and without DI (Table 2). HP + DI group had more pituitary axes involved and were more likely to have had surgery compared to those without DI.

Duration of disease

We next explored whether duration of disease (time from hypopituitarism diagnosis) influenced oxytocin levels. There were no differences in duration of disease between HP + DI and HP − DI. However, regardless of diabetes insipidus status, those hypopituitary patients with a duration of disease longer than 1 year had higher plasma oxytocin values ($p = 0.03$) (Fig. 2).

Questionnaires

We observed no significant differences amongst hypopituitary patients (HP − DI vs. HP + DI) and between either HP subgroup and controls regarding the questionnaire results for subjects. Additionally, in this population, the majority of

Table 1 Participant characteristics

Median (IQR) n	Control [A] N = 20	HP − DI [B] N = 9	HP + DI [C] N = 9	p-value [A vs. C]	p-value [B vs. C]
Age	37.0 (30.5–48.0)	54.0 (47.0–59.0)	57.0 (52–72.8)	0.029	0.990
Weight[a]	69.0 (56.6–94.0)	79.0 (72.0–86.0)	107.0 (86.0–134.0)	0.050	0.013
BMI[a]	25.4 (21.7–30.4)	27.1 (25.0–29.7)	32.0 (29.4–38.7)	0.059	0.024
Oxytocin[b]	20.6 (17.0–31.3)	28.5 (20.4–40.3)	44.3 (29.8–72.8)	0.032	0.099
Male, n(%)	6 (30.0)	4 (44.4)	7 (77.8)	0.025	0.158
DM2, n(%)[b]	3 (15.0)	1 (11.1)	4 (44.4)	0.854	0.252
HTN, n(%)[b]	5 (25.0)	5 (55.6)	4 (44.4)	0.294	0.284
HL, n(%)[b]	4 (20.0)	3 (33.3)	4 (44.4)	0.733	0.819
Osteoporosis/-penia, n(%)[b]	1 (5.0)	2 (22.2)	1 (11.0)	0.441	0.883
Anxiety, n(%)[b]	3 (15.0)	2 (22.2)	2 (22.2)	0.452	0.203
Depression, n(%)[b]	3 (15.0)	1 (11.1)	2 (22.2)	0.216	0.217

Hypopituitary subjects grouped by absence (HP − DI) and presence (HP + DI) of diabetes insipidus

DM2 Type 2 Diabetes Mellitus, *HL* hyperlipidemia, *HTN* hypertension. All non-normally distributed variables were log transformed for analysis

[a]Adjusted for age and sex

[b]Adjusted for age, sex, and weight

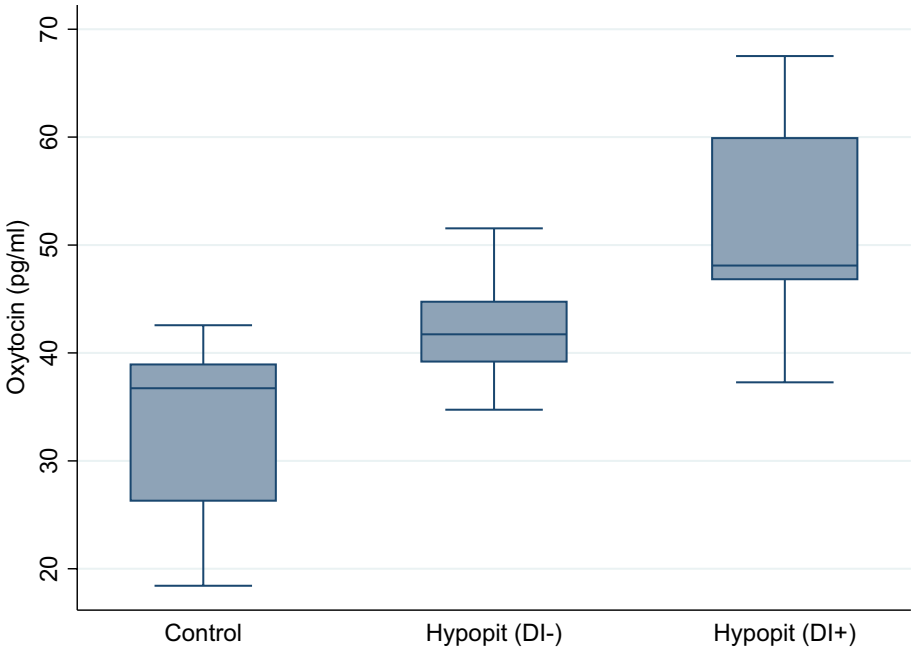

Fig. 1 Oxytocin levels for hypopituitary subjects and controls. Oxytocin levels were highest in hypopituitary subject with DI (HP + DI) compared to controls. Data is represented as raw OXT values with statistical analysis performed on logOXT values and adjusted for age, sex and BMI

Table 2 Characteristics of subjects with hypopituitarism

	HP − DI N = 9	HP + DI N = 9	p-value
# of axes involved, median (IQR)	2 (1–3)	4 (1–5)	0.012
Surgery (%)	5 (55.6)	9 (100)	0.023
Mass effect (%)	3 (33.3)	0 (0)	0.058
XRT (%)	3 (33.3)	2 (22.2)	0.599
Duration hypopituitarism (years),SD	10.7 ± 12.3	14.4 ± 14.9	0.566

Subjects with diabetes insipidus (HP + DI) had more pituitary axes involved compared to without (HP − DI)

respondents had PCL-C scored below the suggested threshold for a positive PTSD screening in the civilian setting (72% HP vs. 80% controls) but there were no differences between groups. When looking at QLS-H scores, HP + DI subjects tended to have lower quality of life compared to HP − DI group (p = 0.056). EQ5D results showed HP + DI subjects had more difficulty with usual daily activities and mobility compared to controls (55.6% vs. 15%, p = 0.033). However, once adjusted for age and gender, significance was lost. Analog scale responses were also not different between subject groups (data not shown).

Emotion recognition tasks

Hypopituitary subjects with DI performed worse on the ER 40 task compared to control, with lower scores out of 40 (31 correct vs. 35 correct, p = 0.028) and longer median response times (3022.5 ms (2440–3295) vs. 2204 (1757.5–2699), p = 0.028) (appendix table). Additionally, for the DARE task hypopituitary subjects appeared initially to have a longer time to response [3.6 ± 1.3 s (control) vs. 4.7 ± 1.8 s (HP − DI) vs. 5.0 ± 1.7 s (HP + DI), p = 0.024] as well as longer time for correctly identified responses [3.4 ± 1.0 s (control) vs. 4.2 ± 1.6 s (HP − DI) vs. 4.6 ± 1.5 s(HP + DI), p = 0.023]. Unfortunately, adjusting results for age and sex eliminated the significant differences.

Discussion

Oxytocin derangements in patients with hypopituitarism is a logical, but under- investigated area of neuroendocrine research. Those lacking AVP, manifest clinically as diabetes insipidus, might be expected to be missing the related peptide OXT given similar anatomic location. Few studies have attempted to define OXT abnormalities in this unique population. The first cross-sectional cohort study included only childhood survivors of craniopharyngioma [17]. While initial results showed no differences between hypopituitary subjects and controls, those with a subset of hypothalamic injury (Grade I lesions) were found with lower salivary OXT levels. Other factors in this study such as gender, presence of DI, or XRT therapy had no influence on OXT measures. Meal consumption also failed to show expected changes in salivary OXT from this study.

Daughters et al. included a broader group of subjects with underlying the hypopituitary diagnosis and also looked to correlate OXT changes with empathy-related tasks [19]. Again, saliva OXT measure was employed and while hypopituitary subjects had lower values than controls, there were

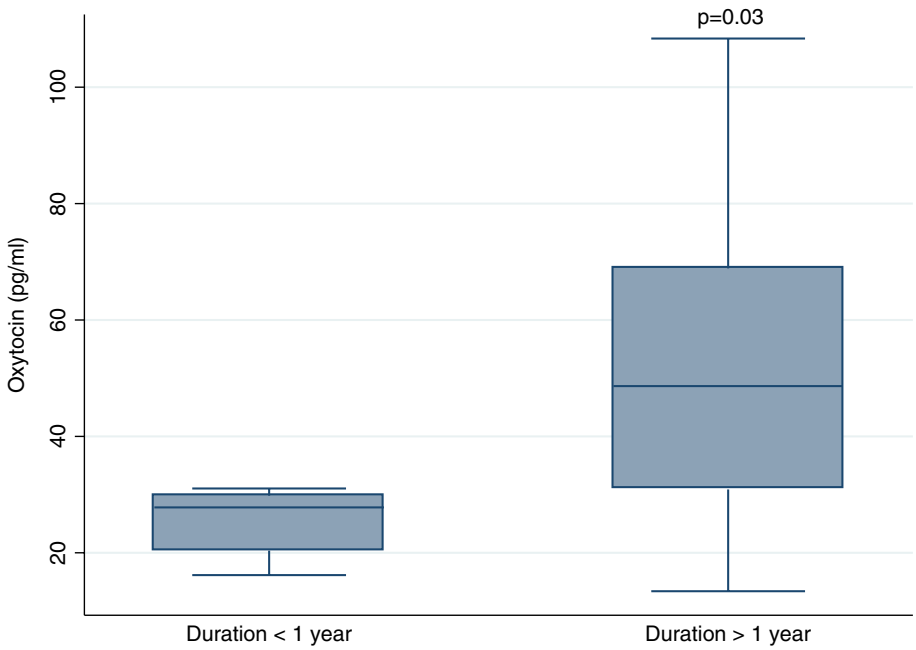

Fig. 2 Oxytocin levels by duration of disease in hypopituitary subjects. Duration of disease greater than 1 year showed significantly higher OXT levels, after adjustment for age, sex and BMI. Disease duration represented as years from diagnosis of hypopituitarism

no differences based on presence or absence of DI. Hypopituitary subjects performed worse on a cognitive empathy task (Reading the Mind in the Eyes Test-RMET) as well as a facial emotion recognition task. In this report, OXT levels did predict a small subset of the RMET responses for DI patients. The only other similar study by Gebert et al. showed a blunted salivary OXT response to exercise with no differences in baseline OXT values between craniopharyngioma patients and controls [20]. Again, diabetes insipidus diagnosis did not affect the OXT results, and OXT levels only predicted a minority of assessed depression and anxiety scores.

Our study represents the first attempt to define plasma OXT differences in subjects with hypopituitarism. Quite surprisingly, we found plasma OXT values were higher in hypopituitary subjects, with highest values in those with DI. There are several possible explanations for the unexpected findings, and contradictory results to other attempted measures of salivary OXT in similar cohorts. OXT released centrally from the posterior pituitary is believed not to reliably cross the blood–brain barrier [29]. If injury to OXT producing machinery (PVN/SON neurons) results in reduced delivery of centrally produced OXT to the periphery, there may be stimulation of OXT overproduction from peripheral sources (ovaries/testes, thymus) due to inadequate or deranged regulation.

The extent of injury to the oxytocinergic system in patients with peri-sellar disease is very difficult to categorize in humans and the resultant regulatory changes are near impossible to characterize. Daubenbüchel et al. attempted to define radiographic evidence of hypothalamic involvement, likely the best surrogate measure, but failed to produce logical results. Those with most extensive disease did not have lowest salivary OXT measures [17].

Neuroadaptive changes to injury within the hypothalamus and pituitary regions are well described. Postoperative diabetes insipidus occurs clinically but often resolves without permanent detriment, in part due to regenerative capacity of axonal projections. Hypophysectomized rats have been studied with clear regenerative changes occurring post-surgery, although more dramatically found in immature animals [30, 31]. In fact, in-vivo OXT production within the hypothalamus as well as peripheral measure of OXT was shown to be higher after hypophysectomy in rats [32, 33]. Whether this occurs in humans has not been defined.

Given the scarcity of data on OXT in human subjects with hypopituitarism there are no data describing oxytocinergic changes over time. Our novel finding that longer duration of disease appeared to correspond to higher OXT levels is intriguing. In animal models of hypophysectomy, neuroadaptive changes occur differently for different cell types (e.g. vasopressinergic vs. oxytocinergic) and change when measured over time postoperatively [33]. Some studies suggest higher OXT levels which are more prominent farther from the time of surgery [34, 35]. Longitudinal data on OXT changes in human subjects after surgery might reveal a critical time to developing OXT derangements and identify an ideal time to intervene.

We did not observe differences between groups of subjects regarding measures of stress, depression, and quality of life. OXT plasma measures were also not predictive of scores for the questionnaires and emotion recognition tasks we employed. Several confounders exist including possible undiagnosed psychological disease within

the control group, as well as treated anxiety/depression within the hypopituitary cohort. The small sample size also likely contributed to a lack of observable difference between groups.

Significant controversy exists regarding oxytocin measurements. There is no consensus on ideal body fluid utilized (blood, saliva, urine, cerebrospinal fluid (CSF)), and the correlation between these fluids has not been clearly defined [36–38]. A standardized methodology of OXT detection is sorely lacking (enzyme immunoassay vs. radioimmunoassay) in addition to a question of the need for solid phase extraction during sample processing [39]. Numerous paradigms of OXT stimulus have been tried in other populations (exercise, food consumption, MDMA administration, sexual activity) but have yielded inconsistent results [17, 20, 40].

In addition to the methodological uncertainty inherent to OXT research, our study has additional limitations. Small sample size (partly due to rarity of disease), subject heterogeneity, and a single time point are some of the acknowledged limitations. Also, subjects with DI were on desmopressin therapy, and while there is potential for cross-reactivity between vasopressin and oxytocin, the likelihood is very low according to the Oxytocin ELISA kit manufacturer datasheet and would therefore be unlikely to influence our results [41].

Despite limited data regarding OXT differences in HP patients, anecdotal evidence supports OXT intranasal spray is already being utilized by patients in the community. Case studies showed favorable behavioral and metabolic effects of OXT administration for several children and most certainly, more rigorous clinical study is needed [42, 43].

Conclusion

Oxytocin is an important neuropeptide with a wide range of potential psychological and metabolic effects. OXT levels appear deranged in those with hypothalamic/pituitary disease and may be influenced by duration of disease. And finally, the role that OXT plays in morbidity and mortality in patients with hypopituitarism warrants further clinical investigation.

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Compliance with ethical standards

Disclosure The authors have nothing to declare.

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