

RETROSPECTIVE ANALYSIS OF THE EFFECTIVENESS OF TREATMENT OF THE PITUITARY MICRO ADENOMAS IN NULLIPAROUS WOMEN, TAKING INTO ACCOUNT THE FRACTIONATION OF PROLACTIN AND CORRECTION OF THE LUTEAL PHASE DEFICIENCY

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Summary. Prolactin synthesizing pituitary body (PB) tumors are in the third flight among nervous systems neoplasms and constitute up to 17% of brain tumours. Prolactinoma is the most frequently met endocrine active tumour of PB, and it accounts for 30% of all adenomas. Manifesting sign of PB adenoma is the increase of prolactin level. The retrospective analysis of conservative treatment efficacy of micro adenomas in nulliparous women of the early reproductive age had been done. Molecular polymorphism of prolactin and correction of luteal phase deficiency was taken into account. Objective. To determine qualitative and quantitative context of lutein and, first of all, the level of its “little” fraction in the patients with micro adenomas of PB, determine the relation between clinical signs and data of hormonal examination, substantiate differentiated approach to the treatment of organic pathology of PB. Materials and Methods: 40 nulliparous women with micro adenoma of PB, aged 18 – 26 y.o. General clinical, gynecological, hormonal, ultra sound examinations and CT of brain have been. A prolonged therapy with microdoses of *dostinex* under the control of prolactin fractions has been offered. Clinical effect was gained at 40% of cases and in 4 patients there was a complete recovery. The positive dynamics in the state of vision analyzer has been noted, as well as improvement of hormonal state, rehabilitation of reproductive function. High acceptability of the treatment has been registered.

Key words: micro adenoma, luteal phase deficiency, reproductive function.

РЕФЕРАТ. Ретроспективный анализ эффективности лечения микроаденом гипофиза у нерожавших женщин с учетом фракционирования пролактина и коррекцией недостаточности лютеиновой фазы. А. А. Трушкевич, А. А. Степур (Крымский государственный медицинский университет им. С. И. Георгиевского, Симферополь). Пролактинсинтезирующие опухоли гипофиза занимают третье место среди новообразований нервной системы и до 17% опухолей

головного мозга. Пролактинома - наиболее часто встречающаяся эндокринно активная опухоль гипофиза, на долю которой приходится до 30% всех аденом. Манифестирующим признаком аденом гипофиза является повышение уровня пролактина. Был проведен ретроспективный анализ эффективности консервативного лечения микроаденом гипофиза у нерожавших женщин раннего репродуктивного возраста с учетом молекулярного полиморфизма пролактина и коррекцией недостаточности лютеиновой фазы. Цель – определить качественный и количественный состав пролактина, прежде всего уровень фракции «little» у пациенток с микроаденомами гипофиза, установить взаимосвязь клинических проявлений и данных гормонального обследования, обосновать дифференцированный подход к лечению органической патологии гипофиза. Материалы и методы: 40 нерожавших женщин с микроаденомой гипофиза в возрасте 18-26 лет. Проведено общеклиническое, гинекологическое, гормональное, УЗИ-исследование, КТ головного мозга. Предложена длительная терапия микродозами препарата достинекс под контролем фракции пролактина. Клинический эффект получен в 40% случаев, у 4 пациенток микроаденома излечена полностью. Отмечена положительная динамика в состоянии зрительного анализатора, улучшение гормонального статуса больных, реабилитация репродуктивной функции, хорошая переносимость терапии пациентками.

Ключевые слова: микроаденома, недостаточность лютеиновой фазы, репродуктивная функция.

The organic lesions of pituitary body (PB) with its prolactin synthesizing tumours (macro-and microprolactinomes) are out front among causes of pathological hyperprolactenemia according to WHO's classification. The frequency of the last ranks third among tumors of the central nervous system and they constitute, according to different authors, from 4 to 17% of all brain tumors. The most common endocrine active pituitary tumor (PT) is a prolactinoma - a tumor originating from the cells of the adenohypophysis (lactotrophes) secreting prolactin. It constitutes about 40-50% of hormonally active adenomas and 30% of all adenomas (Osborn A., 2004). Pituitary adenomas (PA) are classified by size: less than 10 mm in diameter are considered microadenomas, 10 mm are macroadenomas.

Clinical manifestations of PA depends on the size of the tumor, the presence or absence of hormonal activity, type of the hormone produced and the type of the degree of extracellular spreading (Kovacs K., 2005).

It is generally recognized that the manifesting sign of pituitary prolactinoma is the increase of prolactin level, which leads to a whole complex of symptoms in

the form of violations of ovarian-menstrual cycle with a tendency to oligo-opsomenorrhea until sustained amenorrhea, infertility, galactorrhea, pain and engorgement of the mammary glands, headaches, impairment of vision and abundance of vegetative complaints, etc.

That the above mentioned complaints lead a patient to the gynecologist, who determines the timeliness of diagnosis, the adequacy of the prolonged therapy, monitor of the treatment effectiveness.

However, in their practice physicians are often faced with dissonance between the level of serum prolactin and severity of the clinical manifestations of this disease. For example, when micro/ macro PA are diagnosed and when according to the data of literature the expected increase in prolactin levels should exceed 2000 mIU /l (T. F. Tatarchuk et al., 2007), there are "silent," "deleted" forms of clinical manifestations of hyperprolactinemia. The level of prolactin ranges from 800 to 1600 mIU /l. Conversely, at higher numbers of serum prolactin (over 3000 - 5000 mIU /l) expression of clinical symptoms may be vague and organic pathology in a PT (prolactin secreting tumour) is not diagnosed, the menstrual cycle remains unchanged, no phenomenon of galactorrhea are observed, etc.

It is possible that the overall high level of serum prolactin as a biochemical marker of failure of the hypothalamus - PB - ovaries, does not always certificate in the favor of organic disease of PB. As well as "normal and subnormal" prolactin levels in the presence of symptoms of hyperprolactinemia should not be a cause of reduced vigilance of the doctor as this may be for veiled serious pathology, requiring careful examination and treatment of the patient.

Clinical activity of prolactin is determined by its total amount, the state of receptors in the target organs, and most importantly, the ratio of fractions in the total pool of prolactin.

According H. L. Fideleff et al., (2000), four fractions of prolactin are distinguished:

- "little" PRL has high biological activity (22 000 MM);
- "Big" PRL with 50 000 MM;
- " big- big» PRL with 100 000 MM;
- glycosylated PRL with 25000 MM.

The determination in the total pool "biologically aggressive" prolactin of "little" form resulting in realization of pathological manifestations even at a slight increase of the total PRL level is of great importance for practical activity of a doctor. On the other hand, long-existing hyperplasia and hyperactivity of pituitary lactotrophes are a provoking background for emergence and growth of PT. Conditionated by PT, chronic hyperprolactinemia causes a decrease in the sensitivity of the hypothalamus to the suppression of estrogen synthesis of

gonadotrophin-releasing hormone (GnRH), thereby disrupted cyclicality of pituitary LH and FSH damages, reduced frequency and amplitude of LH secretion peaks are observed. Prolactin, competitively binding to receptors of gonadotrophin in the ovaries inhibits the effect of gonadotropins on steroidogenesis and reduces the sensitivity of the ovaries to exogenous and endogenous GT, which leads to the formation of hypogonadism syndrome with impaired fertility and menstrual function in women in more than 25 - 30% of cases (Gilyazutdinov I.A., 2006). Hyperprolactinemia directly reduces the secretion of progesterone by the corpus luteum and induces early luteolysis (Niswander G. D., 2002). Essentially, the result of violations of folliculogenesis is insufficient luteal phase (NLF) of the menstrual cycle, which manifests itself in the corpus luteum hypofunction due to insufficient synthesis of progesterone, which is a cause of violation of the secretory transformation of the endometrium, subsequently leading to infertility and abortion in early pregnancy.

We carried out a retrospective analysis of the effectiveness of conservative treatment of pituitary microadenomas in nulliparous women of an early reproductive age with the view of the molecular polymorphism of prolactin and NLF correction.

The objective: to determine qualitative and quantitative determination of prolactin composition and first of all, the level of PRL "little" fractions in the patients with diagnosed pituitary microadenomas, trace a connection between clinical manifestations and the data of hormonal examination and substantiate differentiated approach in the treatment of the patients with organic pathology of PB - microadenomas, including pathogenetically reasonable correction of LPD. MATERIALS AND METHODS.

The complex examination of 40 nulliparous women aged 18-26 years with diagnosed pituitary prolactinomas has been conducted. 20 of these patients (Group I) were treated by the usual method - therapy with dopamine agonists (Dostinex) to the normalization of serum prolactin levels and disappearance of clinical symptoms of hyperprolactinemia and 20 patients (Group II) - according to our procedure to normalization of PRL "little" fraction with subsequent correction of LPD.

The control group consisted of 20 nulliparous women of similar age without somatic and endocrine pathology.

The comprehensive examination of the patients included: general clinical and gynecological examination, hormonal tests, ultrasound of pelvic organs, thyroid and mammary glands, examination the visual analyzer functions with computer perimetry (Humphry) and definition of peripheral visual fields. To confirm organic damages of the PB CT of the brain with intravenous enhancement or MRT was performed.

Determination of the hormonal profile of the patients included:

- definition of PRL at the 4-6 days of menstrual cycle, at amenorrhea it was done at the moment of a patient's resort;
- fractionation of prolactin by chemiluminescence;
- the levels of TSH, FSH, LH, T3, T4, antibodies to thyroperoxydase, estradiol, testosterone, progesterone were determined with standardized methods.

Complex of therapeutic and preventive measures included: a prolong treatment (18-36 months) with *dostinex* microdoses in combination with *utrogestan*.

The correction of doses and duration of the treatment depended on the transformation of low molecular PRL to its high molecular weight fraction, as well as other hormonal changes, elimination of clinical signs and symptoms of hyperprolactinemia and clinic of LPD.

RESULTS AND DISCUSSION.

The patients were randomly assigned by groups. Before the examination the detailed cases histories were collected to exclude pharmacological hyperprolactinemia.

Structural analysis of the main manifestations of the pathology under study showed that in 60% of cases occurred later menarche (mean 15 y. o.) which is unusual for the girls dwelling in the southern region. 40% of the patients had timely menarche, but after 2-5 years in this group of patients appear first recurrent, once per 3-6 months "loss" of menstrual cycles, later on the process aggravated to stabile secondary amenorrhea.

The complaints of the patients were within the nosology of hyperprolactinemic states: prevailed symptoms of ovarian-menstrual syndrome (hypomenstrual type) and amenorrhea - 2 of different duration and frequency, pain and engorgement of mammary glands at 7-10-15 days before menstruation, infertility, headache, abundance of vegetative complaints. Incidence of galactorrhea did not exceed 10%. Breast tenderness faded at amenorrhea-2 (over 4 months). The pathology of breast was observed in 50% of patients and was proved ultrasonographically. It consisted of the following changes: moderate and severe ductectasia in peripapillary zone or in all quadrants; presence of cysts in the breast sized 0.5 - 1.2 cm the last were presented by single or multiple entities. In the group under study only 40% of women worried about pregnancy beginning. Among them, infertility-1 limited to 2-5 years in length was the reason for seeking medical attention.

The clinical-laboratory, hormonal and thyroid gland dopplerographic study did not reveal any violations of its function almost in all patients. Primary hormonal examination had revealed the following data:
- fluctuations of PRL general level were 750 - 2800 mIU /l (norma 300-500 mIU

/l); in 70% of patients level of PRL fluctuated in the range of 750-1250 mIU /l; - percentage of PRL of low molecular weight composition with respect to PRL general pool of was as follows:

- 90-100% in 85% of cases;
- 80 - 90% in 10% of cases;
- 70 - 80% in 5% of cases, i.e., predominance of PRL low molecular weight fractions prevailed in the patients with pituitary microadenomas.

There was no proportion between the severity of clinical manifestations and the total level of PRL, but the direct correlation between the severity of menstrual disorders and the percentage superiority of PRL of low molecular weight in relation to the high molecular weight fraction.

At the preserved menstrual cycle progesterone level was 15 - 28 ng/ml. It was determined at the end of the 2nd phase of the menstrual cycle and was indicative of LPD.

At amenorrhea-2 and hypomenstrual syndrome a significant decrease of progesterone down to zero (0 - 8 ng / ml) was marked in the patients. A significant decrease in serum estradiol was observed during prolonged amenorrhea-2 (more than 6 months); at the preserved menstrual cycle estradiol had indexes 25 to 240 ng / ml, depending on the phase of the menstrual cycle. Thyrotropic and thyroid gland hormones were in the limits of norm. The examination of the visual analyzer by computed perimetry following changes had revealed: the syndrome of "dry eye" was present in 40% of patients; the initial stagnation of the optic disc in 20% of patients; expansion of the blind spot was observed in the 35% of cases; bitemporal hemianopsia in 75% of cases; progressive complicated high myopia combined with the initial stagnation of the optic disc of both eyes was revealed in 15% of patients.

Macroprolactinomas of PB with supra cellular growth involve in the pathological process opto-chiasmal area, and thus bitemporal hemianopsia of the upper square is their classical ophthalmologic sign and complete bitemporal hemianopsia is a rare one.

In the group of patients under study the changes both in the optical fundus and in the peripheral visual fields have been revealed. The most significant changes in the peripheral visual field were registered in the group of patients with predominance of PRL of low molecular weight fractions. While in 25% of patients with PB's microadenomas and prevalence of PRL of high molecular weight none serious ophthalmologic problems as violations of the visual fields were observed. These facts indicate that visual analyzer is highly sensitive and the first "reacts" to failure of the hypothalamic-pituitary-ovarian axis, especially with the prevalence of biologically "aggressive" PRL of low molecular weight. It is possible that the study of the visual analyzer functions in conjunction with the definition of

qualitative and quantitative condition of PRL would be a base marker of trouble in the hypothalamo-pituitary zone, forecast of PB's prolactinoma growth and the criterion of the effectiveness of the treatment conducted.

CT and MRI examinations with intravenous enhancement gave the following data:

- isodensive formations with smooth contours, rounded, 5-10 mm in diameter, moderately accumulating contrast agent were determined;
- median structures are symmetrical, are not displaced;
- the width of the anterior horns of the lateral ventricles and the third ventricle are in the limits of norm;
- there were no bone-destructive changes;
- convexital subarachnoid liquor spaces are not expanded.

Therapy of hyperprolactinemic disorders in the 1st group of patients began with prescribing of dopamine agonists reducing prolactin secreting activity of lactotrophes, i.e. cabergoline preparation – *dostinex*. The dose prescribed depended on the initial level of PRL. The therapeutical effect was assessed by reduction of PRL to norm, restoration of menstrual cycle, disappearance of galactorrhea complaints, pain in mammary glands before periods and other vegetative complaints. Usually within 2-3 months, first the recovery of menstrual-like reactions followed by complete recovery of menstruation in patients with amenorrhea-2 and sufficiently rapid relief of hypomenstrual syndrome during the first 2 or 3 menstrual cycles in the women with oligomenorrhea was observed. However, within a year after treatment at the background of PRL stable indicators there were recurrences of the main disease in 70% of cases. They were in the form of interruptions of periods "jumps" of PRL total level with refund or without vegetative symptoms.

Administration of *dostinex* according to our procedure went on in the supporting mini-doses (1/4 tabl. once per week) for 18-36 months. During the treatment of the second group patients PRL ratio changes, hormonal changes and visual analyzer state were controlled quarterly.

After the restoration of menstrual function the treatment was complemented by micronized progesterone vaginally (*utrozgestan*, 200 mg per day) during the 2nd phase of the cycle in order to correct LPD. Ultrasonic evaluation of changes in endometrial thickness in periovulatory period and mid-luteal phase were conducted as well.

The state of endometrium was monitored by ultrasound and is presented in Table 1.

Table 1

Ultrasonic indicators of changes in endometrial thickness in women with microadenomas and LPD during the treatment in periovulatory and mid-luteal phase of the menstrual cycle before the treatment and in 12 months

Endometrium thickness, mm	Periovulatory period		Lutein phase	
	Gr.I	Gr. II	Gr.I	Gr.II
Before treatment	5.12±0.21	5.56±0.22	6.84±0.18	6.78±0.19
After treatment	7.42±0.12	9.68±0.18	8.36±0.23	11.23±0.17

$P < 0.05$

Once a year, CT or MRT with intravenous enhancement was done to monitor the effectiveness of the therapy. It was estimated by changes in tumor size, degree of contrast uptake.

In the first group of patients the reduction of tumor's size by 20% was observed in 2 patients. In the second group of patients where the treatment was carried out by our procedure, there was a complete recovery in 4 cases (or 20%) and in four patients the decrease of adenoma's sizes (average by 30%) was registered. All the data were confirmed by CT data.

CONCLUSIONS

1. The treatment of PB's microadenomas by *dostinex* (0.125 milligrams) during 18- 36 months under the control of PRL 'little " fractions provides a significant clinical benefit in 40% of cases. It is manifested in the changes of microadenoma's size or even complete recovery.

2. Positive changes in the state of the visual analyzer is a criterion for the effectiveness of the therapy.

3. Complex *dostinex* + *utrogestan* was well tolerated by the patients, gave stable improvement of the hormonal status of the patients. It, in its turn, lead to effective correction of LPD and contributes to the rehabilitation of the reproductive function of women with organic pathology of PB (microadenomas).

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