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Role of extrapolative factors in the development of Hyperprolactinemia Mediated Depression (HMD) in schizophrenics susceptible to thyroid disorders

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Abstract

A cross sectional prospective study was designed to find out the prophetic effect of hyperprolactinemia mediated depression (HMD) in schizophrenics susceptible to thyroid disorders. One hundred newly diagnosed patients (61 males and 29 females) suffering from schizophrenia in the age group of 24-67 years were recruited in the study. Fifty age and sex matched, healthy individuals (25 males and 25 females) were included as controls (23-63 Years). Important biomarkers like T3 (Triiodothyronine), T4 (Thyroxine), TSH (Thyroid stimulating hormone), tumor necrosis factor alpha (TNF-α), Dopamine, Prolactin, Estradiol, Serotonin, Zn and Cu were estimated and compared in schizophrenics and controls. Higher levels of FT4, TSH, TNF-α, Zn, prolactin and serotonin were recorded (25.12±3.05 pmol/L, 4.48±.18 IU/L, 34.75±2.09pg/ml, 0.30±0.0019mg/L, 30.60±2.08ng/ml and 175.85±7.06ng/ml respectively) in schizophrenia patients as compared to healthy controls. While lower levels of FT3, Cu, dopamine and estradiol were measured (3.94±0.35µg/dl, 1.03±0.056mg/L, 3.87±0.668pg/ml and 6.75±0.97pg/ml respectively) in schizophrenia patients as compared to healthy controls. The present study depicts that hypoestrogenism and disturbed prolactin-serotonin-dopamine interactions are the major role players in the pathogenesis of schizophrenia. Hypoestrogenism and reduced copper levels affect dopamine levels negatively while high levels of zinc induce serotonin production, both of these effects result in hyperprolactinemia mediated depression (HMD) and susceptibility to hyperthyroidism. Thus, by regulating these factors not only schizophrenic symptoms but also progression to thyroid disorders can be controlled.

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Introduction

Schizophrenia is a state of mental disorder in which there is breakdown of thought processes and emotional deficit (Kreyenbuhl *et al.* 2010). It includes behavioral disturbances like thinking, feeling and gross distortion from reality (Ciobica *et al.* 2011). Among the psychiatric disorders, schizophrenia is the most common with its prevalence of 0.7-1.0% in entire population (Santos *et al.* 2012). These people have high suicidal tendency and overall mortality rate in schizophrenics is twice than general population, for this reason it is called as a "Life shortening disease" (Leucht *et al.* 2007). Symptoms that aid in establishing diagnosis do not appear until young adulthood but prodromal symptoms and certain features related to cognitive and social deficits, may develop earlier (Bitanihirwe and Woo 2011). It is a chronic debilitating disease with most of the patients gives poor response to treatment with frequent relapses. Furthermore, it is a financial burden not only for the patient but also for his/her dependents as it leads to loss of productivity and has very expensive treatment (MacDonald and Schulz 2009).

Nowadays, the focus of researchers is diverted to hormonal variations in schizophrenia as they are considered important in its pathogenesis and by controlling their levels; the schizophrenic symptoms can be prevented and treated as well. It has been revealed that hypoestrogenism and disturbed prolactin-dopamine-serotonin interactions are the main culprits in the initiation and progression of schizophrenia (Peterson *et al.* 2015; González-Blanco *et al.* 2016). Reduction in estrogen levels affects pro-inflammatory cytokines and dopamine production resulting in decreased neurogenesis and hyperprolactinemia leading to schizophrenic symptoms (Weickert *et al.* 2016).

The main regulating factors behind hormonal regulations in schizophrenia are copper and zinc as they are important in the synthesis of dopamine and serotonin respectively (Liu *et al.* 2015).

With the increase in prolactin levels, there is also increase in thyroid stimulating hormone (TSH) as both are released from anterior pituitary and are under the effect of prolactin activating factors like thyrotropin releasing hormone (TRH) and vasoactive inhibitory peptide (VIP), and prolactin inhibiting factor (Dopamine) (Halbreich *et al.* 2003). It has been also suggested that there is also disturbed TSH response to TRH, thus schizophrenics may have susceptibility to thyroid disorders (Dejong *et al.* 2013; Wysokiński and Kłoszewska 2014).

The aims and objectives of the present study were to assess the extrapolative factors having role in the development of hyperprolactinemia mediated depression (HMD) in schizophrenics susceptible to thyroid disorders.

Materials and methods

Study Design and Data Collection

One hundred newly diagnosed patients (61 males and 39 females) suffering from schizophrenia in the age group of 24-67 years were included in the study. Fifty normal healthy individuals (25 males and 25 females) were included as controls. Informed written consent was obtained before being included in this study (23-63 Years old). General characteristics of participants in presented in table 1. All the selected patients were screened at the Department of Psychiatry, Social Security Hospital Lahore, Fountain House Lahore and mental Hospital Lahore. According to a positive and negative syndrome scale (PANSS), total score prescribed by the number of psychiatrists lies in between 75 to 120. Inclusion criteria specify that subjects included should be moderately ill so it may respond to the treatment and quality of study can be increased. Also, it is necessary that one should add severely ill patients and threshold value for such severely ill should not be less than 120 and such patients should not be considered handicapped. The experimental protocols were approved by the Research

Ethical Committee of the Institute of Molecular Biology and Biotechnology, the University of Lahore.

Processing of Blood Samples for all Clinical Parameters

Five ml of venous blood sample were taken from the antecubital vein of each participant. The sample bottles were centrifuged within one hour of collection, after which the serum were separated and stored at -70°C until assayed. None of the controls were on any medication, history of chronic infections, malnutrition syndrome, and metabolic dysfunction e.g., diabetes mellitus and liver diseases that may interfere with thyroid hormone status.

All chemical reagents of analytical grades were purchased from Sigma/Invitrogen Chemical Co. (St. Louis, Mo, USA). Sera were separated by centrifugation for 10 minutes at 3000 rpm and stored at -80°C until biochemical analysis. T3 (Triiodothyronine), T4 (Thyroxine) and TSH (Thyroid stimulating hormone) were estimated by using human ELIZA kits (DiaMetra) (Supit and Peiris 2002). Zn, Cu were determined by atomic absorption spectroscopy (Kurz *et al.* 1972). The levels of tumor necrosis alpha (TNF-α) were determined using commercial ELISA kits (Affimatrix, Japan) (Blankenstein *et al.* 1991). Dopamine, Prolactin, Estradiol and Serotonin were estimated using Elisa kits (Cloud-Clone Corp, Enzo Life Sciences, MP Biomedicals and Cayman Chemicals) (Kim *et al.* 2008; Kema *et al.* 2000; Naber *et al.* 1980; Azcoitia *et al.* 2011).

Statistical Analysis

SPSS version 18 were used for statistical analysis. Results were expressed by mean and standard deviation. Correlations between various parameters and different subgroups were also determined. $p < 0.05$ was considered as statistically significance.

Table 1. General characteristics of schizophrenia patients and controls.

Characteristics	Schizophrenics (N = 100)	Controls (N = 50)
Age (Yearrs)	24-67	23-63
Male (n)	61	25
Females (n)	39	25
Weight	61-78	59-73
SBP	131.25	120.21
DBP	87.29	81.25
BMI	22.09	20.14

Results

The data presented in table 2 clearly demonstrate that the thyroidal hormones picture of schizophrenic patients presented with thyroid disorders plays a crucial role in the pathogenesis and progression of the disease. The levels of FT4 (pmol/L), FT3 (µg/dl) and TSH (IU/L) in diseased group differed significantly (p=0.010, 0.001and 0.000 respectively) compared to healthy controls. Higher FT4 levels was recorded (25.12±3.05) in patients suffering from schizophrenia as compared to healthy control subjects (13.25±2.32). The same trend was also observed in male and female patients with levels of 23.59±2.06 and 27.21±4.06 respectively. The lower levels FT3 (µg/dl) was recorded in schizophrenics (3.94±0.35) as compared to healthy controls (5.06±0.29) but higher levels of TSH (IU/L) was observed in schizophrenics (4.48±0.18) vs healthy control subjects (2.33±0.16). Higher levels of TNF-α (pg/ml) were observed in schizophrenics (34.75±2.09) as compared to controls (25.06±4.06). The highest level was found to be in male patients (37.06±1.99).

The role of trace elements plays a crucial role to establish the homeostatic balance of the body but the increasing and decreasing their levels shift the homeostatic balance which resultantly become a major cause of disease progression and aggravation. The data depicted in table 2 also portrays the same picture as by increasing trend of zinc in patients and decreasing trend of copper was recorded which ultimately decrease the dopamine.

The levels of zinc in diseased group versus healthy control (0.30±0.0019mg/L vs 0.19±0.0046) differed significantly (p=0.002). The same trend of increasing levels of zinc was also recorded in male and female patients but differed non-significantly among each other. The significant (p=0.001) levels of copper (mg/L) in schizophrenics and control group was recorded. The highest levels of copper were recorded in controls as compared to patients of schizophrenia

(1.77±0.036 Vs 1.03±0.056), and same was true for male versus female patients (0.99±0.033 and 1.08±0.037 respectively).

The decreasing trend regarding serum levels of dopamine (3.87±0.668 pg/ml) and estradiol (6.75±0.97 pg/ml) were estimated as compared to controls (8.99±1.26 pg/ml and 10.28±1.95 pg/ml respectively). There was no gender difference regarding dopamine and estradiol was established but differed significantly as compared to control (p=0.001 and 0.041 respectively). Reverse is true regarding the levels of Prolactin (ng/ml) and

Serotonin (ng/ml) differed significantly (p=0.003 and 0.041) as compared to controls. The highest levels of prolactin were recorded in schizophrenics (30.60±2.08) followed by healthy controls (18.26±1.06). The serotonin (ng/ml) levels in schizophrenics were higher (175.85±7.06) as compared to controls (75.85±6.29). The highest level of Serotonin was recoded in female patients (180.65±6.19).

Table 2. Profile of different prognostic variables in schizophrenics and controls.

Variables	Schizophrenics Vs Control (Mean ± SD)				P-Value (<0.05)
	Healthy Controls	Mean Value Schizophrenics	Male Schizophrenics	Female Schizophrenics	
FT4 (pmol/L)	13.25±2.32	25.12±3.05	23.59±2.06	27.21±4.06	0.010
FT3 (µg/dl)	5.06±0.29	3.94±0.35	4.01±0.41	3.88±0.22	0.001
TSH (IU/L)	2.33±0.16	4.48±0.18	4.11±0.67	4.86±0.68	0.000
TNF-α (pg/ml)	25.06±4.06	34.75±2.09	37.06±1.99	32.45±2.09	0.008
Zn (mg/L)	0.19±0.0046	0.30±0.0019	0.29±0.0033	0.31±0.0088	0.002
Cu (mg/L)	1.77±0.036	1.03±0.056	0.99±0.033	1.08±0.037	0.001
Dopamine (pg/ml)	8.99±1.26	3.87±0.668	3.08±0.759	4.66±0.899	0.001
Prolactin (ng/ml)	18.26±1.06	30.60±2.08	31.55±3.55	29.65±2.88	0.003
Estradiol (pg/ml)	10.28±1.95	6.75±0.97	7.13.55±0.68	6.37±0.88	0.037
Serotonin (ng/ml)	75.85±6.29	175.85±7.06	171.06±5.66	180.65±6.19	0.041

Table 3. Pearson s' correlation coefficients of different variables playing role in development of HMD.

Variables	FT4	FT3	TSH	TNF-α	Zn	Cu	Dopamine	Prolactin	Estradiol	Serotonin
FT4	1	-0.326	0.235	0.326	-0.362	-0.225	0.195	0.368*	-0.235	0.256
FT3		1	0.325	-0.265	0.336	0.158	-0.265	0.325	-0.156	0.237
TSH			1	0.118	0.201	-0.235	-0.265	0.213	0.099	-0.254
TNF-α				1	0.325	0.235	0.235	-0.458**	-0.501**	0.235
Zn					1	-0.398*	0.335	0.356	0.159	0.532**
Cu						1	0.427**	-0.325	0.235	0.221
Dopamine							1	-0.867***	0.448**	-0.488**
Prolactin								1	-0.264	0.745***
Estradiol									1	0.235
Serotonin										1

*Significant (p-value<0.05).

Discussion

The present study shows that hyperprolactinemia and hypoestrogenemia occur in drug naive schizophrenics. Hypothalamus secretes prolactin (PRL) activating factors such as thyrotropin releasing hormone (TRH), vasoactive inhibitory peptide (VIP) and prolactin inhibiting factor (dopamine). Prolactin activating factors act on anterior pituitary to release prolactin and thyroid stimulating hormone (TSH) while prolactin inhibiting factor (Dopamine) inhibits release of prolactin. Pearson's correlation matrix was calculated for all important variables playing role in schizophrenia patients and summarized in table 3.

In hyperprolactinemia, there is a positive feedback on serotonin which has positive effect on prolactin activating factors but a negative feedback on dopamine (Halbreich *et al.* 2003). A positive correlation between prolactin and serotonin (PRL Vs serotonin, r = 0.745***) while an inverse correlation between prolactin and dopamine (PRL Vs dopamine, r = -0.867***) was observed in the present study that also supports some previous studies (González-

Blanco *et al.* 2016; Gragnoli *et al.* 2016). These variables cause hyperprolactinemia leading to anxiety and depression.

The increase in TSH response to TRH has been identified which has a direct effect on thyroid gland and causes hyperthyroidism (Wysokiński and Kłoszewska 2014). Contrary to this effect it has been shown that there is decrease in TSH response to TRH in depression which leads to hypothyroidism (Dejong *et al.* 2013).

It has been revealed that estrogen has neuromodulator, pro-cognitive and anti-inflammatory effects. Estrogen receptors (ER-α and ER-β) expressed in hypothalamus, amygdala and hippocampus. Reduction in estrogen levels results in excessive pro-inflammatory cytokines like interleukins (like IL-1, 6, 10) and tumor necrosis factor-alpha (TNF-α) promoting NMDA receptors hyper-activation leading to increase in neuronal sensitivity to apoptosis (Gillies and McArthur 2010; Malashenkova *et al.* 2016).

The pro-inflammatory cytokines not only inhibit brain derived neurotrophic factor (BDNF) by NF-κB activation but also abate c-AMP response element binding protein (CREB) phosphorylation, both of these processes suppress hippocampal neurogenesis and long term potentiation (LTP) resulting in decreased synaptic activity and dendrite length (Kaur *et al.* 2015). Bethea *et al.* (2002) reported that hypoestrogenism also causes inhibition of dopamine production and dopamine D2 receptor blockage resulting in hyperprolactinemia mediated depression (HMD) (Bethea *et al.* 2002). The current study presented inverse correlation between estrogen and TNF-α (estrogen Vs TNF-α, r=-0.501**) while positive correlation between estrogen and dopamine (estrogen Vs dopamine, r= 0.448**) respectively.

There is a strong association between elevated heavy metals and schizophrenia. The reason behind this toxicity is that these heavy metals require metallothionein, a metal removing protein but in schizophrenics defective transcription pathways of this protein have been revealed (Prabakaran *et al.* 2004). Copper (Cu) toxicity has been found the most common reason in schizophrenia which results in enhanced catecholamine oxidation, the resultant end products are toxic hallucinogens (Vidović *et al.* 2013). Conversely, most recent reports proposed that copper is reduced in schizophrenia and the present study demonstrates similar results (Asare *et al.* 2014; Liu *et al.* 2015). It has an important part in the proper functioning of cytochrome c oxidase, superoxide dismutase (SOD), dopamine beta hydroxylase and tyrosine hydroxylase thus reduced levels of copper cause oxidative stress and abnormal dopamine norepinephrine interaction [29], as in this study copper has a positive correlation with dopamine (Cu Vs dopamine, r = 0.427**).

It has been also suggested that low thyroid function allows heavy metal retention as there is diminished hepatic synthesis of metallothionein (Pataracchia 2005). On the other hand, heavy metals interrupt T4 to T3 conversion by inhibiting peripheral enzymes (Gupta and Kar 1999), thus may be due to this fact in the present study T4 levels were raised in comparison to T3. In contrast to heavy metal toxicity, deficiency of zinc is very frequent in schizophrenia and this deficiency is race specific as Zn is reduced in Asians but not in European and also depends on dietary habits (Cai *et al.* 2015). In the present study, zinc levels were higher in schizophrenics as it is antagonist to copper (Johnson 2001), supported by an inverse correlation between these two metals (Cu Vs Zn, r = -0.398*). Zinc has various important functions as it is necessary for serotonin synthesis, proper functioning of metallothionein, formation of CuZn SOD and activity of nitric oxide synthase (NOS) which are important in the prevention of oxidative damage hampers lipid peroxidation in neurons and plays a major role in maintaining blood brain barrier (Johnson 2001; Yanik *et al.* 2004). The present study depicts a positive correlation between Zn and serotonin (Zn Vs serotonin, r = 0.532**). Thus, reduction in dopamine levels due to deficiency of copper and zinc dependent increase in serotonin results in hyperprolactinemia leading to anxiety and depression.

Conclusion

The present study concludes that hormonal imbalance plays a significant role in the induction of cognitive decline in schizophrenics.

The hormonal variations depend on dopamine and serotonin levels and their quantity is regulated by copper and zinc respectively. Hyperprolactinemia results in schizophrenic symptoms and increase in TSH induces hypothyroidism in schizophrenics as an allied disease. Hyperprolactinemia and hypoestrogenism are the main health problem in schizophrenics and by controlling their levels within normal range will prevent and treat schizophrenia. Thus, mineral and hormonal therapy may be helpful in restraining cognitive deficit.

Conflict of interest

Authors declare no conflict of interest.

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