Age and Gender Related Neuroendocrinological Abnormalities in Schizophrenics

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Abstract

Background & objectives: This study aims to determine the status of plasma estrogen, prolactin and thyroid stimulating hormone in schizophrenic patients with different age groups**.**
***Methods*:** A total of 60 schizophrenic patients of age group 18-65 years of both sexes from good socio-economic background were selected and the patients were divided into three groups based on age namely young, adult and elderly subjects. They all met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria for schizophrenia. Sixty age and sex-matched healthy normal control subjects with no individual and familial history of mental illness were recruited to participate in this study (30 males and 30 females). Fresh blood samples were collected and plasma was separated to measure the status of hormones by ECLIA method in the plasma of 60 schizophrenia subjects and 60 healthy controls.
Results: Results showed that plasma levels of hormones indicated abnormalities significantly among the different age groups. There is also significant difference in the levels of these hormones in the male and female subjects also. These data reveal that age and gender has influence on the levels of the hormonal status in schizophrenic patients.
***Interpretation & conclusion*:** Understanding these basic pathologic processes may yield novel targets and hormonal therapy for the development of more effective treatments foe the different age groups and male and female schizophrenics.

KEYWORDS: Schizophrenia, Symptoms, Estrogen, Prolactin, TSH, Abnormalities

Introduction:

Schizophrenia, one of the most debilitating and baffling mental illnesses, defines a group of disorders that cause distorted thought and perception. Thoughts can be scrambled or jump from subject to subject. Perception can be distorted beyond reality, causing people to hear or see things that are not there [1].

People with schizophrenia go through periods of getting better and worse – remission and relapse. They can go for long periods of time without any symptoms, but because schizophrenia is often a chronic illness it requires ongoing medical attention, like hypertension and diabetes [2].

Hormonal influences on the development of schizophrenia in both sexes were postulated. The new theory goes beyond serotonin and nor epinephrine, which are clearly involved in depression, to look at stress hormones. Many people with mood problems have others in their family who also has mood problems; the same is true of anxiety

problems. Stress hormones within the brain may be the basis for these lasting changes [3].

Some early psychiatrists already believed that schizophrenic disorders were associated with a disturbed balance of sexual hormones also. This belief was based on the observation of a. an "insufficient functioning of the sexual glands" with so-called " hypoestrogenism", and b. an influence of ovarian function on schizophrenic psychoses. As the review of Riecher –Rossler, 2002 [4] showed there are findings from recent research that seem to confirm that estrogens may have a protective effect in schizophrenia). The estrogen hypothesis also posits that this hormone serves as a protective factor in the development of schizophrenia.

Gender and age differences in patients with schizophrenia have been noted in studies of age at onset, symptoms, course of illness, and cognitive deficits. . Males are more prone to schizophrenia than females on average, women are diagnosed with schizophrenia 2 to 10 years later than men [5]. In addition to a delayed peak of onset of schizophrenia for women, some, but not all, investigators have found an additional smaller peak after ages 40 to 45, around the time of decreasing levels of estrogen [6]. The timing and gender specificity of this increased prevalence of schizophrenia have led some researchers to speculate that estrogen levels protect women from developing schizophrenia and that the drop in estrogen levels associated with menopause may put women at risk to develop schizophrenia later in life [7].

There are also occasional hints at a possible "hypoestrogenism" in schizophrenia. Riecher- Rössler, 2002 [7], by his own epidemiological, clinical and animal studies the hypothesis of a protective effect of oestrogens was for the first time systematically examined and confirmed.

Highly elevated prolactin seemed to be an overwhelming aberration in schizophrenics. Enhanced prolactin levels in schizophrenic patients may be the results of anti-psychotic medication [8]. Nevertheless, prolactin abnormality was already described in un-medicated, drug-naive schizophrenics about one decade ago [9]. Hyperprolactin in schizophrenia is not an obligatory consequence of neuroleptic treatments. Apart from neuroleptic treatments, there are some other factors such as stress or cytokines (e.g. IFN-gamma and TNF-alpha) that could have impacts on prolactin release. With the advent of prolactin sparing anti-psychotics, ample consideration needs to be given to the physiological consequences of hyperprolactinaemia in schizophrenic patients.

The lifetime prevalence of depression in schizophrenia patients with TSH abnormalities is doubles that of the general population and has been reported to reduce the efficacy of antidepressant treatment; it is associated with anxiety [10] and changes in mood and cognitive functioning. There is also evidence that exercise capacity may be impaired due to significant reduction of exercise-related stroke volume, cardiac index, vital capacity and reduced anaerobic thresholds [11]. All these factors may affect subjective perception of health status of schizophrenics.

Though there is accumulating evidence of altered hormonal status in schizophrenia, Studies of endocrine abnormalities in schizophrenia has produced the usual medley of conflicting results. In the present study, we investigated the effect of age and gender on the levels of these hormones in schizophrenic patients and compared the levels of these hormones with controls. The present study was undertaken during the month of September 2004 to June 2007, in the Postgraduate and Research department of

biochemistry, Dr. N.G.P Arts and Science College, with the collaboration of Kovai Medical Centre and Hospital (KMCH), a multispeciality hospital.

Materials and Methods

Patients: A total of 60 schizophrenic patients of age group 18-65 years of both sexes from good socio-economic background were selected from Udhayam Mananala kaapagam, a mental Health care center, Coimbatore, Tamilnadu, India. They all met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria (American Psychiatric Association, 2000) [12] for schizophrenia. Schizophrenic subjects were divided into three groups i-e young, elderly and adult (1) Schizophrenics with age range between 15-30 years, (2) schizophrenics with age range between 31-45years, (2) schizophrenics with age range 46-65 years.

Control: Sixty age and sex-matched healthy normal control subjects with no individual and familial history of mental illness were recruited to participate in this study. They included 30 males and 30 females. Their ages ranged from 15 to 65 years with mean age (28.9±14.1) years.

Ethical Considerations: The design and the layout of this project was carried out with the approval the Chairman, Kovai Medical Center and Hospitals, and due permission was obtained from the board of institutional review Committee of the Kongu mananala Arakkattalai, before the start of the work. Informed and written consent was obtained from all subjects prior to examination.

Assay of Hormones: The tests were performed at the biochemistry division of Diagnostic laboratory, Kovai Medical Center and Hospitals, Coimbatore. Blood was collected using standard methods as described by Varley, 1956, and plasma was separated. Hormones were measured by an electro-chemiluminescence immunoassay 'ECLIA' using Roche Elecsys E170 immunoassay analyzers (Roche Diagnostics, UK). The Elecsys prolactin test had been calibrated against the 3rd IRP WHO Reference Standard 84/500. The *Elecsys estrogen test had been calibrated via ID-GC\MS (isotope dilution – gas* chromatography-mass spectrometry. The Elecsys TSH test had been calibrated against the 2nd IRP WHO Reference Standard 80/558.

Results and Discussion

Results in Table 1 summarize all analyzed biochemical parameters. Table 1 shows significant decrease in estrogen levels in all the study groups compared to the control group. Within the control groups, people with age group of above 45 were facing more estrogen deficiency compared with the subjects who were of below 45-age range ($p<0.01$). Among schizophrenia patients, it was found that the estrogen levels decreased which is statistically significant in adult and elderly schizophrenics ($p <0.001$) compared with schizophrenic patients with age group of below 30. The Prolactin levels are very highly increased ($p<0.001$) in adult schizophrenic patients when compared to normal young and elderly subjects (Table 1). The prolactin levels are increased in normal adult group when compared to normal young and elderly subjects ($p<0.01$) where as it is highly increased in young and adult schizophrenics patients ($p<0.001$) when compared to the normal elderly controls (Table1). It is observed from the results that the level of TSH is increased significantly in all schizophrenic groups when compared with normal control

subjects. Results also showed that there was no significant decrease in the level of TSH among normal elderly subjects compared with normal young and adult control subjects.

As far as gender concerned, we found significant difference in the tested parameters of estrogen between male and female subjects in both schizophrenia and control groups. This hormone was highly deficient in males compared with females. However, there were significant differences among the study and control subjects with the same gender in some test parameters (Table 2). The levels of prolactin and TSH increased significantly in females compared with males of schizophrenia patients. In general, the level of TSH increased noticeably in schizophrenia patients compared with control groups. Also there is no notable difference between males and females of normal controls.

Table 1

Circulatory levels of Estrogen, Prolactin and TSH in Young, Adult and Elderly subjects with schizophrenia and Healthy controls

Hormonal Status	Schizophrenics			Controls		
	Young (n+23)	Adult (n+19)	Elderly (n=18)	Young (n=17)	Adult (n=24)	Elderly (n=19)
Estrogen (pg/ml)	19.77±2.21a	14.27±2.39ab	7.90±0.58ab	33.21±2.61	27.43±0.65	12.77± 0.83
Prolactin (ng /ml)	16.1±0.24	19.4±0.23	13.7±0.10	14.3±0.83	17.9±0.70	11.3±0.71
TSH (µIU/mL)	6.172±0.012a	6.261±0.018ab	6.989±0.012a	5.968±0.018ab	5.14±0.019acd	5.17±0.026

(Values are mean ± SD) Statistical comparison was done between: age-matched Controls and Schizophrenia subjects.

a $p<0.01$, a* $p<0.001$; b $p<0.01$, b*<0.001

a statistical comparison between age group < 30 and > 30 of control vs schizophrenics.)

b (statistical comparison of age group < 30 and > 30 among schizophrenia patients.

Table 2

Circulatory levels of Estrogen, Prolactin and TSH levels of Control and Schizophrenia Male and Female subjects (Values are mean ± SD)

Hormonal Status	Schizophrenics		Controls	
	Male (n = 28)	Female (n=32)	Male (n = 30)	Female (n = 30)
Estrogen (pg/ml)	13.39 ±0.44a	19.36±0.79bc	27.43±0.65	34.93±1.98
Prolactin (ng /ml)	11.77±0.09a	12.76±1.14bc	8.91±0.56	9.98 ± 0.37
TSH (µIU/mL)	5.12±0.08a	6.998±0.012bc	3.93±0.045	3.10±0.032

Statistical comparison was done between gender matched Controls and Schizophrenics; a. Controls and Schizophrenics (male) ; b. Controls and Schizophrenics (female). c. male and females of schizophrenia patients .a,b,c , $p<0.01$.

A growing body of research suggesting that estrogen has an important role in mental processes in normal women [13] as well as in women with Alzheimer's disease [14] and other neuropsychiatric diseases such as schizophrenia [15].

Much remains to be learned about the complex interaction among the hormonal status and schizophrenia. Many of the studies contain small samples, resulting in inconsistent findings regarding the effects of estrogen on the woman with schizophrenia. It is clear that there are gender differences in the age of onset and the presentation of schizophrenia. Estrogen appears to be related to psychopathology in the menstrual cycles of premenopausal women and in postpartum psychosis.

Estrogen has been hypothesized to have a protective and antipsychotic-like effect in women at risk for schizophrenia [16]. In our results we found that the estrogen levels decreased significantly in adult and elderly schizophrenic patients. It is also noticed from our results that normal and schizophrenia males are having very low levels of estrogen compared than that of normal and schizophrenic females.

A study of hospitalized patients reported that when estrogen levels were rising, women with schizophrenia required lower doses of neuroleptics [17]. The therapeutic response, as measured by duration of hospitalization, amount of neuroleptics, and clinical status at discharge, was measured in 65 women with a diagnosis of schizophrenia and 35

women with a diagnosis of affective disorder. The women with schizophrenia required lower doses of neuroleptic medication if they were admitted during phases of menstrual cycle when estrogen levels were low.

Estrogen is postulated to exert a multimodal protective effect on brain cells [18]. When estrogen receptors are activated, the brain is aroused and memory systems function more efficiently. Estrogen neutralizes the neurotoxic effects of a variety of stressors, thus explaining, perhaps, the later onset of schizophrenia symptoms in women when compared with men. Estrogen action on neurotransmitter systems may also explain why women respond to antipsychotics faster than men and at lower doses, and why side effects differ [15].

In terms of clinical outcomes, women with schizophrenia seem to fare better then men, but appear more vulnerable to psychotic illness in the period after birth and menopause. As these vulnerable periods to psychosis are associated with estrogen withdrawal, this hormone has been proposed as a treatment for schizophrenia.

Clinical research results indicate that symptoms in women frequently vary with the menstrual cycle, worsening during low estrogen phases. Pregnancy is often, though not always, a less symptomatic time for women, but relapses are due to frequent postpartum. Some work suggests that in the younger age groups women require lower antipsychotic dosages than men but that following menopause they require higher dosages. Estrogen has been used effectively as an adjunctive treatment in women with schizophrenia. Estrogen may also play a preventive role in schizophrenia. These findings suggest that estrogen may provide valuable adjunctive therapy for women with psychosis.

Prolactin has been found to stimulate proliferation of oligodendrocyte precursor cells. These cells differentiate into oligodendrocytes, the cells responsible for the formation of myelin coatings on axons in the central nervous system. In our study elderly patients and males have significantly increased levels of prolactin. Our results are confirmed and supported by the study of Alice Kuruvillaet al., 1992 [19]. Serum prolactin levels were measured in large cohorts of schizophrenic patients (67 males and 42 females) and normal subjects (78 males and 42 females). Results showed that there was no significant difference between the serum prolactin levels of patients and controls, except in the age group 15–29 years. There were no significant differences between the serum prolactin levels of males and females, either among the patients or the control subjects. The rise in serum prolactin levels after the commencement of neuroleptic medication in the patients was greater in females than in males even though the female patients received neuroleptics at lower doses.

IFN gamma and TNF- alpha have the potential to act directly on anterior pituitary cells to slow the rate of prolactin release. The hyperprolactin in our patients could be partly due to decreased TNF-alpha and, particularly, IFN- gamma. But both IFN-gamma and TNF-alpha have no effect on the inhibition of prolactin release mediated by dopamine. The dopaminergic tuberoinfundibular pathway is responsible for dopamine-mediated prolactin release; this pathway is inhibited in acute stress, leading to increased prolactin levels [9,20].

The datas of Alice Kuruvilla indicate that serum prolactin levels in unmedicated males and females are similar; however, the prolactin response to neuroleptic medication is greater in females than in males. Present results also indicated that the levels of TSH

are also elevated significantly in schizophrenia patients especially females have elevated TSH levels so as we found many females were hypothyroid symptoms.

Most pituitary hormone production is controlled by signals that come in the form of other hormones. That means the pituitary acts only when it receives a stimulating hormone message from elsewhere in the body. For example, when thyroid activity is low, the hypothalamus, a higher brain center, releases the hormone TRH to stimulate the pituitary to release thyroid stimulating hormone (TSH).Surprisingly the hormone TRH, in addition to stimulating the pituitary release of TSH, also, triggers the release of prolactin.

To synthesize these hormones, the thyroid gland requires iodine, selenium, zinc, niacin, vitamin B12, lipoic acid, and the antioxidants vitamin C and E [21], who wisely included hypothyroidism as one of the causes of schizophrenia. Many literatures indicate that the levels of these elements are low in schizophrenia patients. Present findings indicated that schizophrenic patients should be examined for hypothyroidism. When there are clinical symptoms and signs of this condition, thyroid should be added to the program.

Hypothalamus secretes dopamine which inhibits the release of prolactin. Dopamine travels from the hypothalamus to the pituitary in a small network of veins called a venous portal system. Anything that interferes with this fine network may prevent this inhibitory message from reaching the pituitary gland. The result is that the pituitary will produce too much prolactin. When the hypothalamus sees that the prolactin levels are too high, it manufactures more dopamine, trying to get prolactin levels back to normal. Unfortunately, if the message doesn't get through, the pituitary continues to produce and release prolactin.

In conclusion, hormones are playing a vital role in the disease progression of schizophrenia. Also the influences of these hormones vary based on gender and age groups. Our data, as well as those of other investigators, suggest a significantly later age at onset of schizophrenia in women than in men. There is somewhat more direct evidence from animal studies indicating that estrogen modulates dopamine systems in a manner similar to neuroleptics, although there are some inconsistencies in the literature. Few studies have examined the effects of estrogen administration in conjunction with neuroleptics on psychotic symptoms. The relations between schizophrenia hormonal influence-role of age, gender underline the clinical interest of our study. But these results need to be confirmed by further studies by taking larger number samples and further advanced techniques should be adopted to make sure of the current results.

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