Psychiatria Danubina, 2015; Vol. 27, Suppl. 1, pp 261–265 *Conference paper*

EFFECTS OF HORMONES ON COGNITION IN SCHIZOPHRENIC MALE PATIENTS – PRELIMINARY RESULTS

Agnieszka Bratek, Agnieszka Koźmin-Burzyńska, Krzysztof Krysta, Katarzyna Cierpka-Wiszniewska & Irena Krupka-Matuszczyk

Department of Psychiatry and Psychotherapy, Silesian Medical University, Katowice, Poland

SUMMARY

Background: *Schizophrenia is a prevalent neurodevelopmental disorder of an unknown etiology and a variable phenotypic expression. In the recent years, the impact of hormones on the course of schizophrenia has been investigated. This study is aimed at assessing the level of correlating serum levels of hormones in schizophrenic male patients with their cognitive functioning measured with neuropsychological tests.*

Subjects and methods: *In the index group there were 15 medicated male schizophrenic patients. In the control group there were 15 age and education matched healthy men. All subjects underwent analysis of serum hormones level (TSH, testosterone, estradiol, FSH, LH, progesterone and prolactin) and a battery of tests (Trail Making Test A and B, Stroop Test, Verbal and Semantic Fluency Test).*

Results: *The mean serum levels of the following hormones were higher in the index group than in the control group: TSH (1.76 mIU/L vs 1.58 mIU/L; p=0.66), progesterone (0.85 ng/ml vs 0.69 ng/ml; p=0.22) and prolactin (558.71 uIU/ml vs 181 uIU/ml; p=0.025). The mean levels of estradiol (24.36 pg/ml vs 25.40 ng/ml; p=0.64), FSH (3.17 mIU/ml vs 5.72 mIU/ml; p=0.019), LH (3.85 mIU/ml vs 5.77 mIU/ml; p=0.056) and testosterone (2.90 ng/ml vs 5.38 ng/ml; p=0.003) were higher in the control group. In the index group there were significant negative correlations between FSH and semantic fluency (ρ=-0.678606), progesterone and: TMT B (ρ=-0.586763), Stroop 1 (ρ=-0.701880) and Stroop 2 (ρ=-0.601074) and prolactin and TMT A (ρ=-0.579607).*

Conclusions: *The preliminary results of our study show that serum levels of FSH and testosterone are significantly lower, whereas the level of prolactin is markedly higher, in schizophrenic male patients than in healthy men. There is an inverse correlation between serum levels of progesterone, FSH and prolactin and the results of certain cognitive functioning tests in schizophrenic men.*

Key words: *schizophrenia – cognition – hormones - males*

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INTRODUCTION

Schizophrenia is a chronic and complex mental disorder with a variable phenotypic expression. This is one of the most prevalent psychiatric illnesses, it affects approximately 1% of the population (Saha 2005). The disorder is typically characterized with positive symptoms (hallucinations and delusions), negative symptoms (social withdrawal, apathy) and impairment of cognitive functions (memory, thought, perception and volition), resulting in chronic and severe social and occupational dysfunction. The etiology of schizophrenia is multifactorial and not yet completely understood (Freedman 2003). It is widely accepted that schizophrenia is rather a group of clinically and biologically heterogeneous entities than a single disease (Jablensky 2010), therefore it is not surprising that the symptom presentation vary significantly in particular patients. The differences are especially prominent between female and male patients.

Gender differences in schizophrenia have long been recognized. Already Kraepelin observed, that men tend to present the clinical picture of schizophrenia with early manifestation, deficits in premorbid development, affective flattening and social anhedonia (González-Rodríguez 2014). Kraepelin's findings were later confirmed in a number of studies. One of the most consistent findings across the studies was that during reproductive years schizophrenic females have a more favorable illness course than their male counterparts, respond better to treatment and require less hospitalizations (Riecher-Rössler 2000, Grigoriadis 2002, Häfner 2003, Desai 2013, Heringa 2015). In particular, differences in the age of onset have been consistently reported across the studies. Typically, the illness onset in females is approximately four years later than in males – it is 26.5 years in males and 30,6 years in females (Häfner 2003). However, the second peak of onset in women is in the perimenopause (Lindamer 2003). Also, men are more likely to develop schizophrenia than women, with an incidence risk ratio of 1.4 (Slotema 2012). Additionally, there are substantial gender differences in syndrome presentation, with women tending to present with more affective and paranoid psychotic symptoms and men tending to present with more negative symptoms (Heringa 2015). Gender differences in the course of schizophrenia underlie the "estrogen protection hypothesis". Estrogen is regarded an antipsychotic factor taking into account later onset, less severe course in women and loss of that protection in the perimenopause when estrogen production declines (Seeman 1996). However, the exact mechanism of antipsychotic action of estrogen is not yet fully understood.

Not only estradiol, but also other sex hormones were found to be involved in the pathophysiology of schizophrenia. In men with schizophrenia, serum testosterone was found to be inversely correlated to negative symptoms and impaired cognition (Akhondzadeh 2006). There is relatively low data on interdependencies between

cognition and serum hormones level in schizophrenic males (Krysta 2013). This study aims at broadening the knowledge on psychoendocrinological features of schizophrenia.

SUBJECTS AND METHODS

This is a naturalistic, case-control study on 30 males, 15 of whom were diagnosed with schizophrenia and the remaining 15 were age and education matched healthy volunteers. Patients were excluded from the study if they had a clinically significant neurological disorder, any severe medical condition, any known endocrine disorder, were currently using hormonal therapy, were dependent on alcohol and/or illicit drugs or had a cognitive impairment (MMSE <25). All the participants gave written informed consent to taking part in the study. The trial was approved by ethics committee at Silesian Medical University in Katowice.

Procedures

Blood samples were collected from all the participants from 9:00 to 10:00 AM. The sera were analysed within 8 hours All samples were examined in the same lab. The hormones studied were testosterone, prolactin, estradiol, progesterone, thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH). Within the same day, all participants underwent a brief medical interview and a battery of tests.

Instruments

1) The Trail Making Test (TMT) is a pen and paper test which consists of two parts. In Part A the task is to connect the numbers from 1 to 25 in ascending order. This part measures mainly psychomotor speed, attention and spatial organization. Part B is more complicated, the task is to connect alternately numbers (1-13) in ascending order and letters (A-L) in alphabetical order (i.e. 1-A-2-B-3-C etc.). This part additionally measures attention switching, mental flexibility and recall (Corrigan 1987). Cognitive impairment can be presumed when the time required by a patient to complete the task is longer than 78 s for Part A and 273 s for Part B.

2) The Stroop Test is a neuropsychological tool based on the Stroop effect – an observation that it takes longer to read a name of a color when it is printed in a color not denoted by the name (e.g. the word "BLUE" printed in yellow ink). The test measures selective attention, ability to discriminate interfering stimuli, cognitive flexibility, and processing speed. There are several variants of this test. We performed two subtasks – in the first one the text was printed in black, participants were asked to read it aloud to measure their speed of reading. In the second part the subjects were asked to name the color in which the words denoting other colors were printed.

3) Verbal Fluency Tests – measure attention, memory, verbal fluency and executive functions.

The FAS Verbal Fluency Test – the participants were asked to say as many words as possible starting with a particular letter (F, A and S), they had one minute per letter. The words had to be common nouns, names were not allowed, of which the patients were informed before starting the test. The Semantic Fluency Test – patients were asked to name as many animals, fruits and vegetables as possible, they had one minute per category. Scores were presented as the sum of correct words in three minutes.

4) The Positive and Negative Symptom Scale (PANSS) is a tool designed to use only in patients already diagnosed with schizophrenia, so we administered in only in the index group. This scale is useful to evaluate general non-psychotic psychiatric symptoms, positive psychotic symptoms and negative symptoms (Kay 1987).

RESULTS

In the index group there were 15 medicated schizophrenic males, mean age 36.60±7.54 years old (range 26-55 years old). The mean time from the diagnosis was 12.4±5.55 years (range 3-21 years). When examined with PANSS, all of our patients presented mainly with negative symptoms of schizophrenia (social withdrawal, aspontaneity, blunted affect). None of them presented any residual psychotic symptoms (i.e. hallucinations and delusions). Regarding the level of education, one patient completed vocational training, nine patients finished high school and five patients began or completed a university degree.

In the control group there were 15 healthy volunteers, mean age 37.27±7.83 years old (range 25-54 years old). As for their education, one participant completed vocational training, eight men finished high school and six men began or completed a university degree.

There were significant group differences in the marital status – in the index group only one patient was married, the rest of them were single, living in most cases with their parents. In the study group the vast majority (73.33%) was married, one participant was divorced and three were bachelors.

Control group performed better in all neuropsychological tests (for details see Table 1).

It is worth noticing that in both parts of TMT and Stroop Test lower scores are reflecting shorter time required to complete the task and indicate better cognitive functioning (i.a. psychomotor speed, attention switching, recall). Conversely, in Verbal and Semantic Fluency Tests, higher scores, i.e. more words in three minutes, show better functioning (i.a. memory, attention and verbal fluency). In our study, statistically significant differences were observed in semantic fluency (40.13±8.61 vs 48.80±11.93; p=0.036) and Stroop Task part 2 (234.73±54.81 vs 178.86±40.93; p=0.003). The difference in TMT Part B was also prominent, however it did not reach statistical significance (110.26±49.34 vs 78.00±37.57; p=0.054).

Table 1. A comparison of the results of cognitive functions tests in the index and control groups. Results are presented as means ± standard deviation. P value <0.05 is considered significant and marked with an asterisk

	Index group	Control group	P
TMT A (s)	32.8±7.94	30.33±10.88	0.240
TMT B (s)	110.26±49.34	78.00±37.57	0.054
Stroop Test 1 (s)	74.46±13.13	77.00±14.32	0.690
Stroop Test 2 (s)	234.73±54.81	178.86±40.93	0.003*
Verbal Fluency Test (words/3 minutes)	28.26±10.58	33.67±13.61	0.290
Semantic Fluency Test (words/3 minutes)	40.13±8.61	48.80±11.93	0.036*

Table 2. Serum levels of TSH, estradiol, FSH, LH, progesterone, testosterone and prolactin in male patients with chronic schizophrenia and healthy controls. Results are presented as means ± standard deviation. P value <0.05 is considered significant and marked with an asterisk

	Index group	Control group	P
TSH (mIU/L)	1.76±1.08	1.58±0.95	0.660
Estradiol (pg/ml)	24.36±9.32	25.40±7.43	0.640
FSH (mIU/ml)	3.17±1.17	5.72±4.54	0.019*
LH (mIU/ml)	3.85±2.29	5.77±3.25	0.056
Progesterone (ng/ml)	0.85±0.35	0.69±0.27	0.220
Testosterone (ng/ml)	2.90±1.51	5.38±2.15	0.003*
Prolactin (uIU/ml)	558.71±542.19	181.00±54.50	0.025*

Table 3. Correlations between levels of hormones and cognitive functions tests results. Correlations are expressed with the Spearman's rank correlation coefficient (ρ). ρ<0 indicates an inverse correlation, and ρ>0 a positive correlation. Statistically significant correlations are marked with an asterisk

	TSH (mIU/L)	Estradiol (pg/ml)	FSH (mIU/ml)	LH (mIU/ml)	Progesterone (ng/ml)	Testosterone (ng/ml)	Prolactin (uIU/ml)
Both groups							
TMT A	0.059806	-0.042428	0.133296	-0.261276	0.112052	-0.176503	-0.129384
TMT B	0.045080	-0.000890	-0.050417	-0.292743	-0.157965	-0.289149	0.095259
Verbal Fluency Test	-0.161172	0.206482	0.043992	0.150813	-0.210093	0.236998	-0.372606*
Categorial Fluency Test	-0.350791	0.092479	0.089137	0.081012	-0.322635	0.155209	-0.150178
Stroop Test 1	0.217285	-0.328508	0.035078	-0.156810	-0.492649*	-0.160579	-0.130052
Stroop Test 2	0.123971	-0.241349	-0.126182	-0.113065	-0.133111	-0.342050	-0.102136
Index group							
TMT A	0.375112	-0.100179	0.289804	-0.389785	-0.198925	0.209490	-0.579607*
TMT B	0.003575	-0.125000	0.117857	-0.407872	-0.586763*	-0.226988	-0.042857
Verbal Fluency Test	0.063620	0.125336	-0.127127	0.007175	-0.306727	0.115592	-0.420771
Categorial Fluency Test	-0.409499	0.130708	-0.678606	-0.111211	-0.294171	-0.227599	0.055506
Stroop Test 1	0.264758	-0.398570	0.226988	-0.420770	-0.701880*	-0.241503	-0.230563
Stroop Test 2	0.323503	-0.392857	0.078571	-0.220036	-0.601074*	-0.296694	-0.353571
Control group							
TMT A	-0.025090	0.060987	0.243729	-0.021506	0.290584	-0.222224	0.107528
TMT B	0.219839	0.166369	0.184093	0.148347	0.033989	-0.207328	-0.001787
Verbal Fluency Test	-0.293119	0.382826	0.146559	0.121537	-0.023256	0.241287	-0.332440
Categorial Fluency Test	-0.270855	0.129265	0.290586	-0.111212	-0.118493	0.012556	0.005381
Stroop Test 1	0.114490	-0.297225	-0.094812	0.105546	-0.313339	-0.082290	0.073345
Stroop Test 2	-0.162645	-0.013417	0.110813	0.446828	-0.168157	0.078642	-0.554066*

There were also group differences in the level of hormones – the levels of TSH, progesterone and prolactin were higher in the index group, whereas the levels of estradiol, LH and testosterone were higher in the index group (see Table 2). The differences in the following hormone levels were statistically significant: FSH (3.17±1.17 vs 5.72±4.54; p=0.019), testosterone (2.90±1.51 vs 5.38±2.15; p=0.003) and prolactin (558.71±542.19 vs 181.00±54.50; p=0.025). Also, the level of LH was markedly lower in the index group (3.85±2.29) than in the control group (5.77±3.25), however the difference was not statistically significant (p=0.056).

In the next step, we correlated the level of all hormones and the results of all neuropsychological tests in the whole sample and also separately in the index group and control group using Spearman's rank correlation coefficient (for details see Table 3). In the sample as a whole, we found statistically significant negative correlations between Stroop 1 test (ρ=-0.492649) and verbal fluency test (ρ=-0.372606) and prolactin level. When divided into subgroups, in the index group we found significant negative correlations between: FSH and semantic fluency (ρ=-0.678606), progesterone and TMT B (ρ=-0.586763), progesterone and Stroop 1 (ρ=-0.701880), progesterone and Stroop 2 (ρ=-0.601074) and prolactin and TMT A (ρ=-0.579607). In the control group, the only significant correlation was found between prolactin and Stroop 2 (ρ=-0.554066).

DISCUSSION

Our study aimed at assessing the level of hormones (namely TSH, testosterone, estradiol, FSH, LH, progesterone and prolactin) in schizophrenic male patients, their cognitive functioning measured with certain neuropsychological tests and correlation between those variables. We found that the levels of TSH, progesterone and prolactin ($p<0.05$) were higher in the index group, whereas the levels of estradiol, FSH ($p<0.05$), LH and testosterone ($p<0.05$) were higher in the index group. The majority of studies which investigated endocrinological features of schizophrenia consistently reported lower level of testosterone in schizophrenic males compared to healthy controls (Taherianfard 2004, Huber 2005, Ashonzadekh 2006, Ko 2007, Van Rijn 2012), which stays in line with our findings. Testosterone level was also found to be inversely correlated with negative symptoms of schizophrenia, as measured with PANSS (Ko 2007). Ashonzadekh and colleagues (2006) assessed testosterone, FSH, LH, prolactin in 54 medicated patients divided into subgroups of non-predominant and predominant negative symptoms according to PANSS. Similarly to our study, the authors found significantly lower levels of testosterone and free testosterone in patients compared to controls. They also reported significantly lower levels of FSH and LH and higher of prolactin only in the group with predominant negative symptoms. As our patients presented mainly with negative symptoms, those findings are also consistent with our study. Lower testosterone level in males with schizophrenia compared to healthy controls was confirmed in several studies (Taherianfard 2004, Huber 2005) Additionally, it was observed, that level of testosterone measured in saliva is significantly lower in adolescents with pre-psychotic, prodromal symptoms as compared with healthy controls (Van Rijn 2012). Furthermore, studies have shown that exogenous testosterone supplementation may reduce negative symptoms in men with schizophrenia (Ko 2008). In contrast, Moore et al. (2013) did not find any significant difference in serum testosterone levels between a group of 29 chronically ill men with schizophrenia or schizoaffective disorder and 20 healthy controls. Testosterone levels were not related to positive or negative symptom severity. However, testosterone levels significantly predicted performance on verbal memory, processing speed, and working memory in men with schizophrenia, but not in healthy controls.

In contrast, some authors suggest that testosterone impacts cognitive function also in non-schizophrenic individuals (Cherrier 2005). In our study, cognitive functions were found to be related to progesterone, FSH and prolactin, but not to testosterone. Interestingly, progesterone is being rarely investigated in relation to cognitive functions in schizophrenic males. We were not able to identify any studies that found a similar relationship. Halari et al. (2004) investigated the effects of serum levels of estrogen, progesterone, testosterone and cortisol on neuropsychological functioning. No significant relationships were found for progesterone and testosterone, however the group reported that estrogen was associated with low positive symptom scores, and cortisol predicted poor performance on information processing in males.

The increased level of prolactin in our index group is largely due to antipsychotic medications, as all our patients were medicated. The majority of them (86.67%; n=13) were receiving antipsychotics with prolactin-raising potential (Risperidone, Olanzapine and Amisulpirid).

The major shortcoming of our study is a small study sample and the lack of female schizophrenic patients comparison group. However, this is an ongoing project and future plans include significantly expanding the study group and recruiting female patients.

CONCLUSIONS

We found that the levels of prolactin was significantly higher in the index group, whereas the levels of FSH and testosterone were markedly lower. In the index group, we found significant negative correlations between: FSH and categorial fluency; progesterone and TMT B, Stroop 1 and 2 and prolactin and TMT A. However, as those are preliminary results, it is too soon to draw any definite conclusions before further investigating the subject.

Acknowledgements:

The study was financed by the Silesian Medical University in Katowice

Conflict of interest: None to declare.

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Correspondence:
Agnieszka Bratek, MD
Department of Psychiatry and Psychotherapy
Independent Public Clinical Hospital No. 7 of Silesian Medical University
Ziołowa 45-47, Katowice, Poland
E-mail: agn.bratek@gmail.com