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Sexual differences in the clinical features of antipsychotic-induced hyperprolactinemia in patients with schizophrenia

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ABSTRACT

The goal was to identify gender differences in the clinical features of antipsychotic-induced hyperprolactinemia in patients with schizophrenia.

Materials and methods. 98 patients from the Department of Endogenous Disorders of the Research Institute of Mental Health Clinic in Tomsk were examined. Persons aged 18–50 were included with follow-up treatment for at least 1 year, whose condition corresponded to the ICD-10 schizophrenia criteria. Prolactin levels were determined by ELISA using the PRL Test System reagent kit (MonobindInc., USA). The base map of sociodemographic and clinical-dynamic features for patients with schizophrenia was used. Statistical processing of data was performed using the Statistica 12.0 software package. Mann–Whitney *U* test, Pearson's χI criterion, including Yates correction, and Fisher's two-sided test were used for comparing small samples.

Results. The average serum concentration of prolactin in women was 52.4 ± 39.1 ng/ml, in men it was 26.7 ± 19.7 ng/ml. Hyperprolactinemia was detected in 23 (47.9%) women and 25 (50%) men. Among women with hyperprolactinemia, statistically significant "Weight Gain" and "Headache" parameters were more common ($p = 0.044$ and $p = 0.005$, respectively). Men with hyperprolactinemia had higher BMI rates ($p = 0.0066$). For the rest of the UKU paragraphs, no significant differences were found in both men and women. Men presented fewer complaints and were less willing to discuss sexual dysfunction.

Conclusion. Antipsychotic-induced hyperprolactinemia in patients with schizophrenia does not always have a full range of specific clinical manifestations and needs careful examination of patients with account of gender characteristics, as well as regular monitoring of the prolactin level in the serum of patients.

Key words: schizophrenia, antipsychotic therapy, hyperprolactinemia.

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Conformity with the principles of ethics. All patients signed informed consent to participate in the study.The study was approved by the local Ethics Committee at the Mental Health Research Institute, Tomsk (NRMC) (Protocol No. 665 of 24.10.2016).

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Половые различия в клинических особенностях антипсихотик-индуцированной гиперпролактинемии у больных шизофренией

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РЕЗЮМЕ

Цель – выявление половых различий в клинических особенностях антипсихотик-индуцированной гиперпролактинемии у больных шизофренией.

Материалы и методы. Обследованы 98 больных из отделения эндогенных расстройств клиники НИИ психического здоровья г. Томска. Включались лица 18–50 лет с давностью катамнеза заболевания не менее 1 года, состояние которых соответствовало критериям шизофрении по МКБ-10. Определение пролактина проводили иммуноферментным методом с использованием набора реагентов PRL Test System (Monobind Inc., США). Применялись Базисная карта социодемографических и клинико-динамических признаков для больных шизофренией, шкала UKU в адаптированной русской версии. Статистическую обработку проводили с использованием пакета программ Statistica 12.0. Применяли непараметрический *U*-критерий Манна – Уитни, χI Пирсона, в том числе с учетом поправки Йейтса, для сравнения малых выборок был использован двухсторонний критерий Фишера.

Результаты. Средние показатели концентрации пролактина в сыворотке крови у женщин зафиксированы на уровне (52,4 ± 39,1) нг/мл, у мужчин – (26,7 ± 19,7) нг/мл. Гиперпролактинемия была выявлена у 23 (47,9%) женщин и 25 (50%) мужчин. У женщин с гиперпролактинемией статистически значимо чаще встречались показатели «прибавка в весе» и «головная боль» (p = 0,044 и p = 0,005 соответственно), у мужчин с гиперпролактинемией – более высокие показатели индекса массы тела (p = 0,0066). По остальным пунктам UKU значимых различий не выявлено как у мужчин, так и у женщин. Мужчины предъявляли меньшее количество жалоб и были менее доступны для обсуждения сексуальной дисфункции.

Заключение. Антипсихотик-индуцированная гиперпролактинемия у больных шизофренией не всегда проявляется полным спектром специфических клинических симптомов и нуждается в тщательном обследовании пациентов с учетом пола, а также в регулярном мониторинге уровня пролактина в сыворотке крови больных.

Ключевые слова: шизофрения, антипсихотическая терапия, гиперпролактинемия.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Все лица, включенные в выборку, дали информированное согласие на участие в исследовании. Исследование одобрено этическим комитетом НИИ психического здоровья, Томский НИМЦ (протокол № 665 от 24.10.2016).

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INTRODUCTION

The main treatment strategy for schizophrenia is psychopharmacotherapy, aimed at stopping acute conditions, reducing clinical manifestations, preventing relapses, improving the quality of life and ensuring the accessibility of psychosocial rehabilitation of patients [1-2]. Many atypical antipsychotics widely used in schizophrenia in recent years have high intrinsic antipsychotic efficacy, but at the same time, as do conventional ones, they cause pronounced endocrine disorders, including increased serum prolactin [3–4]. According to the literature, the incidence of hyperprolactinemia in patients with schizophrenia is up to 70–88%, depending on the variant of antipsychotic therapy [5–6].

Elevated serum prolactin levels in patients with schizophrenia are associated with the risk of serious complications such as osteoporosis and even cancer , as well as a number of other undesirable symptoms, in particular, amenorrhea, sexual dysfunction, and infertility. These disorders are not always detected by practicing psychiatrists, and hyperprolactinemia itself is considered as a secondary occurrence [7] in relation to therapeutic targets. Hyperprolactinemia has many specific and non-specific clinical manifestations. Most often, it is associated with sexual dysfunction, as well as an increase in body weight due to increased appetite [8]. However, it is known that the asymptomatic course of hyperprolactinemia is observed in 49% of schizophrenia patients with elevated serum prolactin levels [9]. Some of the symptoms are not recognized by doctors due to the reduced time for a thorough physical examination, including a somatoscopic one, due to the recent preference for instrumental and paraclinical methods. It is also known that most specialists do not ask questions about sexual problems in patients with schizophrenia in normal clinical conditions, mainly due to a lack of experience in conducting such interviews, and because the patients themselves feel shame or distrust of medical specialists, as a result of which these symptoms remain unrecognized [10]. Therefore, it is necessary to carefully study the association of hyperprolactinemia, detected using paraclinical methods, with the clinical symptoms of this neuroendocrine dysfunction in patients with schizophrenia, and it is especially important to take into account gender differences in order to develop personalized programs to prevent, partially or completely reduce hyperprolactinemia.

In the middle of the 20th century, M. Yules and M. Hollo [11] pointed out the need for a detailed somatoscopic examination of patients. For example, assessment of the skin (presence of striae, moisture, hair growth, distribution of adipose tissue), palpation of the mammary glands, testicles, thyroid region, and measurement of body weight, and taking past medical history. It was noted that for men it is especially important to conduct a survey on the topic of the intensity of sexual activity, and for women,the regularity of the menstrual cycle. This situation still remains relevant and serves as a reason, among other paraclinical studies, to monitor the level of hormones in the blood serum, in particular prolactin. Symptoms of hyperprolactinemia can be detected by doctors of various profiles, and among women, first of all, by gynecologists, so continuity and consistency between specialists is especially important.

In endocrinological practice, the specificity of clinical pictures is described for hyperprolactinemia caused by pituitary adenomas. So, most

often in women there is a combination of symptoms such as oligomenorrhea and galactorrhea, less frequent menstrual irregularities and headaches, as well as oligo- or amenorrhea along with weight gain and galactorrhea [12]. In men, first of all, there is a disturbance of libido and erectile dysfunction, as well as weight gain [13]. The spectrum of clinical manifestations of hyperprolactinemia in women with schizophrenia is wider compared to male patients [14]. However, there are practically no detailed descriptions of clinical portraits of patients with elevated prolactin levels in schizophrenia. In psychiatry, the well-known fact is that the less clinically manifested the symptoms of hyperprolactinemia are, the higher the level of depressive disorders and the less effective the antipsychotic therapy [15].

The purpose of the study was to identify gender differences in the clinical features of antipsychotic-induced hyperprolactinemia in patients with schizophrenia.

MATERIALS AND METHODS

The study was performed at the Department of Endogenous Disorders of the Mental Health Research Institute Clinic. The study was carried out in accordance with ethical standards developed in accordance with the Helsinki Declaration of the World Medical Association "Ethical Principles for the Conducting of Scientific Medical Research with Human Participation" as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order of the Ministry of Health of the Russian Federation dated June 19, 2003 No. 266.4

98 patients undergoing inpatient treatment and receiving antipsychotic therapy with conventional antipsychotics (haloperidol, zuclopentixol) or atypical antipsychotics (risperidone, olanzapine, quetiapine) at the recommended therapeutic doses that signed an informed consent for participation in the study were examined. Persons 18–50 years old with a disease history of at least 1 year, whose condition at the time of the examination corresponded to the diagnostic criteria for schizophrenia according to ICD-10 were included. The average age of patients was 36.6 ± 10.5 years, the age of the manifestation of the disease at the time of examination was 23.9 ± 6.4 years. There were 50 (51.0%) men and 48 (49.0%) women.

A study of the prolactin level in the blood serum of patients was usually carried out in the early days of hospitalization. Venous blood sampling from all examined individuals was carried out from 8:00 to 9:00; prolactin was determined by enzyme immunoassay using the PRL Test System reagent kit (Monobind Inc., USA) for the quantitative determination of serum hormone levels. For females of reproductive age, blood sampling was performed in the first phase of the menstrual cycle. Hyperprolactinemia was diagnosed with prolactin levels above 25 ng / ml in women and 20 ng / ml in men.

In all patients, a 6-week antipsychotic therapy was completed with a Side effectiveness scale (the Udvald for Kliniske Undersogelser Scale UKU) [16], which evaluated the clinical manifestations of hyperprolactinemia. An anthropometric study included measuring the height using a medical stadiometer and body weight with an Omron BF508 medical device (Japan) with determination of the body mass index.

Statistical processing was performed using the Statistica for Windows 12.0 software package (StatSoft Inc., USA). The nonparametric Mann – Whitney U-test and χI Pearson were used, including taking into account the Yeats correction, and to compare small samples, the two-sided Fisher test was used. The threshold value of the achieved significance level p was taken as 0.05.

RESULTS

The average serum prolactin concentration in women was fixed at 52.4 ± 39.1 ng / ml, in men 26.7 ± 19.7 ng / ml. Hyperprolactinemia was detected in 23 (47.9%) women and 25 (50%) men.

When studying body mass index indicators, statistically significant ($p = 0.0066$) higher rates were found in men with hyperprolactinemia than without hyperprolactinemia (27 (25.7; 35.2) and 25.5 (20.4; 28.3) respectively). Regarding these indicators in women, it was not possible to establish statistically significant differences in the studied groups (29 (23.3; 34.7) and 26.1 (22.6; 31.7), $p = 0.338$.

When analyzing UKU data on the frequency of occurrence of symptoms such as weight gain or weight loss over the past month in accordance with the prolactin levels in blood serum in men, no statistically significant differences were found ($p = 0.568$; $p = 0.189$, respectively). Among women with hyperprolactinemia, weight gain was present significantly more often (Table 1) than in patients without hyperprolactinemia ($p = 0.044$), and there were no statistical differences in the sub-item "weight loss" ($p = 0.275$).

Table 1

Comparative evaluation of UKU "Weight Gain" and "Weight Loss" categories by sex depending on the presence / absence of hyperprolactinemia

Parameter		Men, abs. (%)		Women, abs. (%)	
		without HPRL	with HPRL	without HPRL	with HPRL
UKU "Weight Gain"	Present	12 (54,5)	10 (45,5)	13 (68,4)*	6 (31,6)
	Absent	13 (46,4)	15 (53,6)	10 (34,5)	19 (65,5)
UKU "Weight Loss"	Present	(83,3)	1 (16,7)	3 (33,3)	6 (66,7)
	Absent	(45,5)	24 (54,5)	20 (51,3)	19 (48,7)

Note. Here and in Tables 2–9: HPRL – hyperprolactinemia, as. – absolute number.
* $p = 0.044$.

It was not possible to establish a connection between the presence of menorrhagia and hypomenorrhea in women with hyperprolactinemia over the past 3 months ($p = 0.469$ and $p = 0.571$, respectively).

Although hypomenorrhea was more often recorded, its frequency in the two studied groups (with the presence of 11 (44.0%) and the absence of 14 (56.0%) hyperprolactinemia) was approximately the same (Table 2).

Table 2

Comparative evaluation of UKU "Menorrhagia" and "Hypomenorrhoea" categories in women depending on the presence / absence of hyperprolactinemia

Parameter		HPRL, abs. (%)	without HPRL, abs. (%)
UKU "Menorrhagia"	Present	3 (60,0)	2 (40,0)
	Absent	20 (46,5)	23 (53,5)
UKU "Hypomenorrhoea"	Present	11 (44,0)	14 (56,0)
	Absent	12 (52,2)	11 (47,8)

The presence of galactorrhea was assessed in both men and women (outside the period of breastfeeding). Among men, not a single case of increased secretion of mammary glands at the time of the examination was recorded, which did not imply statistical processing. Five cases were identified among women, while three of them (60.0%) showed an increased level of prolactin in the blood serum ($p = 0.291$).

On physical examination, the presence of gynecomastia was detected in 10 men (Table 3), hyperprolactinemia was detected in 7 (70%) patients ($p = 0.289$).

One of the indicators assessed by UKU in the studied groups was libido. Approximately half of the examined individuals with hyperprolactinemia reported a decrease in sexual desire - 12 (44.4%) and 13 (52.0%), respectively, but no statistically significant differences were found in the groups (Table 4).

Among the examined men (Table 5) with hyperprolactinemia, 10 people (55.6%) reported a disturbance of the occurrence and maintenance of an erection and 8 (44.4%) did not have an increase in the concentration of prolactin in the blood serum ($p = 0.768$). In most cases, during the collection of complaints a lot of leading questions had to be asked; male patients experienced noticeable worriedness, tried to avoid answers, however, in the process of targeted questioning, it was possible to identify a number of symptoms of sexual dysfunction.

Table 3

Comparative evaluation of "Gynaecomastia" category values in men depending on the presence / absence of hyperprolactinemia

Parameter		HPRL, abs. (%)	without HPRL, abs. (%)
UKU "Gynaecomastia" category	Present	7 (70,0)	3 (30,0)
	Absent	18 (45,0)	22 (55,0)

Table 4

Comparative evaluation of UKU "Increased Sexual Desire" and "Diminished Sexual Desire" categories by sex, depending on the presence / absence of hyperprolactinemia

Parameter		Men, abs. (%)		Women, abs. (%)	
		Без ГПРЛ without HPRL	ГПРЛ HPRL	Без ГПРЛ without HPRL	ГПРЛ HPRL
"Increased Sexual Desire" category	Есть Present	4 (50,0)	4 (42,)	4 (57,1)	3 (42,9)
	Нет Absent	21 (50,0)	21 (50,0)	19 (46,3)	22 (53,7)
UKU "Diminished Sexual Desire" category	Есть Present	12 (44,4)	15 (55,6)	13 (52,0)	12 (48,0)
	Нет Absent	13 (56,5)	10 (43,5)	10 (43,5)	13 (56,5)

Table 5

Comparative evaluation of UKU "Erectile Dysfunction" category values in men depending on the presence / absence of hyperprolactinemia

Parameter		HPRL, abs. (%)	without HPRL, abs. (%)
UKU "Erectile Dysfunction" category	Present	10 (55,6)	8 (44,4)
	Absent	15 (46,9)	17 (53,1)

Men rarely reported impaired ability to control ejaculation (Table 6). Among individuals with elevated prolactin levels, this disorder was detected in 6 (46.2%) patients; it was also observed in patients with normal prolactin levels 7 (53.8%), $p = 1.0$.

Regardless of the serum prolactin level, the same number of men ($p = 1.0$) reported a disturbance of the ability to receive and fully experience a satisfying orgasm. In women, statistically significant differences were also not established ($p = 0.940$), most of them reported the absence of orgasm disorders (Table 7).

The lack of natural moistening of the vagina during sexual stimulation was detected in 13 women examined (Table 8), while an increased serum prolactin level was found in 6 (46.2%) patients. Significant statistical differences in the compared groups were not detected ($p = 0.860$).

Women were significantly more often bothered by headaches in the presence of hyperprolactinemia ($p = 0.005$), men presented this complaint equally (Table 9) both in the group with hyperprolactinemia and in the group without it ($p = 0.568$).

DISCUSSION

The results of the study showed that the spectrum of clinical manifestations of hyperprolactinemia in women with schizophrenia receiving antipsychotic therapy was more diverse and wider than in male patients, recorded both by the UKU and the scope of complaints.

Table 6

Comparative evaluation of UKU "Ejaculatory Dysfunction" category values in men depending on the presence / absence of hyperprolactinemia

Parameter		HPRL, abs. (%)	without HPRL, abs. (%)
UKU "Ejaculatory Dysfunction" category	Present	6 (46,2)	7 (53,8)
	Absent	19 (51,4)	18 (48,6)

Table 7

Comparative evaluation of UKU "Orgasmic Dysfunction" category values by sex, depending on the presence / absence of hyperprolactinemia

Parameter		Men, abs. (%)		Women, abs. (%)	
		without HPRL	HPRL	without HPRL	HPRL
UKU "Orgasmic Dysfunction" category	Present	11 (50,0)	11 (50,0)	8 (44,4)	10 (55,6)
	Absent	14 (50,0)	14 (50,0)	15 (50,0)	15 (50,0)

Table 8

Comparative evaluation of UKU "Vaginal Dryness" category values in women depending on the presence / absence of hyperprolactinemia

Parameter		HPRL, abs. (%)	without HPRL, abs. (%)
UKU "Vaginal Dryness" category	Present	6 (46,2)	7 (53,8)
	Absent	17 (48,6)	18 (51,4)

Table 9

Сравнительная оценка показателей пунктов UKU «головные боли» по полу в зависимости от наличия или отсутствия гиперпролактинемии

Comparative evaluation of UKU "Headache" category values by sex depending on the presence / absence of hyperprolactinemia

Показатель Parameter		Мужчины, абс. (%) Men, abs. (%)		Женщины, абс. (%) Women, abs. (%)	
		Без ГПРЛ without HPRL	ГПРЛ HPRL	Без ГПРЛ without HPRL	ГПРЛ with HPRL
UKU «головные боли» UKU "Headache" category	Есть Present	15 (53,6)	13 (37,5)	20 (62,5) *	12 (37,5)
	Нет Absent	10 (45,5)	12 (54,5)	3 (18,7)	13 (81,3)

* $p = 0{,}005$.

Thus, among women with schizophrenia and antipsychotic-induced hyperprolactinemia, a statistically significantly larger number of people complaining of headaches was noted. In addition, they more often recorded weight gain in the UKU for this adverse event. In men with hyperprolactinemia, a higher body mass index was found in the absence of subjective complaints of weight gain, but there were no differences in any symptoms recorded by the UKU depending on the presence or absence of hyperprolactinemia. This may be due to a higher level of prolactin in

the blood serum of women, on the one hand, and less accessibility of the male part of the sample to discuss issues related to sexual activity, on the other.

This phenomenon is explained by the fact that the internal locus of control (internality) is of greater importance for men than for women [17]. In this regard, it can be stated that the collection of information in men is more difficult, since they tend to limit externalities. Therefore, it seems advisable, before conducting a clinical interview for men, in addition to the informed consent procedure, to remind about the confidentiality of the information provided and other ethical principles in order to overcome the patient's irrational fears of "seeming weak", taking into account the specifics of men's upbringing in the Russian population and the social and environmental factors that form the taboo regarding discussion of the sexual sphere. The doctor's comment that "the patient will significantly help in the treatment process if he is open and honest in the answers" will also be important. Such an approach will help him shift communication from an integrated focus to an external vector of interaction.

CONCLUSION

Antipsychotic-induced hyperprolactinemia in patients with schizophrenia does not always manifest a full range of specific clinical symptoms, which confirms the need for a thorough examination of patients taking into account gender differences and regular monitoring of prolactin levels in the blood serum of patients in order to timely correct this undesirable phenomenon.

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