Association of Serum Cortisol and Dehydroepiandrosterone Sulfate level with Schizophrenia: A case control study

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Abstract— *Schizophrenia is a neuro endocrinal diseases purticularly in volving Hypothalamic-pituitary-adrenal axis dysfunction, which has been widely researched in schizophrenia. Over activation of this axis is known to cause altered blood levels of cortisol and dehydroepiandrosterone sulfate (DHEA-S). Present study was conducted with the objective to compare serum levels of cortisol and dehydroepiandrosterone sulfate in schizophrenia patients and healthy control. A cross sectional case control observational study was conducted including 40 patients with first-episode schizophrenia along with 40 age and sex matched healthy controls. Patients were diagnosed as Schizophrenia according to ICD-10. Serum cortisol and DHEA-S were assessed in both groups. It was observed in this study that mean Serum level of DHEA-S was significantly (p< 0.001) higher in the Schizophrenia group (4320 ± 1120* µg/dL*) as compared to control group (2760 ± 825* µg/dL*), while cortisol level did not differ significantly between the two groups. It can be concluded from this study that the first-episode antipsychotic-naïve schizophrenic patients showed a significantly higher blood level of DHEA-S compared with healthy controls indicating role of DHEA-S in patho-physiology of schizophrenia.*

Keywords: Schizophrenia, Cortisol, Dehydroepiandrosterone Sulphate (DHEA-S).

I. INTRODUCTION

Schizophrenia is a neuro- endocrino- developmental disorder with complex etiology characterized by interactions between genetic and environmental factors that impact sensitive periods of brain development.[1,2] The neuro-endocrinological system, particularly the hypothalamic-pituitary-adrenal axis (HPA) axis, which has been a focus of interest for neurobiological studies aiming at elucidating the cause of schizophrenia. The biological response to stress is mediated through the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), which invoke a number of adaptive behavioral and physiological changes.[3] In response to stressors, neural signals are converted into an endocrine response at the level of the hypothalamus leading to activation of the pituitary gland and finally release of corticosteroids by the adrenal gland. Cortisol and Dehydroepiandrosterone sulfate (DHEA-S) are the two major circulating neuro-steroids in the human body which have their effect on brain. Cortisol exerts widespread actions on Central nervous system ranging from regulation of gene transcription, cellular signaling, modulation of synaptic structure and neurotoxicity. On the other hand, dehydroepiandrosterone (DHEA) and its Sulfated form (DHEA-S) are the major circulating neuro-steroids which has neuroprotective,[4,5] antioxidant[6] and anti-inflammatory[7] effects on brain. It is considered both a neurosteroid, being produced in the brain, as well as neuroactive steroid, produced in the adrenals and having its effect on the brain. DHEA has potent anti-glucocorticoid actions on the brain and can protect hippocampal neurons from glucocorticoid-induced neuro-toxicity.[8]

A systematic review by Pariante [9] noted that there is increase in pituitary volume during the prodromal phase, decrease in volume in chronically ill patients and then an increase as a result of antipsychotic medication intake (typical antipsychotics). Further, administration of DHEA was found beneficial in patients of Depression, Anxiety and negative symptoms in Schizophrenic patients.[10] As compared to healthy controls, DHEA-S levels have been reported to be elevated[11, 12] or having no difference[13] in schizophrenia patients. The state of the psychotic illness, duration of untreated psychosis (DUP) and the medication could be the factors responsible for these inconsistencies. These findings further strengthen the role of neurosteroids in onset and maintenance of schizophrenia.

Studies measuring the levels of cortisol and DHEA-S have provided mixed findings and thus it is difficult to generalize their results and personalize add-on treatments. This study was performed to compare serum levels of DHEA-S and cortisol in drug naïve first episode schizophrenia patients in Indian population and compare it with that in healthy controls.

II. METHODOLOGY

A cross-sectional hospital based observational study was conducted at a tertiary care centre of Rajasthan between March 2017 and February 2018. The study population consisted of Schizophrenia patients admitted in Psychiatric department. Forty patients aged between 18 and 55 years, of either sex, suffering from Schizophrenia (first episode and antipsychotic naïve) were included in the study. The diagnosis in all subjects was confirmed by the same consultant Psychiatrists according to ICD 10 criteria for Schizophrenia. Written informed consent was obtained from participants and a parent or guardian prior to inclusion in the study.

Patients having co morbid medical illness including Diabetes, impaired thyroid function, asthma, and patients on steroid medications or oral contraceptives (verified by means of clinical examination, routine laboratory investigations and previous medical records) or having any history of surgery involving adrenals or ACTH secreting tumor were excluded from the study. Patients with other comorbid psychiatric disorders including affective disorder and substance use disorder (except nicotine) were also excluded owing to different etio-pathogenesis.

Fourty age and sex matched healthy individuals with no past history of psychiatric or medical illness was taken as controls. Controls were taken from hospital staff or care takers of patients who were not blood relatives to the patients included in the study.

Ethical clearance was taken from the research review board & ethical committee of the institution.

Intra venous blood sample was drawn from all recruited patients and controls between 8.00 am and 9.00 am after 30 minutes of rest in similar and comfortable environment. All subjects were advised to avoid exercise and caffeine 24 hours prior to the blood sample. A 20 ml sample of venous blood was withdrawn using all aseptic precautions. Sample was collected into plain tubes and tubes containing EDTA for the serum and plasma, respectively. Serum Cortisol and plasma DHEAS levels were then analyzed in the Central laboratory of the hospital using same technique, under similar conditions and by the same personnel.

Statistical analysis – Continuous data were presented as mean ± standard deviation, while categorical data as number and percentage. Student's t-test was used to compare difference in means. Significance

level was taken at p <0.05. All statistical analyses were done using Epi info version 7.2.1.0 statistical software.

III. RESULTS

Mean age of Schizophrenia group was 25.17 ± 5.8 years and males constituted 65% of them, while the control group had a mean age of 26.12 ± 5.1 years with 60 % of them being males. Both groups are comparable as per age and sex wise. (Table 1).

Table 1
Age and sex wise comparison of study and control groups

S. No.	Variables	Study group	Control group	P Value	LS
1	**Age (Mean ± SD) in years**	25.17 ± 5.8	26.12 ± 5.1	0.439*	**NS**
2	**Male : Female**	26:14	24:16	0.817**	**NS**

**Unpaired 't' test* ***Chi-square test* *LS= Level of Significance*

It was also observed that the DHEA-S level was significantly higher in Schizophrenic patients as compared to controls. No significant difference was seen in serum cortisol levels between the two groups (Figure 1). No significant difference in DHEA-S or cortisol was noted between males and females in the patient group (p=0.93). Among controls, female had significantly lower blood DHEA-S levels compared to male controls (p < 0.01). No significant association was seen between age and sex with Plasma Cortisol levels in both the study groups. (Table 2)

Table 2
Comparison of serum levels of DHEAS and cortisol in Study and Control groups

S. No.	Variables	Study group	Control group	P Value*	LS**
1	**Serum Cortisol (µg/dL) (Mean ±SD)**	9.4 ± 2.6	7.98 ± 2.7	0.080	**S**
2	**Serum DHEAS (µg/dL) (Mean ±SD)**	4320 ± 1120	2760 ± 825	<0.001	**S**

** Unpaired 't' Test* *** LS= Level of Significance which is at significant difference (p value<0.05)*

IV. DISCUSSION

This study was aimed to compare the serum levels of cortisol and DHEA-S in patients with schizophrenia and healthy controls. Findings of present study further strengthen evidence that schizophrenic patients demonstrate significantly higher blood levels of the neuro-steroid DHEA-S. We have found that serum levels of DHEA-S were significantly higher in first episode antipsychotic naïve patients. Similar to present study Gallagher et al. found that DHEA-S levels were significantly higher in schizophrenic patients compared with bipolar patients and controls. They concluded that an elevation in DHEA levels may represent a specific endocrine marker in schizophrenia.[14] In another studies Di Michele and colleagues found significantly higher plasma DHEA plasma levels in schizophrenic subjects compared with healthy, suggesting that DHEA may have some role in the patho-physiology of schizophrenia.[15]

Another finding of present study was that there was not any significant difference in serum cortisol levels between schizophrenic patients and healthy controls. Similar to this finding Ristner et al and Kaneda et al also found that schizophrenia patient didn't demonstrate higher levels of serum cortisol.[13,16] In contrast to present study findings Walder et al found significantly higher levels of cortisol in schizophrenic patients comparing with healthy control.[17] Serum cortisol levels have been shown to be increased in schizophrenic patients compared to healthy controls in some studies; however, it has been

reported that this increase is not directly associated with the patho-physiology of schizophrenia.[18,19] Some studies concluded that increased serum cortisol levels are associated with the negative symptoms of the schizophrenia.[20,21] Contrary to this, Walder et al. and Kaneko et al. found that serum cortisol levels were associated with the positive symptoms of the disease.[17,22]

Since, healthy males show higher DHEA-S levels than healthy females, this difference faded with first-episode schizophrenia where this gender difference appears to have been lost and female patients demonstrating similarly higher levels of DHEA-S as compared to males. Comparatively higher levels of DHEA-S may be a reason for better prognosis of schizophrenia in females. Additionally, DHEA-S has been reported to increase levels of estrogen in women, which further strengthens the argument in favour of neuro-protective function of DHEA-S.[23,24]

It can be deduced from above discussion that higher levels of serum DHEA-S (sulfated form) acts as compensatory, neuro-protective and anti-aggressive factor in FEAN Schizophrenia patients. It may be speculated that as the illness progresses the levels of DHEA-S declines and thus the neuro-protection offered by these neuro-steroids also declines, leading to heightened aggression over time in schizophrenia. Chronic schizophrenia patients often demonstrate diminished neuro-steroid levels, elevations of which, achieved by augmentative administration of DHEA, correlates with clinical improvement in negative symptoms, mood, anxiety and depression. It can be opined that, DHEA-S levels have some role in patho-physiology of the disease but the exact mechanism of this biological interaction still remains unclear. The question which remains unanswered is that, is there a biological mediator which can precisely correlate with the clinical symptoms in first presentation of Schizophrenia and direct the further course of illness.

This study provides evidence on identifying a biological mediator in Schizophrenia patients. Further studies with prospective design and larger sample size are required to establish the DHEA-S role in pathogenesis and prognosis of schizophrenia.

V. CONCLUSION

It can be concluded from this present study that patients with first-episode schizophrenia have significantly higher levels of the serum DHEA-S compared to healthy controls. It can be speculated that this measure may serve as a biological adaptive mechanism which antagonizes the neuronal damage caused by cortisol in hippocampus. This study may add to the existing knowledge about patho-physiology of Schizophrenia and give a direction to research for novel treatment strategies also. However, the complex interaction between neuro-steroids, dopamine pathways and neurotransmitters in brain warrant further investigation.

CONFLICT OF INTEREST

None declared till now.

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