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MODERN APPROACHES TO THE TREATMENT OF PROLACTINOMAS IN WOMEN

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ABSTRACT:

Hyperprolactinemia syndrome is one of the most common neuroendocrine disorders. In 60% of cases, hyperprolactinemia outside lactation is caused by lactotrophic adenomas of the pituitary gland (prolactinomas), which account for about 40% of all pituitary adenomas. The incidence of prolactinomas, on average, ranges from 6 to 10 new cases per 1 million adult population per year. The article is dedicated to topical issues of the treatment of prolactinomas.

KEYWORDS: Prolactin, hyperprolactinemia, hypophysis, macroprolactinoma, micro prolactinoma, cabergolin, clomiphene citrate.

INTRODUCTION:

Prolactinoma is the most common pituitary tumor (about 40%). The annual morbidity rate ranges from 6-10 to 50 cases per 1 million population, and its average prevalence in women is 30 cases per 100,000 population [1, 5]. Most often, the disease is registered in women aged 20-50 years (the peak prevalence is 25-34 years). More than 90% of prolactinomas are microprolactinomas (<1.0 cm in diameter), while the rest are macroprolactinomas (≥1.0 cm) [2, 15].

The goals of treatment of patients with prolactinoma are as follows: normalization of prolactin levels; reduction of tumor size; elimination of symptoms of hyperprolactinemic hypogonadism and restoration of fertility; prevention of recurrence and resumption of tumor growth.

In the treatment of hyperprolactinemic conditions, 3 generations of drugs can be distinguished. Preparations of the first generation – Bromocriptine, Lizurid, Pergolide, Terguride, Abergin [4, 7, 11].

In 1982, a third – generation dopamine agonist, cabergoline, was introduced. This is ergoline selective agonist of D2-dopamine receptors, with a long half-life and pronounced prolactin-inhibiting activity. The drug has a prolonged effect – a decrease in the level of PRL in blood plasma

is noted 3 hours after administration and persists for 7-28 days in patients with hyperprolactinemia. The initial dose is 0.5 mg (1 tablet) in two doses (1/2 tablet 2 times a week) with a meal for 4 weeks, followed by monitoring the blood PRL level and, if necessary, "titrating" the dose [7, 8, 9]. Control of the PRL level is carried out after 4 weeks, followed by titration of the dose if necessary: if the PRL level has not normalized, the weekly dose is increased by 0.5 mg at intervals of 4 weeks until the prolactin level normalizes. Usually, the average therapeutic dose is 0.5-1.5 mg per week. Side effects include nausea, headache, low blood pressure, dizziness, abdominal pain, dyspeptic symptoms, weakness, constipation. Usually, these symptoms are mild or moderate, appear during the first two weeks of treatment and then go away on their own, without being a reason to stop treatment. Many authors have shown that cabergoline normalizes the blood prolactin content in women and men in 86-92%, causes regression микроаденомof pituitary microadenomas in 16-74%, macroadenomas in 44-91%, and promotes ovulation restoration in 67-89% of cases [10, 12]. Described cases the effectiveness of cabergoline in the giant prolactinomas and adenomas of the mixed genesis. Cabergoline therapy normalizes metabolism, improves blood lipid profile, and reduces weight [14, 15]. The average frequency of adverse events associated with cabergoline administration varies from 13 to 70% in different studies [6, 16].

Among patients with prolactinomas, there are a certain number of patients with tumor resistance to dopamine agonists. Clinically, this is manifested by the preservation of an increased level of bioactive BPD against the background of maximum tolerated doses of dopamine agonists and the absence of a 50% reduction in the tumor size from the initial one. In patients with resistant prolactinomas, it is recommended to increase the dose of the drug to the maximum tolerable one. If bromocriptine is intolerant, it should be replaced with cabergoline or another dopamine agonist [15, 16].

Surgical treatment is required for a small number of patients and is not the method of choice for prolactin treatment. Indications for surgical intervention are: increase in the size of the tumor, despite optimal treatment; pituitary apoplexy; intolerance to a medical therapy; macro prolactinoma, which resistant to treatment with dopamine agonists; macroadenoma patients planning pregnancy; compression of the optic chiasm, remaining on the background of drug therapy; a prolactinoma cystic component, are resistant to treatment; liquorrhea on the background of the reception of dopamine agonists; macroadenoma patients with mental diseases in the presence of contraindications to the appointment of dopamine agonists [16, 17]. Tumor removal can be performed by transcranial or transsphenoidal access [16].

In the case of partial removal of the adenoma combined treatment is indicated: use of dopamine agonists or radiation therapy [3,14]. Since the positive effect after irradiation of pituitary adenoma develops gradually and it takes up to 12-18 months to develop the full effect12-18, as well as due to complications (brain tissue necrosis, damage to the optic nerves, in the long term-hypopituitarism as a result of radiation damage to the hypothalamus), лучевая prolactin radiation therapy is used in exceptional cases: as an additional effect after surgery in patients when a

large volume of tumor tissue remains; ineffectiveness and intolerance of drug therapy; in patients who are contraindicated for surgery or who refuse surgical treatment [15, 17].

With normalization of the content of PRL in the blood, but the absence of ovulation, ovulation induction is performed-clomiphene 50-100 mg from the 5th to the 9th day of the menstrual cycle. In the absence of ovulation, an additional ovulatory dose of human chorionic gonadotropin is prescribed-7500-10000 units. in the presence of a dominant follicle of 18-20 mm. Given the decrease in progesterone levels in hyperprolactinemia, it is advisable to prescribe Progestogens in the second phase of the cycle (Duphaston 20 mg /day or utrogestan 200 mg /day from the 16th to the 25th day of the menstrual cycle). In the absence of pregnancy, surgical laparoscopy (PCOS, endometriosis) is indicated. The effectiveness of infertility treatment in hyperprolactinemia is determined by the level of gonadotropins. The maximum effect of infertility treatment was obtained with a low level ofgonadotropins-80.6%, in patients with a high level of gonadotropins, the reproductive function is not restored [18, 19]. During pre-gravidas preparation for pregnancy, all women planning pregnancy should undergo pituitary imaging (MRI or CT), as well as visual field assessment [20]. During treatment with dopamine agonists, barrier contraception is recommended, since fatality is restored fairly quickly when the level of PRL normalizes. In patients with micro - and macroprolactinomas that are resistant to dopamine agonists or who are intolerant to this treatment, it is advisable to consider surgical treatment before pregnancy [18, 20]. The growth of macroprolactinomas during pregnancy occurs in 31% of cases, and after pre-gestational surgical treatment it decreases to 2.8 — 4.3%. Optimal for conception is a stable normalization of the level of PRL in the blood and a reduction in the size of the tumor (less than 10 mm). In this situation, contraception is canceled, and pregnancy planning is carried out [17, 19].

PURPOSE OF THE STUDY:

To estimate the results of the treatment in patients with prolactinomas.

MATERIALS AND METHODS:

Examination of patients was done on the basis RSNPC name Ya.K.Turakulov in 2018-2020. 90 women with hyperprolactinemia were examined, All examined patients were divided into 3 groups: 30 patients with prolactinomas, 30 patients with polycystic ovary syndrome and 30 patients with hypothyroidism. All patients underwent standard research methods (General clinical and biochemical blood tests, radioimmunological hormonal methods of blood testing, pituitary MRI, pelvic ultrasound).

RESULTS AND THEIR DISCUSSION:

The age of patients in our study at the time of treatment was 33.5±11.5 years, minimum-17.0 years, maximum-49.0 years. The duration of the disease ranged from 6 months to 16 years.

Of all patients with prolactinoma, including those who underwent surgery, 27 women received cabergoline. 3 women with prolactinoma received cabergoline and bromocriptine. Among women with prolactinoma, 25 had a microadenoma (microprolactinoma) and 5 had a macroadenoma (macroprolactinoma).

Cabergoline dose selection was individual. The scheme of selection of an

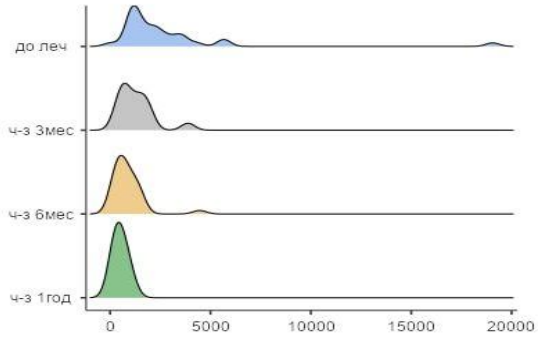
optimal dose of the following: initial dose 0.25-0.5 mg 2 times a week at 20.00, after meals for 4 weeks followed by control-level PRL and by titration of doses if necessary, increase weekly dose by 0.25, 0.5 mg a week with an interval of 4 weeks and selection of the optimal dose (the minimum, against which the normal level of PRL with good endurance). Control was carried out according to the level of total PRL and then the optimal therapeutic dose was maintained.

The total prolactin level in women with prolactinoma is shown in table 4.

Table No. 4. Prolactin levels before and after cabergoline therapy in women with prolactinoma

PRL MIU/l	Before treatment	In 3 months.	After 6 months.	After a year
The median	1812	656	495	368
Lower quartile	1224	515	231	230
Upper quartile	2973	1095	856	610

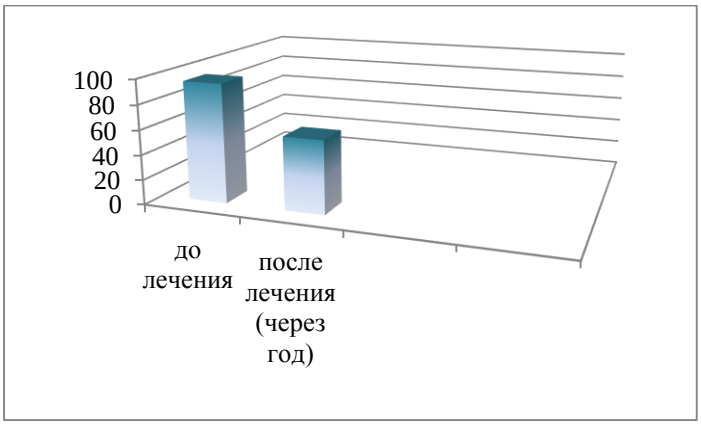
Normalization of total prolactin levels to reference values during treatment with cabergoline (dostinex) in the General group occurred in 66.7 % of patients with prolactinoma. The level of total prolactin in the examined group in dynamics is shown in figure 16.



16. Dynamics of prolactin levels in women with prolactinoma treated with cabergoline

Restoration of the menstrual cycle in women was observed in 70.0% (21) of cases, 22.7 % (5) of women with infertility became pregnant, galactorrhea decreased or disappeared in 56.7% (17) of women with prolactinoma.

During treatment with cabergoline, a decrease in the pituitary tumor volume was noted. In women with prolactinoma, the median tumor volume was 95.58 mm3 (lower quartile 18.32 mm3, upper quartile 783.15 mm3), after treatment 58.64 mm3 (lower quartile 6.11 mm3, upper quartile 224.43 mm3), differences in tumor volume were statistically significant, p = 0.00002, figure 17.



17. Change in tumor volume (mm3) during cabergoline treatment

In our study, the duration of cabergoline administration in women ranged from 6 months to 4 years, with a median and interquartile range of 2 years (1 year, 3 years).

Cabergoline doses required to normalize total prolactin levels in women ranged from 0.125 mg / week to 3 mg / week. Median and inerquartile range are 2 mg (0.5 mg; 1 mg).

Resistance to cabergoline treatment was 3.33 % (in the 1st patient). Complete remission was obtained in 73.3% (21), incomplete remission in 10.0% (3).

In our study, the duration of cabergoline administration in women

ranged from 6 months to 4 years, with a median and interquartile range of 2 years (1 year, 3 years).

In 17 women with prolactinoma who complained of infertility, after treatment with cabergoline for at least 1 year, pregnancy did not occur, we prescribed Clomiphene citrate for ovulation induction and fertility restoration. Treatment regimen Clomiphene citrate is the following: Clomiphene citrate (Klofat) 50 mg 1 tablet 1 time per day at 20: 00 from 2 till day 6 of the menstrual cycle for 2 cycles, then 2 tablets 1 time a day at 20.00 with a 2 to 6 day cycle for 2 cycles. Taking into account the decrease in progesterone levels in hyperprolactinemia, we prescribed progestins in the second phase of the cycle (Duphaston 20 mg /day or utrogestan 200 mg /day from the 16th to the 25th day of the menstrual cycle). In case of pregnancy, we canceled clomiphene citrate, and prescribed Duphaston 20 mg / day or Utrogestan 200 mg / day during the first 12 weeks of pregnancy to prevent spontaneous abortions and miscarriages. And we also gradually eliminated cabergoline, reducing the dose of the drug by 0.5 mg per week. In 12 patients during treatment Pregnancy occurred with clomiphene citrate (40.0% of the total number of women with prolactinoma). 5 patients with prolactinoma who, after treatment, Clomiphene citrate for 4 months, pregnancy did not occur, about which we sent to the gynecologist for ovulation induction using human chorionic gonadotropin.

During the treatment, there was a significant increase in progesterone levels (p=0.0002) in the middle of the luteal phase of the cycle, apparently due to the postponement of ovulation in women with prolactinoma.

CONCLUSIOS:

From the results obtained, we concluded that cabergoline effectively reduces the level of total prolactin in patients with prolactinoma, while reducing the size of the tumor. And also against the background of treatment with cabergoline, women with prolactinoma have a restoration of the two-phase menstrual cycle and the onset of pregnancy at a fairly high frequency. In women with prolactinoma and infertility, if pregnancy does not occur spontaneously after cabergoline treatment for at least 1 year, Clomiphene citrate is the drug of choice for restoring ovulation and fertility.

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