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ROLE OF REPRODUCTIVE HORMONES IN SCHIZOPHRENIA

CHITRA Y. DHUME[*1], SUNANDA AMONKAR[2] AND MITCHELLE MENEZES[3]

*[*1]Chitra Y. Dhume; Professor and head, Department of Biochemistry, Goa Medical College- Bambolim-Goa- India.*
[2]Sunanda Amonkar: Associate Professor, Department of Medicine, Goa Medical College- Bambolim-Goa - India.
[3]Mitchelle menezes, post graduate student, Department of Biochemistry, Goa Medical College- Bambolim-Goa - India.

ABSTRACT

Schizophrenia is a clinical syndrome of variable, but profoundly disruptive psychopathology that involves cognition, emotion, perception and other aspects of behaviour. It ranks among the top ten causes of disability in developed countries worldwide. Gonadal hormones have recently been implicated in the psychopathology, sex differences in onset, prognosis and treatment of schizophrenia. The present study investigated the effects of serum levels of testosterone, follicle stimulating hormone, luteinizing hormone and prolactin in a group of sixty patients. The study was conducted over a period of 18 months in the Goa Medical College and the Institute of Psychiatry and Human Behaviour. Diagnosis of Schizophrenia was made using the ICD-10 classification. A control group of sixty healthy subjects was recruited. As compared to matched controls, the acutely admitted patients suffering from Schizophrenia exhibited significantly low serum levels of the reproductive hormones suggesting a possible role for hormones in the psychopathology of the disease.

KEY WORDS: **Schizophrenia, testosterone, prolactin, F.S.H., L.H.**

CHITRA Y. DHUME
[1]Chitra Y. Dhume; Professor and head, Department of Biochemistry, Goa Medical College- Bambolim-Goa- India

INTRODUCTION

Schizophrenia is a mental disorder characterized by disintegration of thought processes and of emotional responsiveness. It most commonly manifests itself as auditory hallucinations, paranoid or bizarre delusions or disorganized speech or thinking and it is accompanied by significant social or occupational dysfunction[1.] Schizophrenia affects around 0.3–0.7% of people at some point in their life[2], or 24 million people worldwide as of 2011[3]. It occurs 1.4 times more frequently in males than females and typically appears earlier in men[4] —the peak ages of onset are 20–28 years for males and 26–32 years for females[5]. It causes approximately 1% of worldwide disability adjusted life years[4] . Approximately three-fourths of people with schizophrenia have on-going disability with relapses and 16.7 million people globally are deemed to have moderate or severe disability from the condition. The aetiology of schizophrenia remains unknown in a majority of cases. An important clue to the genesis of this disorder is the distribution of ages at onset, which closely parallels the ages of onset and decline of the reproductive period[6]. Between childhood and adulthood, pulsatile secretion of luteinizing hormone (LH), the hormone that stimulates gonadal growth and gonadal hormone secretion, increases more than 30-fold in boys and 100-fold in girls[7]. These hormonal changes are associated with the cascade of somatic, temperamental and behavioural changes characteristic of puberty and of adult sexual and social behaviour—and with the onset of schizophrenia in 0.5%–1% of the population. During the onset and duration of the reproductive period, circulation of the generally neuroexcitatory reproductive hormones to the brain and to the body requires compensatory changes in neurophysiology to augment the action of specific brain inhibitory systems or to diminish the action of endocrine excitatory systems. Failure to establish such equilibrium is likely to be pertinent to the precipitation of schizophrenia in susceptible individuals[8]. The human PRL gene is located on chromosome6. Secretion of prolactin is under the inhibitory control of dopamine, which is largely produced by the tuberoinfundibular (TIDA) cells and the hypotdopaminergic system. Prolactin is essential for human species survival by milk production during pregnancy and lactation. Additional biologic functions include reproductive and metabolic effects and mammary development[9.] Gonadotrophic cells secreting FSH and LH compose about 10-15% of the functional anterior pituitary cells. FSH and LH regulate gonadal steroid hormone biosynthesis and initiate and maintain germ cell development in concert with peripheral hormones and paracrine soluble factors. Although both the homologous FSH and LH molecules are co-secreted by a single gonadotrophic cell, their regulatory mechanisms are not uniformly concordant[9]. Estrogen is the primary female sex hormone. Estrogens are naturally occurring C-18 steroidal sex hormones produced by the ovaries, adrenal glands and the placenta during pregnancy. The biologically active estrogen is estradiol which is synthesized during pregnancy. During the reproductive years of life, natural estrogens are principally produced by the graffian follicles in response to pituitary gonadotropins. Estrogen is responsible for the development of secondary sex characters, including the breasts, provides the negative feedback signal to the pituitary gland and hypothalamus and maintains adequate mineralization of bones[10]. Testosterone, a 19-carbon steroid secreted by the testis, is the primary circulating androgen in the male human. Androgens directly or indirectly affect almost all body systems during foetal and pubertal development and in adult life. Testosterone regulates the differentiation of the Wolffian ducts into epididymis, vas deferens and in some species seminal vesicles in the foetus. In addition increasing testosterone levels during puberty, promote somatic growth and virilisation of boys. In the adult animal, testosterone has additional effects on muscle, fat, bone, haematopoiesis and coagulation, lipid, protein and carbohydrate metabolism and psychosocial and cognitive behaviour[9]. The goal of this study was to estimate and evaluate levels of gonadal and pituitary hormones in patients with schizophrenia.

MATERIALS AND METHODS

The subjects for the study were chosen from the patients attending O.P.D. of Medicine, the Institute of Psychiatry and Human Behaviour. The total numbers of subjects involved in the study were 160.The study was conducted during the year 2009- 2012, jointly by the Department of Biochemistry and the Institute of Psychiatry and Human Behaviour and the Department of Medicine of Goa Medical College. This study was carried out on sixty healthy Schizophrenic patients and sixty age and sex matched normal subjects. Diagnosis of Schizophrenia was based on the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, the ICD-10. This criterion uses the self-reported experiences of the person and reported abnormalities in behaviour, followed by a clinical assessment by a mental health professional. The total number of subjects involved in this study was 160 and they were divided into two groups: Test and Control. Informed consent was taken from the subjects and an Institutional Ethics Committee clearance was obtained

TEST GROUP

The test group comprised of sixty subjects, thirty males and thirty females, age between fifteen to fifty years and Schizophrenia was the primary diagnosis.

CONTROL GROUP

The control group comprised of sixty age and sex matched normal subjects who did not suffer from any psychiatric disorder or medical conditions especially those that cause hormonal imbalance.

EXCLUSION CRITERIA

Subjects with current affective disorder including manic episode, concomitant substance abuse, mental retardation and severe medical illness were excluded from the study. Fasting venous blood samples were collected from the subjects and serum concentration of testosterone, follicle stimulating hormone, luteinizing hormone and prolactin were estimated using Chemiluminescent Micro particle Immunoassay (CMIA). Biological Principle of Chemiluminescent Micro particle Immunoassay: It is a two-step immunoassay to determine the presence of hormone in serum and plasma using CMIA technology with flexible assay protocols, referred to as chemiflex. In the first step, sample and anti-hormonal coated paramagnetic micro particles are combined. Hormone present in the sample binds to the anti-hormonal coated micro particles. After washing, the anti-hormone acridinium labelled conjugate is added to the second step. Pre-Trigger and Trigger solutions are then added to the reaction mixture, the resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of hormone in the sample and the RLUs detected by the ARCHITECT i optical system.

RESULTS

A total of sixty patients suffering from first episode of Schizophrenia and sixty age and sex matched healthy mean and standard deviation values of Serum testosterone, Serum Prolactin, Serum FSH and normal subjects were evaluated.

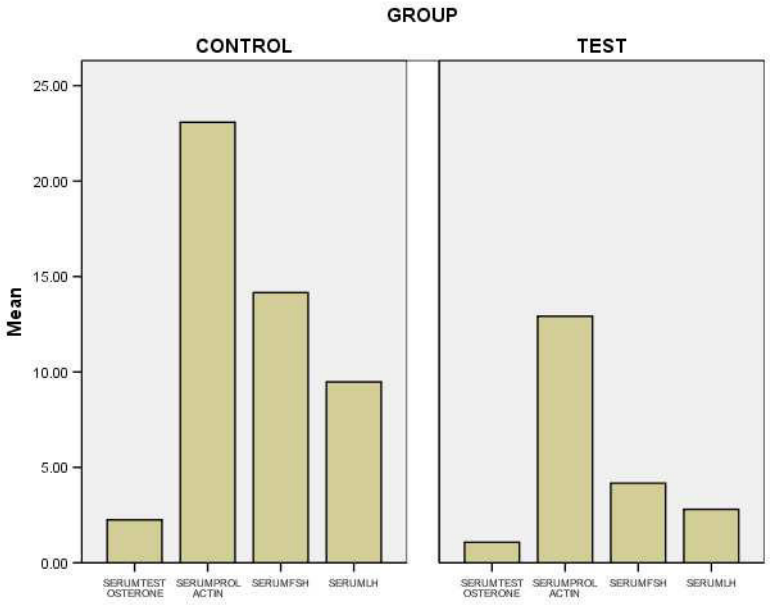
Table 1
Comparison of Serum testosterone, Serum FSH and Serum LH in Test (schizophrenia) and Control patients

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
SERUM TESTOSTERONE	CONTROL	60	2.2483	2.38452	0.30784
	TEST	60	1.0778	1.31186	0.16936
SERUM PROLACTIN	CONTROL	60	23.0818	23.49707	3.03346
	TEST	60	12.9193	22.63241	2.92183
SERUM FSH	CONTROL	60	14.1597	21.85980	2.82209
	TEST	60	4.1747	6.98783	0.90213
SERUM LH	CONTROL	60	9.4812	11.28573	1.45698
	TEST	60	2.8050	4.00521	0.51707

Table 2
Comparison of Independent Samples t-Test values of Serum testosterone, Serum Prolactin, Serum FSH and Serum LH

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
SERUM TESTOSTE-RONE	Equal variances assumed	12.361	0.001	3.331	118	0.001	1.17050	0.35135	0.47473	1.86627
	Equal variances not assumed			3.331	91.718	0.001	1.17050	0.35135	0.47265	1.86835
SERUM PROLACTIN	Equal variances assumed	0.517	0.474	2.413	118	0.017	10.16250	4.21177	1.82206	18.50294
	Equal variances not assumed			2.413	117.835	0.017	10.16250	4.21177	1.82194	18.50306
SERUM FSH	Equal variances assumed	23.677	0.000	3.370	118	0.001	9.98500	2.96277	4.11791	15.85209
	Equal variances not assumed			3.370	70.933	0.001	9.98500	2.96277	4.07731	15.89269
SERUM LH	Equal variances assumed	33.609	0.000	4.318	118	0.000	6.67617	1.54601	3.61464	9.73769
	Equal variances not assumed			4.318	73.630	0.000	6.67617	1.54601	3.59541	9.75692

Figure 1
Bar diagram comparing the mean values of Serum Testosterone, Serum Prolactin, Serum FSH and Serum LH in Test (schizophrenia) and Control patients



DISCUSSION

Schizophrenia is a group of psychotic disorders characterized by disturbances in perception, behaviour, and communication. A person with schizophrenia has deteriorated occupational, interpersonal, and self-supportive abilities. The chemical nature of a schizophrenic brain is not completely understood[11]. The onset of schizophrenia at the beginning of or during the reproductive period suggests a relationship between this disorder and the dramatic changes in the brain and the body that take place during adolescence and throughout the fertility period. The increase in circulating androgens and estrogens associated with sexual maturation leads to other significant changes in brain axons and receptors as well as the well-known physical, physiologic, psychological, and behavioural changes associated with the flood of hormones to brain and body during this period[12, 13]. Hence during the onset and duration of the reproductive period, circulation of the generally neuroexcitatory reproductive hormones to the brain and to the body requires compensatory changes in neurophysiology to augment the action of specific brain inhibitory systems or to diminish the action of endocrine excitatory systems. Inhibitory activity is provided by the high concentration of dopamine D3, 5-HT, and GABA-nergic terminals and receptors in this region. The action of these inhibitory systems must be increased to balance the effect of the entry of the excitatory reproductive hormones into specific brain areas at puberty and throughout the reproductive period. However, excessive inhibitory response to these physiologic events via dopamine, 5-HT or GABA can cause psychosis in susceptible individuals[14,15]. Further neuroendocrinological studies have suggested that estrogen may have a protective effect in women vulnerable to schizophrenia[16]. The functions of estrogen, its complex receptor organization and its numerous actions are the focus of on-going research activity. Of particular interest are its neuroprotective properties, particularly with regard to cognitive impairment, and its involvement with neurotransmitter systems.

CONCLUSION

In conclusion, gonadal hormones like testosterone, FSH and LH are significantly reduced in patients with first episode of Schizophrenia as compared to age and sex matched healthy controls, hence suggesting that reproductive hormones play a significant role in the pathophysiology of the disease. However, future research is needed before clinical applications are justified

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