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Thyroid Stimulating Hormone in Acute Psychiatric Patients with Positive Urine Toxicology Drug Screen: A Retrospective Study

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Abstract

Background: The effect of recent exposure to illicit substances on the hypothalamic-pituitary-thyroid axis hormones during acute psychiatric hospitalization remains largely unknown. The aim of this study was to examine thyroid stimulating hormone (TSH) levels in patients admitted to the Los Angeles County hospital psychiatric emergency room with positive urine toxicology screening [Utox(+)].

Methods: The medical records of all patients admitted to the psychiatric emergency room (ER) (2002-2007) were reviewed (n=18,836) to extract TSH and Utox data. Serum TSH levels are routinely measured by radioimmunoassay and Utox is routinely tested using the enzyme immunoassay technique as part of clinical care. A general linear model was used to compare geometric mean TSH values between Utox(+) and Utox(-) groups adjusting for age, sex, and race.

Results: Utox data were available for 57% (n=4,470) of final study cohort. 39% (n=1,726) were Utox(+). A significant race effect on TSH levels was detected regardless of Utox(+) status, with African American patients having significantly lower mean TSH compared with non-Hispanic white patients: 0.98 ± 2.19 *vs.* 1.29 ± 2.43, mean ± SD, P<0.0001). Furthermore, TSH levels were significantly lower in the Utox(+) group compared with the Utox(-) group (1.01 ± 2.41 *vs.* 1.26 ± 2.26, P<0.0001) adjusted for age, gender, and race. Within the Utox(+) group, there was no significant gender difference observed (males *vs.* females: 1.00 ± 2.32 *vs.* 1.04 ± 2.57, P=0.1).

Conclusion: We observed an association between Utox(+) status and low serum TSH levels in both males and females admitted for acute psychiatric conditions. While the stress caused by acute substance intoxication or withdrawal may play a role in altering TSH levels in this group of patients, the neuroendocrinological underpinnings of this observation require further research.

Keywords: Thyroid stimulating hormone; Hypothyroidism; Benzodiazepine; Legal stressors

Introduction

Large scale epidemiological studies document high prevalence of substance use disorders among the general population and more so among psychiatric patients [1-7]. Almost one-third of all patients enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [8] and about two-thirds of patients suffering from bipolar disorder [9] have a co-morbid substance use disorder diagnosis.

Routine thyroid stimulating hormone (TSH) screening is the gold standard to evaluate for hypothyroidism or hyperthyroidism. Abnormal TSH results are seen in 7%-24% of patients during acute psychiatric hospitalization [10-20]. Spontaneous normalization of TSH tends to be the trend in most cases. It is not entirely clear, however, how much impact mental illnesses, substance use disorders, the stress associated with psychiatric hospitalization, or intoxication/withdrawal have on the observed change in TSH levels. Animal studies show that amphetamines [21], sub-lethal doses of heroin [22], or repeated morphine administration [23] result in reduction of serum thyroid hormone levels. In humans however, the effect of substance use on thyroid function has been inconsistent. Results vary from elevation in psychiatric inpatients with comorbid substance use disorders [15] and in heavy methamphetamine users [24], to no significant change in cocaine users [25] and in healthy volunteers given 20 mg of d-amphetamine orally [26], to actual reduction among alcohol-dependent patients [27]. One possible reason for this apparent inconsistency is the timing of hormonal assay whether during active use, early intoxication/withdrawal phase of the illness, or during abstinence.

The aim of this study was to investigate the effect of recent substance use on serum TSH levels in acute psychiatric patients. A second goal was to look for the effect of certain epidemiological variables such as age, sex, and race on TSH levels.

Methods

The study was conducted at the Los Angeles County psychiatric emergency room. Study protocol (HS #00066) was approved by the Institutional Review Board of the University of Southern California. Given the anonymous nature of this retrospective study, obtaining informed consents was waived.

Subjects

Charts of all patients admitted to psychiatric ER during the interval from January 1, 2002, through December 31, 2007, at Los Angeles County Hospital were reviewed (n=18,836). Subjects younger than 18 or older than 65, those with no available TSH values at the study visit, or

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with more than one admission during the study interval were excluded from the analysis.

Setting

The Los Angeles County Hospital is one of the largest acute care hospitals in America. Annually, over 3,000 cases receive treatment at the psychiatric ER. The vast majority of patients are admitted on involuntary commitment (California Welfare and Institutions Code Section 5150 psychiatric hold) for either danger to self, danger to others, or grave disability. Typically, patients present with acute psychosis, agitation, or suicide attempts other than overdose (overdose patients are admitted to the medical ER); 50% of all patients receive an emergency antipsychotic and benzodiazepine within the first day of admission. Less than 1% of all cases receive mood stabilizers or anticonvulsants during hospitalization. The average length of stay in the psychiatric ER is 29 hours. Patients presenting with severe alcohol withdrawal syndrome are admitted to the medical ER. Those with mild to moderate manifestations are treated with symptom-triggered p.r.n. benzodiazepine. Patients suffering from mild to moderate opioid withdrawal are also treated symptomatically with clonidine and supportive measures such as nonsteroidal anti-inflammatory medications for pain. Patients with severe withdrawal manifestations are admitted to the inpatient unit for medically assisted opioid withdrawal. Except for lithium [28], none of the antipsychotic or benzodiazepine medications used are known to have significant effects on serum TSH levels [29,30].

Blood and urine collection

Samples are routinely collected upon admission. On average, about half of the patients are either unable or unwilling to give verbal consent for sample collection.

Serum TSH assay

TSH levels are measured using ultrasensitive radioimmunoassay method [31] and analyzed with the IMMULITE automatic chemiluminescent immunoassay analyser according to the manufacturer's instructions. To avoid inter-assay variation, a single batch of IMMULITE commercial kits was used. The intra-assay coefficient of variation was 5.0% for TSH.

Urine toxicology screening (Utox)

An enzyme immunoassay technique (EMIT; Behring Diagnostics, San Jose, CA) was used to screen for the several classes of substances with the following thresholds for detection: amphetamines 500 ng/mL; cocaine 300 ng/mL; opiates 300 ng/mL; barbiturates 200 ng/mL; benzodiazepines 100 ng/mL; and phencyclidine 25 ng/mL. Detection of other substances such as alcohol or tetrahydrocannabinol is not routinely done.

Statistical analysis

The frequency TSH values was determined for each group and plotted for distribution. TSH values were log transformed to make the variable TSH normally distributed. Geometric means and standard deviations were based on log-transformed values of TSH, i.e., the geometric mean of TSH is exp of the mean of ln (TSH). The 95% confidence range is exp [mean of ln (TSH) ± 1.96* standard deviation (ln (TSH))].

Geometric means and standard deviations for TSH were calculated by exponentiation the arithmetic means and standard deviations of log(TSH). P-values for unadjusted differences in TSH by groups were calculated using independent sample t-tests on the log(TSH) variable. All comparisons were pair wise with no adjustment for multiple comparisons. Adjusted comparisons used general linear models with log(TSH) as the dependent variable. When adjusting for age, a continuous age variable was used; when adjusting for race, dichotomous "dummy" variables were used for each racial/ethnic category (i.e., non-Hispanic white, African American, Hispanic and other – Yes/No). Comparisons of patients with low TSH (<0.5) and high TSH (>5.0) were performed using chi square tests for unadjusted comparisons and logistic regression for adjusted comparisons. All analyses were done on SAS version 9.0.

Results

Demographics and Utox(+) status

Among the 18,836 patients admitted to the psychiatric ER during the study interval, 50.3% (n=9,571) were excluded for lack of TSH data, younger than 18 or older than 65, or for having more than one admission during the study interval. A final sample of 7,896 patients was included in the study (41.9% of the initial sample). Males constituted 63% (n=4,984) of the cohort with a mean (± SD) age of 36.5 ± 11.3 years, (females 37.5 ± 11.4 years). The racial profile showed 26.4% (n=2,089) non-Hispanic white, 26.3% (n=2,080) African Americans, 35.6% (n=2,811) Hispanic Americans, and 11.6% (n=916) of mixed or other races. Utox data were available for 56.6% (n=4,470) of subjects, of whom 38.6% (n=1,726) tested positive for an illicit substance [Utox(+)].

Among Utox(+) patients, 54% (n=940) tested positive for cocaine alone (n=592) or in combination with other substances (n=348), and 26% (n=457) for methamphetamine alone (n=294) or in combination with other substances (n=163). 44% (n=761) tested positive for substances other than cocaine or methamphetamine.

To examine the effect of age on Utox(+) status, patients were categorized into four age groups: (18-29, 30-39, 40-49, 50-65 years). Almost half (49%, n=575) of all patients in the 40-49 years group were Utox(+) compared with 40% (n=274), 39% (n=458), and 29% (n=419) in the age groups 50-65 years, 30-39 years, and 18-29 years respectively.

The effect of age and gender on TSH values

A steady increase in mean geometric TSH values was observed with advancing age (TSH geometric mean ±SD 18-29 years, 1.12 ± 2.15; 30-39 years, 1.12 ± 2.28; 40-49 years, 1.19 ± 2.43; and 50-65 years, 1.30 ± 2.54. the oldest age group (50-65 years) had significantly higher mean geometric TSH values compared with the younger age groups (18-29 years and 30-39 years) P<0.0001. Females (n=2,912) had significantly higher mean geometric TSH values (1.26 ± 2.49) compared with males (n=4984, 1.11 ± 2.22), P<0.0001. However, the gender difference was not statistically significant in the group with Utox(+).

The effect of race on TSH values

African Americans (n=2,080) had significantly lower mean geometric TSH values (0.98 ± 2.19) compared with non-Hispanic whites (n=2,089, TSH 1.29 ± 2.43, P<0.0001) and compared with Hispanic Americans (n=2,811, TSH 1.23 ± 2.32, P<0.0001). Hispanic Americans had significantly lower TSH values compared to non-Hispanic whites (P=0.04). The lower value for African Americans compared to either non-Hispanic whites or Hispanic Americans remained statistically significant after adjusting for age, gender and Utox (+) status among patients with Utox testing.

The effect of Utox(+) status on TSH values

The mean geometric TSH values were significantly lower among Utox(+) patients (n=1,726) compared with Utox(-) patients (n=2,744): Utox(+) 1.01 ± 2.41 vsUtox(-) 1.27 ± 2.26, P<0.0001. The statistical difference remained significant after adjusting for age, gender, and race (P<0.0001).

Given that a significant proportion of our patients tested positive for more than one substance, we re-analyzed the data for patients who tested positive for only cocaine (n=592) or only methamphetamine (n=294). Utox(+) for either drug was associated with significantly lower geometric mean TSH values after adjusting for age, gender and race (P ≤ 0.01) for each.

We then categorized patients based on TSH reference range adopted in our hospital laboratories (0.5-5.0 mIU/liter) into below (<0.5), within (0.5-5.0) and above (>5.0) reference range categories to examine the effect of Utox (+) status on the raw instead of the mean geometric TSH data. Chi square test was used to compare frequencies of Utox(+) and Utox(-) status (yes *vs.* no) in the TSH<0.5 and TSH>5.0 groups. The group with TSH within the adopted reference range (0.5-5.0) was not included in the analysis.

There were significantly more Utox(+) compared to Utox(-) patients in the <0.5 mIU/liter TSH reference range [frequency Utox(+) vs (Utox(-) in the <0.5 IU/mL TSH category = 18% (n=317) *vs* 9% (n=257), P<0.0001], and in the group with cocaine alone or in combination with other substances [frequency Utox(+) *vs* (Utox(-) in the <0.5 IU/mL TSH category = 17% (n=163) *vs.* 12% (n=411), P<0.0001], but not in the cocaine only group [frequency Utox(+) *vs* (Utox(-) in the <0.5 IU/mL TSH category: 14% (n=85) *vs.* 13% (n=489), P=ns], or in the group with methamphetamine alone or in combination with other substances [23% (n=103) *vs.* 12% (n=471), P<0.0028], or in the methamphetamine only group [22% (n=65) *vs.* 12% (n=509), P<0.04], as shown in table 1.

Discussion

This study is the first, to the best of our knowledge, to investigate the changes in thyroid stimulating hormone in acute psychiatric patients with positive urine screening test. Before we discuss the results, several limitations inherent to the retrospective nature of the study are acknowledged. Importantly, our study sample may not represent other less acute patients. Many of our patients struggle with homelessness and severe social and legal stressors. Equally important, we do not routinely test for alcohol or marijuana and we do not collect history of nicotine use. Furthermore, we did not exclude patients with known medical illness that could impact TSH values, and we did not review the pharmacy records for concomitant medications prior to admission to the psychiatric ER. There is a possibility that any of these variables could have confounded the results. Despite these limitations, this report adds more depth to the current literature. We examined a large enough, yet homogenous sample with balanced racial mix, and we confirmed recent substance use history by an objective measure (the Utox screening) and examined the effects of race, gender, and age on the geometric mean as well as the raw TSH values.

Over one-third of all patients tested positive for at least one illicit substance. Keeping in mind that we do not routinely test for tetrahydrocannabinol or alcohol, this could well be an under estimate for the true prevalence of substance use in this group of patients. The vast majority of Utox(+) cases showed cocaine or methamphetamine either alone or in combination with other substances. That is not a surprise given the fact that stimulant intoxication can manifest with acute psychosis, and patients frequently require acute psychiatric hospitalization. Interestingly, Utox(+) status was most commonly observed in the 40-49 year-old patients. It could be speculated that substance use, specifically stimulants, in this group of patients is more dysphoric and psychogenic compared to the younger substance users.

Our results suggest a relationship between recent substance use on the one hand, and hypothalamic pituitary thyroid axis function on the other hand. This observation adds relevance to the few inconsistent studies [15,24-27]. However, a clear understanding for this relationship is, at best, speculative. It could hypothesized be that the combined acute stress of psychiatric hospitalization and recent substance use results in maximal activation of the hypothalamic pituitary thyroid axis masking the subtle gender differences observed under baseline conditions. Several studies document transient elevation of serum thyroid

		TSH reference range (mIU/liter)			Chi square test	
		<0.5	0.5-5.0***	>5.0	p-value*	p-value** adjusted for age, gender and race
Utox (+)		N (%)	N (%)	N (%)		
Any substance	Yes	317 (18)	1,369 (79)	40 (2)	<0.0001	<0.0001
	No	257 (9)	2,376 (87)	111 (4)		
Cocaine alone or in combination with other substances	Yes	163 (17)	760 (81)	17 (2)	<0.0001	0.0004
	No	411 (12)	2,985 (85)	134 (4)		
Cocaine only	Yes	85 (14)	508 (84)	9 (1)	0.02	0.07
	No	489 (13)	3,237 (84)	142(4)		
Methamphetamine alone or in combination with other substances	Yes	103 (23)	342 (75)	12 (3)	0.0028	0.0026
	No	471 (12)	3,403 (85)	139 (3)		
Methamphetamine only	Yes	65 (22)	221 (75)	8 (3)	<0.0001	0.04
	No	509 (12)	3,524 (84)	143 (3)		
Other than cocaine or methamphetamine or combined drugs	Yes	152 (20)	588 (77)	21 (3)	0.0013	<.0001
	No	422 (11)	3,157 (85)	130 (4)		

*P-value calculated using chi-square test comparing those with TSH <0.5 to those with TSH >5.0
**P-value calculated using logistic regression comparing those with TSH <0.5 to those with TSH >5.0
***These patients are not included in P-value calculations

Table 1: The frequencies of TSH values below, within, or above the adopted reference range in patients with Utox(+) status for any substance, for cocaine alone or in combination with other substances, for cocaine only, for methamphetamine alone or in combination with other substances, for methamphetamine only, and for other than cocaine or methamphetamine or combined drugs, shows significantly more patients with Utox(+) falling in the below (<0.5 TSH) category compared to Utox(-) and compared to those above (>5.0 TSH) the adopted reference range.

hormones during psychiatric hospitalization [4-6,13,17]. Further research is required to test this hypothesis.

We found that older patients have significantly higher TSH values. This finding is in agreement with some [32,33], but not all [34-36] studies that reported a correlation between age and TSH Values. It is possible that the sensitivity of thyroid gland to TSH decreases with age.

We also found a gender difference with women having higher TSH values compared to men. Data on gender difference in thyroid hormone levels are conflicting [32,33,37,38]. Moreover, we found that serum TSH in African Americans is lower than in non-Hispanic whites. This is in agreement with other published reports [32,39-41]. The clinical significance for the age, gender, and ethnic differences in TSH values argue for the need to look for specific TSH reference range in certain populations with emphasis on patients with psychiatric disorders. However, this issue is under intense debate and a final conclusion has not yet been reached.

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