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Research Article

Thyroid Function Abnormalities in Patients on Treatment with Antipsychotics: A Comparison between Typical and Atypical Antipsychotics

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Abstract

Objective: The study was designed to study thyroid function abnormalities in patients on treatment with antipsychotics at the University of Port Harcourt teaching Hospital (UPTH) in Rivers State, Nigeria.

Materials and Methods: Two groups of forty consecutive patients on typical and atypical antipsychotics respectively who attended the Neuropsychiatry Department of UPTH from November 2018 and March 2019 were studied. Their blood samples were taken and the concentrations of TSH and free T_3 and T_4 assessed by ELISA method.

Results: The mean age of the 80 subjects was 38.3 ± 9.8 yrs. The largest proportions were male (62.5%), Christian (97.5%), unemployed (75.0%), single (75.0%), of Ibo ethnic nationality (42.5%) had no family history of thyroid disease (92.5%).

There is statistically significant difference between the fT_4 concentration of the subjects on typical antipsychotics compared with those on atypical antipsychotics. (0.835 ± 0.155 ng/ml, 0.940 ± 0.191 ng/ml, p = 0.007). There is no statistically significant difference in the mean TSH and fT_3 levels of the two categories of antipsychotic users. There's negative correlation between TSH and fT_4 levels.

Conclusion: Antipsychotics alter thyroid function. While they generally elevate TSH concentrations, they depress the serum concentrations of fT_4 and there's statistically significant difference between the mean fT_4 levels of patients on typical antipsychotics compared with that of the atypical. Therefore, greater caution should be applied in the use of typical antipsychotics than the atypicals in patients with clear vulnerability for thyroid disease. The thyroid function of the patients should be closely monitored while on these drugs.

Keywords: *Antipsychotics; Typical; Atypical; Thyroid Hormones*

Introduction

Thyroid hormones have been documented to be important in human and adult brain function [1]. Fluctuation in their levels throughout intra uterine development and life have been associated with various neuropsychiatric disorders as wells as with the use of antipsychotic medications.

Endocrine functions in mentally ill patients may be altered by the psychiatric syndrome itself as well as narcoleptic medications. Compared to mood disorders, less attention has been given to the neuroendocrine abnormalities in psychotic patients [2]. Thyroid function abnormalities including thyroid autoimmunity have been documented for various psychotic disorders [3,4].

Some researchers have reported that a majority of schizophrenic patients appear euthyroid with normal thyroid stimulating hormone (TSH) levels and normal TSH response to thyroid releasing hormone (TSH) challenge [2].

Inspite of these reports and many more studies that have been done, there is paucity of studies on the effect of antipsychotic medications on thyroid function, especially in the developed world. This is the reason for this study. It is hoped that results from this study will contribute to better, holistic management of our mentally ill patients in this part of the world.

Methodology

This is a prospective cross-sectional study which was conducted between November 2018 and March 2019 at the out-patient clinic of the Neuropsychiatric department of University of Port Harcourt Teaching hospital (UPTH) in Rivers State, Nigeria. All psychiatric patients who came to the clinic within frame were enlisted in the study. Newly diagnosed psychiatric patients who were antipsychotic naïve as well as those who had been on antipsychotic medication for less than 6 months prior to the commencement of the study, were excluded from the study. Similarly, those will comorbid medical conditions were excluded.

Prior to the commencement of the study, approval was obtained from the ethical committee of UPTH and informed consent obtained from the subjects involved in the study.

Forty consecutive patients each on typical and atypical antipsychotic who satisfied the criteria for the study were selected. They underwent a through clinical evaluation, and psychiatric diagnosis was made using the ICD-10 criteria. The subjects were matched for sex and age with healthy controls drawn from among medical students and hospital staff. A socio-demographic questionnaire designed by the authors, also containing psychiatric illness variables were administered to the subjects. Blood samples were obtained from them as well as the controls for assessment of thyroid function. Thyroid functions tests were performed by the ELISA method using the ACCU-BIND ELISA MICROWELLS kit and the sensitivity of the ELISA test used is 0.078 µIU/ml for the thyrotropin (TSH) test [5], 0.835 pg/ml for the free triiodothyronine (fT_3) test [6] and 0.314 ng/dl for the free thyroxine (fT_4) test [7]. The thyroid stimulating hormone (TSH), free thyroxine (fT_4) and free triiodothyronine (fT_3) serum levels were measured.

These tests were done by one of the authors who is a doctor and specialist in laboratory medicine, assisted by a medical laboratory scientists at the chemical pathology department of UPTH.

Procedural steps for the TSH, fT_3 and fT_4 ELISA assay using ACCU-BIND ELISA microwells

Intended use: The quantitative determination of TSH, fT_3 AND fT_4 concentrations in human serum by microplate immunoenzymometric assay.

Test Procedure: Prior to the commencement of the assay, the reagent, serum references and controls were brought to room temperature (20 - 27^{0}C).

The microplate wells for each serum reference, control and patient specimen to be assayed in duplicates were formatted. 0.05 ml (50 µl) of the appropriate serum reference, control or specimen was pipetted into the assigned wells. The TSH enzyme reagent (0.1ml {100 µl}) was added to each well; the micropipette was gently swirled for 20 - 30 seconds to ensure adequate mixing of the contents before it was covered. After incubating for sixty minutes, the contents of the microplate were discarded by decantation and the plate blotted dry with absorbent paper. 350 µl of wash buffer aspirate was added and then 0.1ml (100 µl) of working substrate was added to all the wells carefully without shaking the plate. 0.05 (50 µl) of stop solution was then added to each well and mixed gently for 15 - 20 seconds; the reagents were added in the same order to minimize reaction time differences between the wells. Finally, the absorbance in each well was read at 450 nm (using a reference wavelength of 620 - 630 nm to minimize well imperfections) in a microplate reader. The results were read within 30 minutes of adding the stop solution.

The above process was repeated for the assays of fT_3 and fT_4 except that the fT_3 enzyme reagent and the fT_4 enzyme reagent solutions respectively were used for the corresponding tests. Furthermore, after adding the reagents, the microplate was incubated at room temperature for 15 minutes before the stop solution was added.

Data analysis

Data analysis was carried out using the statistical package of the social sciences (SPSS, version 16) at 5% level of significance and 95% confidence interval. Frequency distribution tables were used to display the sociodemographic and clinical variables of the subjects. One way ANOVA was used to test for significant differences in mean serum levels of thyroid hormone levels between groups. The Turkey Post Hoc test was used to determine which group was specifically significant from the other. Pearson's correlation test was used to evaluate the relationship between the blood concentrations of the various thyroid hormones.

Results

The mean age of the study cohort of 80 subjects was 38.3 ± 9.8 yrs.

Table 1 shows the frequency of the sociodemographic and clinical variables of the subjects. The largest group of the subjects were male (62.5%), Christian (97.5%), those that had secondary education (67.5%), unemployed (75.0%), single (75.0%), of Ibo ethnic nationality (42.5%), schizophrenic (32.5%), had no family history of thyroid disease (92.5%) and had no history of comorbid psychoactive substance use disorder (62.5%).

		N = 80
Variables	**Frequency (n)**	**Prevalence (%)**
Gender		
Male	50	62.5
Female	30	37.5
Religion		
Christian	78	97.5
Islam	2	2.5
Education		
Primary	6	7.5
Secondary	54	67.5
Tertiary	20	25.0
Employment		
Employed	20	25.0
Unemployed	60	75.0
Marital status		
Single	60	75.0
Married	18	22.5
Separated/Divorced	2	2.5
Ethnic nationality		
Ikwere	22	27.5
Ibo	34	42.5
Yoruba	6	7.5
Ogoni	2	2.5
Kalabari	8	10.0
Ijaw	4	5.0
others	4	5.0
Family history of mental Illness		
Yes	22	27.5
No	58	72.5
Diagnosis		
Schizophrenia	26	32.5
Depression	18	22.5
Bipolar Affective Disorder	20	25.0
Delusional Disorders	4	5.0
Others	12	15.0
Family history of thyroid diseases		
Yes	10	12.5
No	70	87.5
Comorbid substance		
Yes	30	37.5
No	50	62.5

Table 1: *Frequency of the sociodemographic and clinical variables of the subjects.*

Table 2 depicts the means of serum thyroid hormones concentrations of the subjects and the controls. The mean TSH levels for subjects on atypical psychotics is the least (1.500 ± 0.631 uiu/ml) compared with those on typical antipsychotics (1.590 ± 0.887 uiu/ml) and the control group (1.530 ± 1.138 uiu/ml). For the fT_3 mean values, the 'typical' group has the least (2.075 ± 0.297 pg/ml) compared to the 'atypical' (2.985 ± 4.421 pg/ml) and the control group (3.960 ± 5.830 pg/ml); while for the fT_4 mean values, those on typical antipsychotics is least (0.835 ± 0.155 ng/ml) compared to the 'atypical' group (0.940 ± 0.191 ng/ml) and that of the control group (0.905 ± 0.098 ng/ml).

		N	Mean	Std. Deviation
TSH (uiu/ml)	Typicals	40	1.590	.887
	Atypicals	40	1.500	.631
	Control	40	1.530	1.138
	Total	120	1.540	902
FT_3 (pg/ml)	Typicals	40	2.075	.297
	Atypicals	40	2.985	4.421
	Control	40	3.960	5.830
	Total	120	3.007	4.263
FT_4 (pg/ml)	Typicals	40	.835	.155
	Atypicals	40	.940	.191
	Control	40	.905	.098
	Total	120	.893	.158

Table 2: *Means of the thyroid function values of the subjects and control.*

Table 3 displays the results of one way ANOVA tests. There is statistically significant difference between the fT_4 concentrations of the various groups (the two groups of antipsychotic users and the control) but that of fT_3 and TSH concentration are not statistically significant.

		Sum of squares	df	Mean Square	F	Sig.
TSH (uiu/ml)	Between Groups	.168	2	.084	.102	.903
	Within groups	96.720	117	.827		
	Total	96.888	119			
FT_3 (pg/ml)	Between Groups	71.093	2	35.546	1.989	.141
	Within groups	2091.382	117	17.875		
	Total	2162.475	119			
FT_4 (pg/ml)	Between Groups	.229	2	.114	4.907	.009*
	Within groups	2.726	117	.023		
	Total	2.955	119			

Table 3: *Table of ANOVA values.*

**Significant at p < 0.05.*

Table 4 shows the results of the Post Hoc Test results for multiple comparisons. The mean fT_4 level of those on atypical antipsychotics was statistically significantly higher than that of those on typical antipsychotics (0.940 ± 0.191 ng/ml, 0.835 ± 0.155 ng/ml; p = 0.007). The mean difference between the two as shown on the table is -0.105 ± 0.034. Comparison of other subgroups did not identify statistically significantly difference.

Turkey HSD					
Dependent Variable (1)	**Subject (J)**	**Subject type**	**Mean Difference (I - J)**	**Std. Error**	**Sig.**
TSH (uiu/ml)	Typicals	Atypicals	0.090	.203	.898
		Control	0.060	.203	.953
	Typicals	Typicals	.0.090	.203	.898
		Control	-0.030	.203	.988
	Typicals	Typicals	-.060	.203	953
		Atypicals	030	.203	.988
FT_3 (pg/ml)	Typicals	Atypicals	-910	.945	.602
		Control	1.885	.945	.118
	Typicals	Typicals	.910	.945	.602
		Control	-.975	.945	.559
	Typicals	Typicals	1.885	.945	.118
		Atypicals	.975	.945	.559
FT_4 (pg/ml)	Typicals	Atypicals	-.105*	.034	.007
		Control	-.070	.034	.105
	Typicals	Typicals	.105*	.034	.007
		Control	.035	.034	.562
	Typicals	Typicals	.070	.034	.105
		Atypicals	-.035	.034	562

Table 4: *Post HOC test (multiple comparisons).*

**The mean difference is significant at the 0.05 level.*

Table 5 shows the Pearson's Correlation of the various thyroid function test results. There was significant correlation between TSH and fT_4 values (-0.197; p = 0.031).

		TSH	**fT_3**	**fT_4**
TSH (uiu/ml)	Pearson's Correlation	1	-0.82	-.197*
	Sig. (2 tailed)		.374	.031
	N	120	120	120
FT_3 (pg/ml)	Pearson's Correlation	-.082	1	143
	Sig. (2 tailed)	.374		118
	N	120	120	120
FT_4 (pg/ml)	Pearson's Correlation	.-.197*	.143	1
	Sig. (2 tailed)	.031	.118	
	N	120	120	120

Table 5: *Pearson's correlations.*

Discussion

Altered levels of free thyroxine (fT_4) and thyroid stimulating hormone (TSH) thyroid stimulating hormone (TSH) have been associated with various mental disorders as well as with the use of antipsychotic medications [2]. TSH (thyrotropin) is a glycopeptide hormone synthesized and secreted by the anterior pituitary gland which regulates the endocrine functions of the thyroid [8]. TSH stimulates the thyroid gland to secret thyroxine (T_4) and triiodothyronine (T_3) and its concentration is regulated by the circulating free fraction of the hormones via a negative feedback mechanism [9]. Therefore, higher than normal levels of TSH with a high level of T_3 and T_4 indicate dysfunction of the hypothalamus and pituitary glands (e.g. the presence of pituitary adenoma [10]. Conversely, reduction in the levels of T_3 and T_4 suggests abnormally low function of the pituitary (Hyperthyroidism) [3]. Abnormally high level of thyroid hormones due to excessive production by the gland with associated reduced TSH levels indicates hyperthyroidism or Grave's disease [10]. Conversely reduction in the levels of T_3 is seen in congenital hyperthyroidism (cretinism) [10].

The largest percentage of the subjects were male (unemployed, single and had secondary education. This is similar to the results of previous researchers on the sociodemographic characteristics of patients attending the outpatient psychiatric clinic [11-13]. In this study, 92.5% of the patients had no family history of thyroid disease. Nevertheless, previous studies have reported that antipsychotic drug treatment was associated with abnormal thyroid function test results [14] and genetics plays a prominent role in both determination of thyroid hormone and thyrotropin (TSH) concentrations and susceptibility to autoimmune thyroid disease [15]. Nevertheless, studies on the heritability of thyroid function have provided wide varying estimates, probably due to methodological differences [16-18].

An important finding in this study is that the mean serum TSH levels for subjects on atypical antipsychotic is lesser compared with control group and that the serum TSH level of patients on typical antipsychotic medication is higher than that of the control group. However, the differences in means between the various groups are not statistically significant. The elevation of TSH by typical antipsychotics more than the atypical antipsychotics is corroborated by Pearson studies Khalil *et al* [19]. They further noted that non-phenothiazines typical antipsychotics can induce the formation of thyroid antibodies and can elevate TSH levels, and that atypical antipsychotics may decrease TRH stimulated TSH [19]. Stetan., *et al.* added that the production of thyroid stimulating hormone receptor (TSHR) antibodies represent the hallmark of Graves disease pathogenesis [20]. Similarly, the mean fT_4 level of those on typical antipsychotics is lesser than that of the control group while the mean fT4 concentration of subjects on atypical antipsychotics is higher than that of the control group. There was statistically significant difference between the fT_4 concentrations of the various groups but that of fT_3 and TSH were not statistically significant. The result of fT_4 values with use of antipsychotics is at variance with results from studies done elsewhere [12]. Iversen., *et al.* noted that they found significant association between lower fT_4 level and current use of the atypical drugs Quetiapine and Olanzapine [21].

The negative relationship in the concentration of TSH and fT_4 was confirmed through the Pearson's correlation test done. This is as a result of the negative feedback loop where TSH stimulates the secretion of fT_4 which in turn regulates TSH concentrations [9].

Conclusion

Antipsychotic medications alter thyroid function, while they generally elevate TSH concentrations, they depress the serum concentrations of free T_4 and there's statistically significant difference between the mean fT_4 levels of patients on typical antipsychotics compared with those on atypical antipsychotics, with the former lower than the latter. Therefore, greater caution should be applied in the use of typical antipsychotics than the atypicals in patients with clear vulnerability for thyroid disease. The thyroid function of the patients should be closely monitored while on these medications.

Limitation

This is a cross sectional study; therefore caution should be exercised when applying it to the general population.

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