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The status of serum cortisol before and after treatment of schizophrenia and its correlation to disease severity and improvement: A longitudinal study

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Abstract

Background: Hypothalamic–pituitary–adrenal axis functioning, with cortisol as its major output hormone, has been presumed to play a key role in the development of psychopathology of schizophrenia.

Objective: We examined the association of serum cortisol with disease severity and improvement in schizophrenia patients in Jimma, Ethiopia.

Method: A total of 34 newly diagnosed schizophrenics were included in this study. Data on demographic, behavioral, clinical state, serum cholesterol level, and antipsychotic usage were obtained at baseline and after 8 weeks. The Positive and Negative Syndrome Scale was used to assess psychotic symptoms severity. A paired sample *t*-test was used to compare baseline and post-treatment values. Linear regression was used to assess associations.

Result: Post-treatment serum cortisol level was significantly lower than its baseline value ($p = 0.001$). There was also a significant positive and negative psychotic symptoms decrease after treatment (baseline positive psychotic vs post-treatment positive psychotic symptoms: $t(33) = 6.24$ (95% confidence interval = 7.03,13.84, $p = 0.000$) and (baseline negative psychotic vs post-treatment negative psychotic symptoms: $t(33) = 4.21$ (95% confidence interval = 3.82, 10.99, $p = 0.000$).

At baseline, neither positive nor negative subscore on the Positive and Negative Syndrome Scale showed an association with serum cortisol level ($B = -0.016$, $p = 0.794$ and $B = -0.032$, $p = 0.594$). However, serum cortisol level showed strong associations with post-treatment positive sub scores and negative sub scores ($B = 0.167$, $p = 0.007$) and ($B = 0.144$, $p = 0.010$) on the Positive and Negative Syndrome Scale.

Conclusion: We found a significant decrease in serum cortisol level after antipsychotics treatment and that was associated with improvement in psychotic symptoms in schizophrenics in Jimma, Ethiopia.

Keywords

Hypothalamic–pituitary–adrenal axis, schizophrenia, association, Ethiopia

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Introduction

Schizophrenia is a disabling group of mental disorders characterized by symptoms such as hallucinations, delusions, disorganized communication, poor planning, reduced motivation, and blunted affect. A century ago, we had large public institutions for serious mental illness, tuberculosis, and leprosy. Of these three, today only mental illness, especially schizophrenia, remains unchanged in prevalence.[1,2]

There are two major arguments regarding the disease: (1) it is characterized by onset in adolescence or early adulthood, and (2) it has a progressively deteriorating course. In patients with early-onset schizophrenia and middle-age-onset

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schizophrenia, similarities are seen in terms of occurrence in the family, presence of minor physical anomalies, early childhood maladjustment, the severity of positive symptoms, presence of gross structural abnormalities on cerebral magnetic resonance imaging, the overall pattern of neuropsychologic deficits, and qualitative response to neuroleptic medications.[3]

On the contrary, worldwide population growth and aging have led to a large and increasing disease burden attributable to schizophrenia, particularly for middle-income countries.[4,5] A significant and long-lasting health, social, and financial burden, not only for patients but also for families, other caregivers, and the wider society is seen because of the disease.[6]

The correlation of psychotic symptoms with serum cortisol level has not been investigated in schizophrenia patients in Ethiopia. Therefore, this study was designed to investigate the correlation of serum cortisol level with psychotic symptoms severity and improvement in newly diagnosed schizophrenia patients in Ethiopia.

This study, as a study from a new geographical location, will add some useful information to the science in the area.

Materials and methods

Study design and area

A hospital-based longitudinal study was conducted in the Psychiatry Clinic of Jimma University Medical Center (JUMC). The study is part of a mega research project conducted by Jimma University in 2019. JUMC is renowned nationwide for its quality health caregiving and community service. There are more than 2000 permanent staff and 659 active beds. More than 400,000 patients were served at emergency, outpatient departments, and various inpatient units in 2019. The institutional review board of the university approved the study and written consent was taken from the patients. Data collection was conducted from March to August 2019.

Subjects

Study subjects were identified from patients who were enrolled in the outpatient department of the Psychiatry Clinic of JUMC and diagnosed for being schizophrenic according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[7]

All of them were newly diagnosed cases. Patients with prior exposure to antipsychotic medication; those with chronic medical problems; and those taking either statin; and those on estrogen therapy were excluded.

Data collection procedure

Psychotic symptoms of schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS) rating.[8] Baseline data were collected during enrollment of the patients into the clinic and end-line data were taken after 8 weeks of treatment. The demographic, behavioral, and clinical characteristics of the patients were collected using a structured and interviewer-administered questionnaire. It was developed for this specific study. Validation of the questionnaire was not done. However, the consent was translated into Amharic. Data were collected by psychiatrists who had a first degree in the field. Training regarding the data collection procedure and the ethics of the research was done by the principal investigator who is a mental disorder specialist.

Blood was sampled in the afternoon between 8:00 p.m. and 10:00 p.m. for all the patients. Sampling was done at baseline and after 8 weeks of treatment with different antipsychotic medications. For all participants, 24 h preceding study visits; coffee, alcohol, tobacco, smoking, and khat (local stimulant plant) were prohibited. The sample was collected by standard operating procedures for sample collection. The collected sample was immediately sent to the core clinical research laboratory and analyzed by clinical chemistry experts.

Cortisol radioimmunoassay

All samples were measured in a single assay. Serum cortisol concentrations were measured using an extracted radioimmunoassay (RIA). RIA used hydrocortisone (H-4001, Sigma Chemical Company, St Louis, MO, USA) as a standard. The assay utilized 3H-cortisol (Amersham Pharmacia Biotech UK, Buckinghamshire HP, England) as a tracer and a dichloromethane extraction procedure with a mean (±SEM) recovery of 91.2 ± 1.8%. The instrument had a sensitivity of 0.54 ng/ml. The cross-reactivity to chemicals that interfere with the assay result and their concentration (μg/dL) was checked. The cross-reactivity of chemicals were: 11-Deoxycortisol (13.6%), cortisone (1.4%), dexamethasone (2.0%), corticosterone (8.0%), and prednisolone (32.2%).

Data management and statistical analysis

Data were entered into Epi data software version 4.1. Then, it is exported to IBM SPSS version 24 for analysis. Descriptive statistics were computed for demographic, behavioral, and clinical variables. A chi-square test was used for the comparison of demographic, behavioral, and clinical characteristics. A paired sample *t*-test was run to look at the mean difference of serum cortisol level and PANSS scores, at baseline and after treatment. Pearson product–moment correlation was done to look at the correlation between mean serum cortisol level and PANSS scores. Linear regression analysis was done to assess associations. A significance level of 5% (two-sided) was used to declare statistical significance.

Result

Demographic characteristics

Thirty-four patients participated in the study, of whom 25 (73.5%) were males and 29 (85.4%) were aged between 20

Table 1. Demographic characteristics of the patients.

Variable	Frequency	Percentage
Age (mean ± SD)	32.68 ± 11.84	
Sex		
Male	25	73.5
Female	9	26.5
Marital status		
Married	13	38.2
Single	15	44.1
Divorced	4	11.8
Widowed	1	2.9
Separated	1	2.9
Educational status		
No formal education	11	32.4
Primary education	11	32.4
Secondary education	9	26.5
Higher education	2	5.9
Occupation		
Farmer	13	38.2
Private work	7	20.6
Government worker	1	2.9
Student	5	14.7
Labor worker	1	2.9
Others	7	20.6
Residence		
Urban	24	70.6
Rural	10	29.4
Family history of mental illness		
Yes	11	32.4
No	23	67.6
Duration of illness (in months)		
<6	2	5.9
$\geqslant 6$	32	94.1

and 34 years. Around three-fourth of the patients were males and 15 (44.1%) were singles.

The mean age was 32.68 ± 11.84 (range: 20–75). Majority of them, 24 (70.6), were urban residents; and more than two-third, 23 (67.6%), had no family history of mental illnesses. The disease was significantly higher in the young population. About one-third of the patients had no formal education and more than 32 (94%) of them lived with the disease for more than or equal to 6 months. Please see Table 1.

Behavioral and clinical characteristics of the patients

About 11 (32.4%) of the patients believe that stressful life events caused the disease but 10 (29.4%) believe that their illness is caused by witchcraft. More than three-fourths of the patients 26 (76.5%) had not experienced symptom-free time after they had been schizophrenic and went to religious places to seek help for their illness before they came to the hospital. The disease extremely disrupted the family life of 15 (44.1%) of the patients and the social life of 14 (41.2%) of the patients. About 28 (82.4%) patients were alcohol-dependent and 19 (55.9%) were khat-dependent. Majority of the patients took risperidone as a major medication. Please see Table 2 and Supplementary Table 1.

Change in serum cortisol level and psychotic symptoms

The mean serum cortisol level at patients' admission was 8.70 ± 2.76 μg/dL but after 8 weeks of treatment of the patients with antipsychotic, it became 7.41 ± 2.35 μg/dL. The mean difference was 1.29 ± 2.00. A significant mean serum cortisol level decrease was seen after treatment: (t) = 3.74 (95% confidence interval (CI) = 0.58, 1.98), $p = 0.001$.

In a similar manner, paired sample t-test comparing baseline and post-treatment psychotic symptoms revealed that post-treatment positive and post-treatment negative psychotic symptoms showed significantly lower values, $t(33) = 6.24$ (95% CI = 7.03, 13.84; $p = 0.000$) and $t(33) = 4.21$ (95% CI = 3.82, 10.99; $p = 0.000$); see Table 3.

Relationship between serum cortisol and psychotic symptoms

In Supplementary Table 2, the analyses of Pearson's product–moment correlation are indicated.

The result showed no significant correlations between baseline serum cortisol level and baseline PANSS positive psychotic symptoms ($r = -0.047$, $p = 0.794$), baseline serum cortisol level and baseline PANSS negative psychotic symptoms ($r = -0.095$, $p = 0.594$), and baseline serum cortisol level and baseline PANSS general psychotic symptoms ($r = -0.195$, $p = 0.269$). Yet, post-treatment serum cortisol level showed significant correlation with post-treatment PANSS positive psychotic symptoms ($r = 0.454$, $p = 0.007$), PANSS negative psychotic symptoms ($r = 0.435$, $p = 0.010$), and PANSS general psychotic symptoms ($r = 0.439$, $p = 0.009$).

Pearson correlation analysis also showed that change in serum cortisol level is not correlated with change in PANSS positive psychotic symptoms ($r = 0.068$, $p = 0.703$), change in PANSS negative psychotic symptoms ($r = 0.242$, $p = 0.167$), and change in PANSS general psychotic symptoms ($r = 0.084$, $p = 0.637$). Please see Supplementary Table 2.

Further analysis with simple linear regression analyses also revealed that at baseline neither PANSS positive nor PANSS negative subscore showed an association with serum cholesterol level ($B = -0.016$, $p = 0.794$ and $B = -0.032$, $p = 0.594$). Yet, strong associations were seen between post-treatment serum cortisol level and post-treatment PANSS positive subscore ($B = 0.167$, $p = 0.007$) and post-treatment PANSS negative sub scores ($B = 0.144$, $p = 0.010$). Please see Table 4.

Table 2. Behavioral and clinical characteristics of the patients.

	Frequency	Percentage
Belief on the cause of their illness		
Supernatural	3	8.8
Witchcraft	10	29.4
Evil spirits	8	23.5
Ancestral spirits		
Stressful life events	11	32.4
Hereditary (genetic) factors	2	5.9
Patients who had been in symptom-free time (after they had been schizophrenic)		
Yes	8	23.5
No	26	76.5
Patients who started routine activities during symptom-free time		
Yes	8	23.5
No	26	76.5
Patients who visited religious places/organizations (mosque, church, holy water. . .) to seek help for their illness		
Yes	26	76.5
No	8	23.5
Patients who ever used traditional treatment (e.g. herbs) medicine		
Yes	20	58.8
No	14	41.2
Patients who were diagnosed with a chronic physical illness like diabetes mellitus, hypertension, epilepsy, and so on		
Yes	0	0
No	34	100
Patients who are on treatment for chronic diseases		
Yes	20	58.8
No	14	41.2
Khat dependence		
Yes	19	55.9
No	15	44.1
Tobacco dependence		
Yes	8	23.5
No	26	76.5
Alcohol dependence		
Yes	6	17.6
No	28	82.4
Cannabis dependence		
Yes	3	8.8
No	31	91.2
The symptoms have disrupted your work/school		
Mildly	0	
Moderately	5	14.7
Markedly	16	47.0
Extremely	13	38.2
The symptoms have disrupted your social life/leisure activities		
Mildly	2	5.9
Moderately	2	5.9
Markedly	16	47.0
Extremely	14	41.2
The symptoms have disrupted your family life/home responsibilities		
Mildly	2	5.9
Moderately	3	8.8
Markedly	14	41.2
Extremely	15	44.1
Medication		
Risperidone	18	52.7
Haloperidol	6	17.6
Chlorpromazine	6	17.6
Olanzapine	3	8.8
Modecate	1	2.9

Discussion

Many studies reported that hypercortisolism is a feature of various psychiatric illnesses including schizophrenia and has been suggested to be both a causal and exacerbating factor of clinical symptoms and neurocognitive impairment.[9–12] Other studies on the patients, however, have not found elevated basal cortisol levels.[13,14] There is also an evidence, which argues that schizophrenia patients experience both hyper- and hypo-function of hypothalamic–pituitary–adrenal (HPA) axis.[15] Yet, almost all of these studies were conducted in developed countries. Hence, further study to clarify the precise level of serum cortisol in psychotic patients in lower- and middle-income countries was needed.

In this study, we found that following an 8-week treatment period, serum cortisol level was significantly decreased in the patients. A similar finding has been reported by some previous studies.[16–18] The result provides preliminary evidence of a subtle but significant reduction in serum cortisol level following treatments. This may, in part, underlie the putative therapeutic effects of such drugs. Yet both hyper- and hypo-level of serum cortisol have been reported by another study.[15] This likely contributes to poor physiological conditions and premature mortality in the patients, in particular, the high rates of cardiovascular and metabolic disturbance.

In our study, we found strong associations between post-treatment serum cortisol level and post-treatment PANSS positive and post-treatment PANSS negative psychotic symptoms sub scores. This finding is in agreement with other studies conducted previously.[19–22] Studies argue that serum cortisol level may potentially mediate the effects of lifestyle factors on psychotic symptoms and neurological deficits. According to these studies, serum cortisol may serve as biomarkers for diagnosing schizophrenia and monitoring treatment efficacy.[22,23] The authors specifically insist that the determination of afternoon cortisol levels may serve

Table 3. Paired *t*-tests examining the changes in psychotic symptoms and serum cortisol level from admission to 8 weeks.

Variables	Admission	Post-treatment	Mean difference (SD)	*t* statistics	*p*-value
PANSS positive subscore	30.05 ± 8.15	19.61 ± 6.38	10.44 ± 9.75	6.24	0.000*
PANSS negative subscore	26.82 ± 8.08	19.41 ± 7.10	7.41 ± 10.26	4.21	0.000*
PANSS general score	46.47 ± 13.62	39.41 ± 14.88	7.05 ± 20.06	2.05	0.048*
Serum cortisol	08.70 ± 2.76	7.41 ± 2.35	1.29 ± 2.00	3.74	0.001*

PANSS: Positive and Negative Syndrome Scale.
*Significant mean difference.

Table 4. Regression table (baseline and after treatment).

Independent variable	Dependent variable	*B*	SE(*B*)	Beta	95% CI	*p*-value
Baseline PANSS positive subscore	Baseline serum cortisol	−0.016	0.060	−0.047	(−0.138, 0.106)	0.794
Baseline PANSS negative subscore	Baseline serum cortisol	−0.032	0.060	−0.095	(−0.155, 0.090)	0.594
Baseline PANSS general subscore	Baseline serum cortisol	−0.040	0.035	−0.195	(−0.111, 0.032)	0.269
Post-treatment PANSS positive subscore	Post-treatment serum cortisol	0.167	0.058	0.454	(0.049, 0.285)	0.007[a]
Post-treatment PANSS negative subscore	Post-treatment serum cortisol	0.144	0.053	0.435	(0.036, 0.251)	0.010[a]
Post-treatment PANSS general subscore	Post-treatment serum cortisol	0.069	0.025	0.439	(0.018, 0.120)	0.009[a]
Change in PANSS positive subscores	Change in serum cortisol	−0.014	0.036	−0.068	(−0.088, 0.060)	0.703
Change in PANSS negative subscores	Change in serum cortisol	−0.047	0.034	−0.242	(−0.116, 0.021)	0.167
Change in PANSS general subscores	Change in serum cortisol	−0.008	0.018	−0.084	(−0.044, 0.027)	0.637

CI: confidence interval; PANSS: Positive and Negative Syndrome Scale.
[a]Significant association.

to detect potential candidates for specific cognitive intervention in the patients immediately after the first psychotic breakthrough.[22–24]

Regardless of these findings, there is evidence that revealed no association between post-treatment psychotic symptoms and post-treatment serum cortisol.[25] Methodological and/or clinical factors, such as patients' diagnosis or illness phase and severity, might partially account for these inconsistencies.[6] These studies argue that the association of cortisol with psychopathological symptoms is non-specific. In the literature review, we have found that studies that argue the presence of higher cortisol levels in blood samples have been consistently replicated in the literature, whereas saliva studies measuring baseline cortisol levels have exhibited divergent results. Moreover, longitudinal studies have revealed a cortisol upregulation in first-episode psychosis with a subsequent decrease induced by antipsychotic treatment. However, studies should focus on purer diagnostic entities, clearly defined stages of the disorder, and refined methods of hormonal measurement.[6]

In our study, we found no correlation between serum cortisol level and the total duration of illness at baseline serum ($r=0.010$, $p=0.955$). Studies investigating cortisol and other biomarkers' basal levels in schizophrenia patients have yielded mixed findings. A study conducted by Singh et al.[26] reported that this hormonal index is not significantly correlated with psychopathology, the total duration of disease, and age at onset of illness. However, several others found strong correlations between the total duration of the disease and serum cortisol level.[23,27–29] These variations might be attributable, at least in part, to several differential demographic and clinical characteristics across studies, such as age, symptom severity, medication status, and comorbid psychiatric disorders as well as exposure to other environmental factors known to influence the HPA axis functions or cortisol level. Conversely, in our study, we found a correlation between the total duration of illness and post-treatment PANSS positive sub scores.

Majority of our patients were treated with risperidone as a first-line treatment combined with other antipsychotic medications. Studies confirmed that risperidone is more effective on negative symptoms and causes decreased serum cortisol levels more to a greater degree than medications such as haloperidol.[19] Risperidone is an atypical antipsychotic drug with potent serotonin-5-HT2A and dopamine-D2 receptor blocking properties.[30] On the contrary, there is increasing evidence that 5-HT promotes HPA axis activity at the hypothalamic, pituitary, and adrenal levels.[19] Pharmacological stimulation of different 5-HT receptor subtypes, as well as stress-induced 5-HT release, promotes activation of the HPA axis and subsequent release of corticotrophin-releasing hormone, adrenocorticotropic hormone, and glucocorticoids.[31] In general, some arguments say treating schizophrenia with risperidone results in both symptom and serum cortisol level reduction.[32]

Majority of the studies conducted on mental disorders in Ethiopia have a cross-sectional nature. But this study was longitudinal. It had two points of data collection. This is the

strength of this study. Besides, the study included new cases of schizophrenia, which is the other strength of the study. But it has its limitations. The first limitation is that power analysis for sample size calculation/determination was not done. The other limitation is that the study took a small number of patients because of a budget shortage. The questionnaire was developed by a psychiatric expert. We did not do validation. We also did not undergo pilot testing. This is another limitation of the study.

Conclusion

We found a significant decrease in serum cortisol level after antipsychotics treatment of schizophrenia patients in Ethiopia and that was associated with improvement in psychotic symptoms, independent of other factors. To further elaborate on the clinical significance of the effects of antipsychotic treatment on serum cortisol level in Ethiopian schizophrenic patients, sufficiently powered longitudinal studies in drug-naïve patients are needed.

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Author contributions

Y.M.W., I.T.B., and A.A. conceptualized the idea; Y.M.W., I.T.B., L.G., C.F., and A.A. developed the methodology; Y.M.W. and A.A. analyzed the data; and Y.M.W. wrote the result and developed the article. All the authors reviewed and approved the final version of the article.

Declaration of conflicting interests

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Ethical approval

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Informed consent

The participants of the study were included in the study after they provided written informed consent. The study protocol followed the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article

Supplemental material

Supplemental material for this article is available online.

References

1. Insel TR. Rethinking schizophrenia. *Nature* 2010; 468(7321): 187–193.
2. Saha S, Chant D, Welham J, et al. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005; 2(5): e141.
3. Palmer BW, McClure FS and Jeste DV. Schizophrenia in late life: findings challenge traditional concepts. *Harv Rev Psychiatry* 2001; 9(2): 51–58.
4. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. *Schizophr Bull* 2018; 44(6): 1195–1203.
5. Bhugra D. The global prevalence of schizophrenia. *PLoS Med* 2005; 2(5): e151.
6. Knapp M, Mangalore R and Simon J. The global costs of schizophrenia. *Schizophr Bull* 2004; 30(2): 279–293.
7. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing, 2013.
8. Kay SR, Fiszbein A and Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; 13(2): 261–276.
9. Stokes PE and Sikes CR. Hypothalamic-pituitary-adrenal axis in psychiatric disorders. *Ann Rev Med* 1991; 42(1): 519–531.
10. Voinov B, Richie WD and Bailey RK. Depression and chronic diseases: it is time for a synergistic mental health and primary care approach. *Prim Care Companion CNS Disord*. Epub ahead of print 4 April 2013. DOI: 10.4088/PCC.12r01468.
11. Gallagher P, Watson S, Smith MS, et al. Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. *Schizophr Res* 2007; 90(1–3): 258–265.
12. Girshkin L, Matheson SL, Shepherd AM, et al. Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis. *Psychoneuroendocrinology* 2014; 49: 187–206.
13. Borges S, Gayer-Anderson C and Mondelli V. A systematic review of the activity of the hypothalamic–pituitary–adrenal axis in first episode psychosis. *Psychoneuroendocrinology* 2013; 38(5): 603–611.
14. Tandon R, Mazzara C, DeQuardo J, et al. Dexamethasone suppression test in schizophrenia: relationship to symptomatology, ventricular enlargement, and outcome. *Biol Psychiatry* 1991; 29(10): 953–964.
15. Bradley AJ and Dinan TG. A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: implications for mortality. *J Psychopharmacol* 2010; 24(Suppl. 4): 91–118.

16. Venkatasubramanian G, Chittiprol S, Neelakantachar N, et al. Effect of antipsychotic treatment on Insulin-like Growth Factor-1 and cortisol in schizophrenia: a longitudinal study. *Schizophr Res* 2010; 119(1–3): 131–137.
17. Gallagher P, Watson S, Elizabeth Dye C, et al. Persistent effects of mifepristone (RU-486) on cortisol levels in bipolar disorder and schizophrenia. *J Psychiatr Res* 2008; 42(12): 1037–1041.
18. Mondelli V, Ciufolini S, Belvederi Murri M, et al. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. *Schizophr Bull* 2015; 41(5): 1162–1170.
19. Zhang XY, Zhou DF, Cao LY, et al. Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. *Neuropsychopharmacology* 2005; 30(8): 1532–1538.
20. Kaneko M, Yokoyama F, Hoshino Y, et al. Hypothalamic-pituitary-adrenal axis function in chronic schizophrenia: association with clinical features. *Neuropsychobiology* 1992; 25(1): 1–7.
21. Babinkostova Z, Stefanovski B, Janicevic-Ivanovska D, et al. Serum cortisol and DHEA-S levels in schizophrenic patients with different response to antipsychotic therapy: association with psychopathology [Серумски Концентрации На Кортизол И DHEA-S Кал Пациенти Со Шизофренша Со Различен Одговор На Антипсихотичната Терапша Асоци. 1Аци. 1А Со Психопатологшата]. *Pril* 2015; 36(1): 175–182.
22. Labad J. The role of cortisol and prolactin in the pathogenesis and clinical expression of psychotic disorders. *Psychoneuroendocrinology* 2019; 102: 24–36.
23. Peng R and Li Y. Association among serum cortisol, dehydroepiandrosterone-sulfate levels and psychiatric symptoms in men with chronic schizophrenia. *Compr Psychiatry* 2017; 76: 113–118.
24. Havelka D, Prikrylova-Kucerova H, Prikryl R, et al. Cognitive impairment and cortisol levels in first-episode schizophrenia patients. *Stress* 2016; 19(4): 383–389.
25. Karanikas E, Antoniadis D and Garyfallos GD. The role of cortisol in first episode of psychosis: a systematic review. *Curr Psychiatry Rep* 2014; 16(11): 503.
26. Singh M, Solanki RK, Bagaria B, et al. Hypothalamic-pituitary-adrenal (HPA) axis functioning among patients with schizophrenia: a cross sectional comparative study. *J Psychiatry* 2015; 18: 1000211.
27. Misiak B, Frydecka D, Loska O, et al. Testosterone, DHEA and DHEA-S in patients with schizophrenia: a systematic review and meta-analysis. *Psychoneuroendocrinology* 2018; 89: 92–102.
28. Suvisaari J, Mantere O, Keinänen J, et al. Is it possible to predict the future in first-episode psychosis? *Front Psychiatry* 2018; 9: 580.
29. Herceg M, Puljić K, Sisek-Šprem M, et al. Influence of hormonal status and menstrual cycle phase on psychopathology in acute admitted patients with schizophrenia. *Psychiatr Danub* 2018; 30(suppl. 4): 175–179.
30. Horacek J, Bubenikova-Valesova V, Kopecek M, et al. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs* 2006; 20(5): 389–409.
31. Chaouloff F. Physiopharmacological interactions between stress hormones and central serotonergic systems. *Brain Res Brain Res Rev* 1993; 18(1): 1–32.
32. Chan HY, Chang CJ, Chiang SC, et al. A randomised controlled study of risperidone and olanzapine for schizophrenic patients with neuroleptic-induced acute dystonia or parkinsonism. *J Psychopharmacol* 2010; 24(1): 91–98.