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COGNITIVE IMPAIRMENTS IN FUNCTIONAL HYPERPROLACTINEMIA (FHPRL) IN WOMEN OF REPRODUCTIVE AGE DEPENDING ON THE LEVEL AND DURATION OF FHPRL: RESULTS OF A CROSS-SECTIONAL STUDY.

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Abstract

Hyperprolactinemia (HPRL) remains one of the most common endocrinopathies of the reproductive system in women of childbearing age, accompanied by menstrual cycle disorders, reproductive dysfunction, and metabolic disturbances [1, 2]. In clinical practice, the functional form of the disease predominates, the diagnosis of which requires a differentiated approach with exclusion of organic causes of prolactin hypersecretion [3, 4]. Despite well-studied effects of hyperprolactinemia on the reproductive system, the question of the influence of elevated prolactin (PRL) levels on the central nervous system and, in particular, on cognitive functions, remains insufficiently covered in domestic and world literature. Existing data indicate possible neurovegetative symptoms, depression, anxiety, and sleep disorders in patients with HPRL [5, 6]. However, specific cognitive deficits, their pathophysiological mechanisms, and correlation with the level and duration of hyperprolactinemia have been studied fragmentarily. In this article, we present our own research conducted at the Research Institute of Endocrinology depending on the level and duration of fHPRL.

Keywords

hyperprolactinemia, functional hyperprolactinemia, cognitive impairment, prolactin, neuroendocrinology, women of reproductive age, memory dysfunction, attention deficit, visuospatial impairment, hormonal imbalance, dopaminergic system, oxidative stress, metabolic syndrome, cross-sectional study, neurocognitive testing.

Intraduction

The relevance of the topic is determined by several factors. First, modern neuroendocrinology considers prolactin not only as a lactation hormone, but also as a neuromediator involved in the regulation of memory, emotions, and behavior [7, 8]. Experimental studies have demonstrated the expression of prolactin receptors in the hippocampus, prefrontal cortex, and amygdala, confirming their role in cognitive processes [9, 10]. Second, cognitive impairments can significantly reduce the quality of life of patients, limit their social and professional activity, and enhance anxiety-depressive symptoms, which requires systematic assessment and correction [11, 12].

The aim of the present study was to investigate the nature and structure of cognitive disorders in women of reproductive age with functional hyperprolactinemia, as well as to determine the correlation between the severity of cognitive impairments, serum prolactin levels, and disease duration.

Materials and Methods, Recearch Design:A cross-sectional clinical-neurological study was conducted using validated neuropsychological scales. The examination was performed from 2019 to 2023 at Tashkent State Medical University at the base of the Republican Specialized Scientific and Practical Medical Center of Endocrinology involving 200 patients with an established diagnosis of "functional hyperprolactinemia" (fHPRL) aged 18 to 40 years (mean age 31.2 ± 4.8 years). The control group consisted of 20 healthy women of corresponding age with normal prolactin levels (4.8–23.0 ng/ml) and without clinical manifestations of hyperprolactinemia.

Inclusion criteria: - Established diagnosis of functional HPRL (non-tumor genesis) with elevated serum PRL levels above 25 ng/ml;

- Age 18–40 years;

- Absence of organic causes of hyperprolactinemia (according to pituitary MRI data, as well as with normal visual acuity without field defect);

- Informed consent to participate in the study.

Exclusion criteria:

- Organic brain diseases (all types of brain tumors);

- History of traumatic brain injury, brain surgery, patients undergoing radiation therapy, epilepsy;
- Thyroid pathology;
- Depressive and anxiety disorders of moderate and severe degree according to HADS, MADRS scales;
- Use of medications affecting cognitive functions;
- Alcohol and drug abuse;
- Pregnancy and lactation.

To analyze the influence of prolactin levels, the studied patients were conditionally divided into three groups:

Group 1 (n=61): mean PRL level 27.0–34.9 ng/ml;

Group 2(n=86): mean PRL level 35.0–44.9 ng/ml;

Group 3 (n=53): mean PRL level ≥45.0 ng/ml.

To assess the influence of disease duration, parallel subgroups were formed:

Group 1 (n=79): HPRL duration 0–2 years;

Group 2 (n=72): HPRL duration 2–4 years;

Group 3 (n=49): HPRL duration more than 4 years.

The following diagnostic methods were used to assess the condition of patients:

Prolactin level assessment was performed by enzyme immunoassay (EIA) using the "Prolactin-ELISA" test system (Biomerica, USA) on a Stat Fax 2100 analyzer. Blood was drawn fasting during the follicular phase of the menstrual cycle (days 3–5). The control PRL level was determined three times at 2-week intervals when refusing provocative factors.

Neurocognitive testing was conducted using two validated international tests:

1.Mini-Mental State Examination (MMSE) – a screening test for assessing global and deep cognitive functions, including orientation, registration, attention and calculation, recall, language functions, and constructive praxis. Maximum score – 30 points. Cognitive impairments were determined at values ≤24 points [13, 14].

2. Montreal Cognitive Assessment (MoCA) – a more sensitive test for detecting mild cognitive impairments, assessing attention, executive functions, memory, language, visuospatial abilities, conceptual thinking, and orientation. Maximum score – 30 points. Cognitive impairments at values <26 points [15, 16].

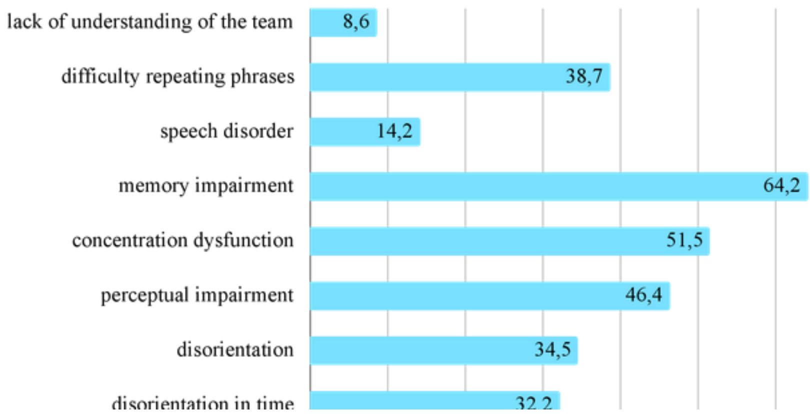
Testing was conducted by a qualified neuropsychologist in standardized conditions during morning hours (9:00–12:00) with exclusion of the influence of circadian fluctuations of cognitive functions.

Statistical processing was performed using SPSS Statistics 26.0 package (IBM, USA). Data distribution normality was checked using the Shapiro-Wilk test. For quantitative variables with normal distribution, arithmetic mean (M) and standard deviation (SD) are presented. Intergroup comparisons were performed using one-way analysis of variance (ANOVA) with subsequent Tukey post-hoc test. To assess correlation relationships, Pearson (r) and Spearman (ρ) correlation coefficients were used. The level of statistical significance was set at $p < 0.05$.

The following results were obtained:

Structure of Cognitive Impairments According to MMSE Data: Analysis of the frequency of cognitive deficits in 200 patients with fHPRL revealed the following structure of impairments (Fig. 1). Memory impairment (perception and delayed recall of memorized words) was diagnosed in 128 patients (64.2%). Concentration deficit (serial subtraction of sevens) was found in 103 women (51.5%). Perception impairments (copying figures) were noted in 93 patients (46.4%). Difficulties in orientation to place and time were found in 69 (34.5%) and 65 (32.2%) patients, respectively. Errors in phrase repetition were made by 77 women (38.7%). Speech impairments (naming objects) were found in 28 patients (14.2%). Misunderstanding of commands was recorded in 17 patients (8.6%). Thus, the dominant cognitive deficits in fHPRL were memory, attention, and visuospatial function impairments, indicating involvement of frontotemporal and parietal areas of the cerebral cortex in the pathological process.

Fig. 1. Frequency of cognitive disorders in examined patients with functional hyperprolactinemia according to MMSE data*



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As the results showed, patients with fHPRL had various cognitive function impairments in the form of memory decline (64.2%), attention concentration disorders (51.5%), and perception disorders (46.4%). Errors were made in phrase repetition (38.7%), orientation to place (34.5%), and time (32.2%). Also, patients experienced difficulties in perception and delayed recall of memorized words (46.4% and 38.7%, respectively).
Influence of Prolactin Level on Cognitive Function.
Comparative analysis of mean MMSE scores depending on the degree of hyperprolactinemia demonstrated a significant decrease in indicators as PRL levels increased (Table 1).

Table 1. Mean MMSE Scores in Patients with HPRL Depending on Prolactin Level (M ± SD)

Groups	Total	MMSE Test, points	Control n=20
1st gr. PRL: 27-34.9 ng/ml	n=61	26.5 ± 2.8	29.3 ± 1.2
2nd gr. PRL: 35-44.9 ng/ml	n=86	25.4 ± 3.1	
3rd gr. PRL: 45 and more ng/ml	n=53	22.6 ± 3.1*	

*Note: * – significance of differences between Group 3 and Group 1 (p < 0.05).*

Analysis of the data indicates that Group 3 with PRL level ≥45 ng/ml showed pronounced cognitive disorders (22.6 ± 3.1 points), corresponding to a predementia syndrome. At the same time, Groups 1 and 2 showed moderate cognitive function decline without statistically significant intergroup differences. However, the trend toward progressive deterioration of cognitive indicators as PRL levels increase has a clear dose-dependent direction (trend analysis, p < 0.001). Similar results were obtained when assessed using the Montreal Scale (MoCA) (Table 2).

Table 2. Mean MoCA Scores in Patients with HPRL Depending on Prolactin Level (M ± SD)

Groups	Total	Montreal Scale, Mean Points	Control n=20
1st gr. PRL: 27-34.9 ng/ml	n=61	22.1 ± 2.7*	29.3 ± 4.3
2nd gr. PRL: 35-44.9 ng/ml	n=86	20.8 ± 3.8**	
3rd gr. PRL: 45 and more ng/ml	n=53	19.5 ± 2.6**	

*Note: * – significance of differences, where *- p < 0.05; **- p < 0.01*

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MoCA data demonstrate higher sensitivity in detecting mild cognitive impairments compared to MMSE. A decrease in mean score by 9.8 units in Group 3 compared to control indicates significant involvement of executive functions, visuospatial abilities, and conceptual thinking. Next, we established the relationship between HPRL duration and cognitive impairments. Analysis of the relationship between disease duration and cognitive indicators revealed prognostically significant patterns (Table 3).

Table 3 – Mean MMSE Scores of Patients Depending on HPRL Duration

Groups	Total	MMSE Test, points	Control n=20
1st gr. 0-2 years	n=79	27.5 ± 2.8	29.3 ± 1.2
2nd gr. 2-4 years	n=72	23.4 ± 2.1*	
3rd gr. more than 4 years	n=49	19.6 ± 2.1***	

*Note: * – p < 0.05, ** – p < 0.01, *** – p < 0.001 compared to control.*

As the results showed, in Group 1 with disease duration up to 2 years, there were no cognitive function impairments, while in Groups 2 and 3, cognitive function impairments were noted from moderate in Group 2 (23.4 ± 2.1 points, p < 0.05), to pronounced changes in patients in Group 3 with HPRL duration of 4 or more years (19.6 ± 2.1 points, p < 0.01).

Table 4. – Mean MoCA Scores in Patients Depending on HPRL Duration (M ± SD)

Groups	Total	Montreal Scale, Mean Points	Control n=20
1st gr. 0-2 years	n=79	23.7 ± 1.9**	29.3 ± 1.2
2nd gr. 2-4 years	n=72	19.6 ± 2.8**	
3rd gr. more than 4 years	n=49	16.5 ± 2.1***	

*Note: * – significance of differences, where *- p < 0.05; *- p < 0.01*

A key fact is the absence of significant cognitive impairments in Group 1 with disease duration up to 2 years when assessed by MMSE (27.5 ± 2.8 points), while MoCA already revealed significant changes (23.7 ± 1.9 points, p < 0.01). This confirms the increased sensitivity of MoCA to subclinical cognitive deficits in the early stages of the disease.

In Group 3 with HPRL duration of more than 4 years, pronounced cognitive function decline was recorded, corresponding to mild cognitive dysfunction syndrome (ICD G31.84) by MMSE (19.6 ± 2.1 points) and moderate cognitive dysfunction by MoCA (16.5 ± 2.1 points). Progressive deterioration of indicators with increasing disease duration has a clear temporal dynamic (p < 0.001 in trend analysis). Conducted correlation analysis revealed a high positive relationship between HPRL duration and cognitive indicators: MoCA ($r = -0.76$, $p < 0.001$) and MMSE ($r = -0.72$, $p < 0.001$). Statistically significant correlation between PRL level and cognitive scores was moderate ($r = -0.48$ for MoCA, $p < 0.01$; $r = -0.42$ for MMSE, $p < 0.05$), indicating a stronger influence of disease chronicity compared to hormone level.

Results and Their Discussion:

The obtained data allow us to assert that functional hyperprolactinemia is a significant risk factor for the development of cognitive impairments in women of reproductive age. The identified structure of deficits (predominant damage to memory, attention, and visuospatial functions) correlates with data on the pathogenesis of HPRL at the neuronal level.

What is this related to?

First: Pathophysiological Mechanisms.Modern concepts of the mechanisms of neurotoxic action of prolactin include several theoretical concepts. First, hyperprolactinemia is accompanied by decreased dopamine secretion in the mesolimbic and mesocortical systems due to stimulation of hypothalamic dopaminergic neurons (tonic inhibitory control) [17, 18]. Dopamine deficiency in the prefrontal cortex and hippocampus leads to dysregulation of working memory and attention processes [19, 20].

Second, it has been experimentally proven that chronic hyperprolactinemia induces oxidative stress in hippocampal neurons with increased production of free radicals and decreased activity of antioxidant enzymes [21, 22]. This causes neurodegenerative changes and impaired synaptic plasticity, which clinically manifests as memory and learning deficits.

Third, hyperprolactinemia is associated with metabolic syndrome, insulin resistance, and dyslipidemia [23, 24], which are independent factors of brain vascular damage and development of cognitive dysfunctions [25, 26]. The correlation we found between disease duration and cognitive impairments may reflect the cumulative effect of metabolic disorders on cerebral hemodynamics and neuronal integrity.

*Comparative Sensitivity of Diagnostic Scales:*An important result of the study is the demonstration of MoCA advantages over MMSE in detecting subclinical cognitive impairments in the early stages of HPRL. In the group with disease duration up to 2 years, MMSE did not reveal significant changes (27.5 ± 2.8 points), while MoCA already showed a significant deficit (23.7 ± 1.9 points, $p < 0.01$). This is consistent with literature data on the greater sensitivity of MoCA to mild cognitive impairments due to the inclusion of tasks on executive functions and fluency [27, 28].

The identified positive correlation between HPRL duration and cognitive indicators (r = –0.76 for MoCA) exceeds in magnitude the correlation with PRL level (r = –0.48), indicating the importance of disease chronicity. This may be explained by neuroplastic changes developing during prolonged hyperprolactinemia, including reduction of D1 and D2 dopamine receptor density in the prefrontal cortex and striatum, which has been proven in experimental models [29, 30].

In the group with duration of more than 4 years, 41 patients (83.7%) showed MMSE values <24 points, which corresponds to the criteria for cognitive disorders requiring differential diagnosis with early stages of neurodegenerative diseases. This necessitates the inclusion of neuropsychological testing in the standard algorithm for examining patients with chronic HPRL.

The obtained results are consistent with literature data by Yamada et al. (2019), who demonstrated a correlation between PRL level and hippocampal volume in patients with functional HPRL [31]. Results by Ferrero et al. (2020) also confirm the presence of working memory and attention deficits in patients with severe hyperprolactinemia [32]. However, our study was the first to systematically assess the influence of disease duration on the structure of cognitive impairments in the Central Asian population, where currently a large part of women of childbearing age hold managerial and important leadership positions at enterprises, which increases its clinical significance.

Conclusion

In conclusion, we would like to note that:

1. Functional hyperprolactinemia in women of reproductive age is associated with the development of polymorphic cognitive impairments, the dominant components of which are memory deficit (64.2%), attention (51.5%), and visuospatial functions (46.4%).

2. The severity of cognitive disorders correlates with prolactin level: at PRL values ≥45 ng/ml, pronounced cognitive impairments are noted (MMSE 22.6 ± 3.1 points), corresponding to a predementia syndrome.

3. The duration of hyperprolactinemia is a more significant predictor of cognitive impairments than PRL level (r = –0.76 versus r = –0.48). With disease duration of more than 4 years, pronounced cognitive dysfunctions are revealed (MoCA 16.5 ± 2.1 points), requiring differential diagnosis with neurodegenerative pathology.

4. The Montreal Cognitive Assessment Scale (MoCA) demonstrates superior

sensitivity to subclinical cognitive impairments in the early stages of HPRL compared to MMSE. 5 . The research results justify the necessity of including neuropsychological testing in the standard algorithm for examining patients with chronic hyperprolactinemia for early detection of cognitive deficits and timely correction.

Practical Recommendations: Based on the obtained data, it is recommended:

- Inclusion of cognitive function screening (MoCA) in the examination protocol for all patients with HPRL duration of more than 2 years;

- Early initiation of drug correction of HPRL in the presence of cognitive impairments regardless of reproductive symptoms;

- Differential diagnosis with depression and anxiety disorders masquerading as cognitive deficits;

- Cognitive impairments in patients with long-standing hyperprolactinemia and pronounced cognitive impairments with antiprolactin therapy for 6 months improve much more effectively.

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