Psychiatria Danubina, 2016; Vol. 28, Suppl. 1, pp 162-164 *Conference paper*

EVALUATION OF THE CORTISOL CONCENTRATIONS IN PATIENTS WITH SCHIZOPHRENIA

Dominika Tobolska[1], Krzysztof Maria Wilczyński[2], Miłosz Lorek[1], Elżbieta Mazgaj[2], Krzysztof Krysta[3], Aneta Gawlik[4] & Marek Krzystanek[3]

[1]*Students' Scientific Association in Department of Pediatrics, Medical University of Silesia, Katowice, Poland*
[2]*Students' Scientific Association in Department of Psychiatric Rehabilitation, Medical University of Silesia, Katowice, Poland*
[3]*Department of Psychiatric Rehabilitation, Medical University of Silesia, Katowice, Poland*
[4]*Department of Pediatrics, Medical University of Silesia, Katowice, Poland*

SUMMARY

Introduction: *The hypothalamus-pituitary-adrenal axis (HPAA) plays a pivotal role in response to a range of external and internal factors often described as a "stress". Growing evidence in a literature, suggest various dysregulations of HPAA, in course of numerous mental disorders. Patients with schizophrenia and bipolar disorder seem to have elevated basal cortisol secretion, what might be caused by the diminution of glucocorticoid receptors' amount. It was of the interest if the cortisol concentrations in patients with diagnosed schizophrenia who underwent treatment, differs from healthy individuals.*

Materials and methods: *Two groups of participants were included into the study. First group (study) consisted of 10 patients with diagnosed schizophrenia and control group which included 38 healthy individuals. Study was divided into two stages, first one (pilot) included only control group, and utilized cortisol concentrations measurement from saliva, blood and 24h urine sample. Second part (main study) involved both groups although focused on a salivary cortisol concentrations.*

Results: *A mean salivary cortisol concentration in patients with schizophrenia who underwent treatment was significantly lower in comparison with healthy individuals.*

Conclusions: *Obtained results indicate that patients who underwent a treatment, and does not present notable clinical signs of schizophrenia may have moderately lowered levels of salivary cortisol. This may be a reflection of relenting psychotic symptoms as well as a direct effect of atypical antipsychotic drugs on a HPA axis activity.*

Key words: *cortisol – schizophrenia - treatment*

* * * * *

INTRODUCTION

The hypothalamus-pituitary-adrenal axis (HPAA) plays a pivotal role in response to a range of external and internal factors often described as a "stress". HPAA response to those agents is a complex process including inter allia excretion of corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol. Although CRH and ACTH may stimulate a range of biological responses, according to the literature cortisol is the core element responsible for exerting stress reaction (Hellhammer et al. 2008, Kirschbaum & Hellhammer 1994). Cortisol is a steroid hormone, produced by a zona fasciculata of the adrenal cortex. It belongs to the glucocorticoid class of hormones and apart from aforementioned release in response to stress, it is also excreted due to the low blood-glucose concentration. Nowadays, together with heart rate (HR) and blood pressure (BP), salivary cortisol is considered to be the key biomarker of a psychological stress (Hellhammer et al. 2008, Brenner et al. 2009). Salivary steroid levels evaluation seems to have plenty of advantages over conventional blood concentrations. First of all, as a noninvasive method, it does not provoke stress reaction which may disturb the outcomes. Furthermore parameters measured in this procedure, are reflecting levels of biologically active, unbound steroids concentration. According to the literature, salivary measurements are considered to be a reliable and widely accepted method of evaluating steroids' levels (Vining et al. 1983, Brenner et al. 2009).

Physiological cortisol stress response seems to be influenced by several factors. A higher body mass index (BMI), age, male gender and certain personality traits are associated with a stronger reaction (Brenner et al. 2009, Kirschbaum et al. 1994, Bauer 2005, Oswald et al. 2006) while opposite effect is observed in cigarette smokers (Brenner et al. 2009). There were also equivocal reports of alcohol, caffeine and dietary habits influencing HPAA in literature sources (Kudielka et al. 2009). It is also important to note that it may also be affected by antipsychotic drugs used in treatment of schizophrenia (Brenner et al. 2009). Among other factors, pregnancy significantly alters HPAA physiology, increasing levels of CRH, ACTH, CBG and cortisol levels (Kudielka et al. 2009).

Growing evidence in a literature, suggest various dysregulations of HPAA, in course of numerous mental disorders such as affective disorders (Mazurka et. al. 2015, Daban et al. 2005), schizophrenia (Pruessner et al. 2011, Holtzman et al. 2013, Jansen et al. 2000, Borges et al. 2013) or anxiety disorders (Hek et al. 2013). Disturbances of HPAA caused by the elevated levels of cortisol are suspected to be the mechanism of chronic stress' transmission to the major depression (Levine et al. 2007).

Furthermore patients with schizophrenia and bipolar disorder also seem to have elevated basal cortisol secretion, what might be caused by the diminution of glucocorticoid receptors' amount (Steen et al. 2014, Daban et al. 2005, Streit et al. 2016). Available literature also shows that increased cortisol levels have been found in patients who developed psychosis shortly after examination (Walker et al. 2013).

Our aim was to evaluate the cortisol concentrations in patients with diagnosed schizophrenia who underwent treatment, and compare them to the healthy population.

MATERIALS AND METHODS

Study was approved by the Ethical Committee of the Medical University of Silesia and written informed consent was obtained from all of patients and healthy participants prior to enrollment in the study. All procedures were conducted in accordance with the Helsinki Declaration of 1975, revised in 2000.

Two groups of participants were included into the study. First group (study) consisted of 10 patients with diagnosed schizophrenia (4 males (40%) and 6 females (60%)), who underwent an anti-psychotic treatment which utilized atypical drugs such as olanzapine. Average age equaled 34.3 years (95% CI: 25.1-43.44). Control group included 38 healthy individuals (15 males (40%) and 23 females (60%)), with an average age of 23.5 years (95% CI: 23.12-24.05). There was no statistically significant difference between control and study groups in terms of a gender division in a χ^2 test.

Study was divided into two stages, first one (pilot) included only control group, and utilized cortisol concentrations measurement from saliva, blood and 24h urine sample. Second part (main study) involved both groups although focused on a salivary cortisol concentrations. All measurements were conducted using CORT-CT2 radioimmunoassay kit, for the quantitative determination of cortisol in human serum, urine and saliva (CISBIO France). Samples of blood and saliva, were collected between 7.30 and 8 am, before breakfast and oral hygiene. 24h urine sample was gathered in a preceding day, started with a second urination and finished with a first urination the next day. Three samples of saliva were collected from each of the participants, in 15 minutes intervals, and therefore values of salivary cortisol concentrations are presented as mean. Additionally all participants had to fill in a set of questionnaires including: Morningness-Eveningess Questionnarie (MEQ), Leibowitz's social anxiety inventory (LAI) and demographical data questionnaire (DDQ). Furthermore a study group was examined using a Positive and Negative Syndrome Scale (PANSS) and did not present notable clinical signs of schizophrenia at the time of participation.

Statistical analyses were conducted using StatSoft Statistica software version 12.0, with an accepted level of significance α=0.05. Mann-Whitney's U test was utilized for sake of a comparison of quantitative variables, and size effects of statistically significant differences was assessed using Wendt's algorithm (r:<0;1>). For qualitative variables, a χ^2 test was used.

RESULTS

A mean salivary cortisol concentration in patients with schizophrenia who underwent treatment was significantly lower in comparison with healthy individuals ($p<0.05$; size effect r=0.5; figure 1). There was no statistically significant difference between groups in terms of chronotype, cigarette smoking, alcohol usage, weight, height and BMI. Outcomes of LAI were significantly lower in patients with schizophrenia ($p<0.05$; size effect r=0.51).

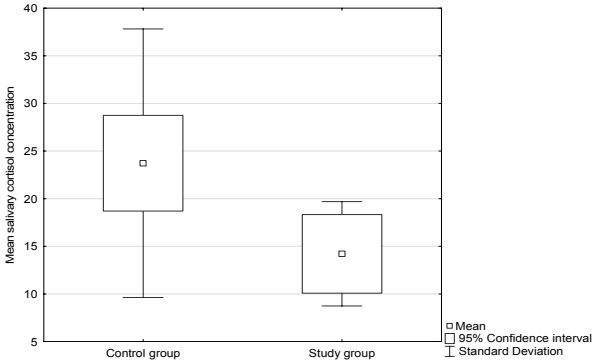

Figure 1. Comparison of a mean salivary cortisol concentration between the control and study group

DISCUSSION

Although study group included into following research is limited (n=10), thanks to tight selection of participants (lack of endocrinological pathologies, similar spread of alcohol consumption and cigarette smoking, similar gender division, homogenous outcome of PANSS scale, similar division of chronotypes and small difference between age spread – size effect r=0.21) as well as careful conduction of all procedures, presented results and conclusions possess relevant statistical significance.

According to the literature, significant alterations to the HPA axis occur in course of the schizophrenia. In particular those changes regard basal cortisol secretion, probably in response to decrease in amount of glucocorticoid receptors (Steen et al. 2014, Daban et al. 2005, Streit et al. 2016). Walder et al. in 2000 revealed a significant, positive correlation between salivary cortisol concentrations and symptoms severity. Furthermore, outcomes of study conducted by Walker et al. (2013), revealed that increased cortisol levels have been found in patients who, shortly after examination, developed psychosis. Therefore hypothesis that HPA axis distortion is closely bound with symptoms and pathophysiology of the schizophrenia is increasingly recognized in literature. It was of the interest if patients who underwent a therapy, which reduced their symptoms, also exhibited increased

levels of salivary cortisol. Our results indicate that cortisol concentrations in those patients are lower than in a general population. This may be caused by the decrease in a HPA axis activity as a reflection of relenting psychotic symptoms (Cohrs et al. 2006) as well as a direct pharmacodynamic effect of atypical antipsychotic drugs, utilized in patients from a study group (Mondelli et al. 2010). Medications such as olanzapine or risperidone lead to the reduction of cortisol concentrations in patients as well as in healthy controls (Cohrs et al. 2006, Mann et al. 2006, Zhang et al. 2005), and according to the Flores et al. study from 2006, this capability is probably responsible for their effectivity.

CONCLUSIONS

Obtained results indicate that patients who underwent a treatment, and does not present notable clinical signs of schizophrenia may have moderately lowered levels of salivary cortisol. This may be a reflection of relenting psychotic symptoms as well as a direct effect of atypical antipsychotic drugs on a HPA axis activity.

Acknowledgements: None.

Conflict of interest: None to declare.

References

1. *Bauer M: Stress, glucocorticoids and ageing of the immune system. Stress 2005; 8:69–83.*
2. *Borges S, Gayer-Anderson C & Mondelli V: A systematic review of the activity of the hypothalamic-pituitary-adrenal axis in first episode psychosis. Psychoneuroendocrinology 2013; 38:603–611.*
3. *Brenner Liu, Laplante DP, Lupien, Pruessner, JC, Ciampi: Cortisol response to a psychosocial stressor in schizophrenia: Blunted, delayed, or normal? Psychoneuroendocrinology 2009; 34: 859-868.*
4. *Cohrs S, Roher C, Jordan W, Meier A, Huether G, Wuttke W, Ruther E, Rodenbeck A: The atypical antipsychotics olanzapine and quetiapine, but not haloperidol, reduce ACTH and cortisol secretion in healthy subjects. Psychopharmacology 2006; 185:11–18.*
5. *Daban C, Vieta E, Mackin P, Young AH: Hypothalamic–pituitary–adrenal axis and bipolar disorder. Psychiatr Clin N Am 2005; 28:469-480.*
6. *Flores BH, Kenna H, Keller J, Solvason HB, Schatzberg AF: Clinical and biological effects of mifepristone treatment for psychotic depression Neuropsychopharmacology 2006; 31:628–636.*
7. *Hek K, Direk N, Newson R, Hofman A, Hoogendijk W, Mulder C & Tiemeier H: Anxiety disorders and salivary cortisol levels in older adults: a population-based study. Psychoneuroendocrinology 2013; 38:300–305.*
8. *Hellhammer D, Wüst S & Kudielka B: Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology 2008; 34:163–71.*
9. *Holtzman CW, Trotman HD, Goulding SM, Ryan AT, Macdonald AN, Shapiro DI, Brasfield JL, Walker EF: Stress and neurodevelopmental processes in the emergence of psychosis. Neuroscience 2013; 249:172–191.*
10. *Jansen L, Wied C & Kahn R: Selective impairments in the stress response in schizophrenic patients. Psychopharmacology 2000; 149:319–325.*
11. *Kirschbaum C & Hellhammer D: Salivary cortisol in psychoneuroendocrine research: Recent developments and applications. Psychoneuroendocrinology 1994; 19:313–333.*
12. *Kudielka BM, Wüst S: Human models in acute and chronic stress: assessing determinants of individual hypothalamus-pituitary-adrenal axis activity and reactivity. Stress 2009; 13:1-14.*
13. *Levine A, Zagoory-Sharon O, Feldman R, Lewis JG, Weller A: Measuring cortisol in human psychobiological studies. Physiol Behav 2007; 90:43-53.*
14. *Mazurka, R, Wynne-Edwards K & Harkness K: Stressful Life Events Prior to Depression Onset and the Cortisol Response to Stress in Youth with First Onset Versus Recurrent Depression. Journal of Abnormal Child Psychology, 2015.*
15. *Mondelli V, Dazzan P, Hepgul N, Di Forti M, Aas M et al. Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: The role of stress and of antipsychotic treatment Schizophrenia Research 2010; 116:234–242.*
16. *Oswald LM, Zandi P, Nestadt G, Potash JB, Kalaydjian AE, Wand GS: Relationship between cortisol responses to stress and personality. Neuropsychopharmacology 2006; 31:1583-91.*
17. *Pruessner M, Vracotas N, Joober R, Pruessner JC, Malla AK: Blunted cortisol awakening response in men with first episode psychosis: relationship to parental bonding. Psychoneuroendocrinology 2013; 38:229-240.*
18. *Steen NE, Methlie P, Lorentzen S, Dieset I, Aas M, Nerhus M et al: Altered systemic cortisol metabolism in bipolar disorder and schizophrenia spectrum disorders. J Psychiatr Res 2014; 52:57-62.*
19. *Streit F et al.: Perceived stress and hair cortisol: Differences in bipolar disorder and schizophrenia. Psychoneuroendocrinology 2016; 69:26-34.*
20. *Vining RF, McGinley RA, Maksvytis JJ, Ho KY: Salivary cortisol: a better measure of adrenal cortical function than serum cortisol. Ann Clin Biochem 1983; 20:329-335.*
21. *Walker EF, Trotman HD, Pearce BD, Addington J, Cadenhead KS, Cornblatt BA: Cortisol levels and risk for psychosis: initial Findings from the North American Prodrome Longitudinal Study. Biol Psychiatry 2013; 74:410-417.*
22. *Zhang XY, Zhou DF, Cao LY, Wu GY, Shen YC: Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. Neuropsychopharmacology 2005; 30:1532–1538.*

Correspondence:
Krzysztof Maria Wilczyński, MD
Zielonogorska st 9/1, 40-710 Katowice, Poland
E-mail: wil.k.m91@gmail.com