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HETEROGENEITY OF CLINICAL MANIFESTATIONS OF HYPERPROLACTINEMIA
(REVIEW AND OWN OBSERVATIONS)


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Abstract.

Objective The article is devoted to the features of the clinical picture of hyperprolactinemia, which can be partially determined by both gender and age of patients. Along with the well-known “classic” manifestations of hyperprolactinemic syndrome, such as clinical signs of hypogonadism and mechanical pressure of the pituitary tumor on adjacent anatomical structures, there are others that are poorly known to a wide range of practicing physicians. Less frequent manifestations of hyperprolactinemia include the development of hypopituitarism, osteoporosis or osteopenia, alopecia. The analysis of literature data is illustrated with clinical examples from our own practice. It is noted that the pronounced heterogeneity of the clinical manifestations of hyperprolactinemia determines the need to develop continuity and consistency between doctors of different specialties for timely diagnosis and adequate treatment of this pathology.

Key words. Hyperprolactinemia, clinical manifestations, hypogonadism, alopecia, galactorrhea, prolactinoma.

Introduction.

Hyperprolactinemia, defined as an increase in serum prolactin (PRL) above the upper limit of the reference values, on the one hand, is characterized by heterogeneity and diversity of clinical manifestations, on the other hand is considered the most common cause of hypogonadotropic hypogonadism with the appearance of hormonal and metabolic disorders [1,2].

Increased PRL levels decrease gonadotropin pulsatile secretion through inhibition of hypothalamic gonadotropin releasing hormone production. In addition, there may be direct effects of hyperprolactinemia on testes and ovaries.

Typical clinical signs of hyperprolactinemia in women include different types of menstrual disorders (more often amenorrhea or oligomenorrhea), infertility, galactorrhea. Decreased libido and dyspareunia may also be present. Long term estrogen deficiency may lead to osteoporosis or osteopenia [3]. In young women presenting with infertility PRL concentration should be determined accurately, whether or not the patient has other symptoms suggestive of excess PRL such as galactorrhea or menstrual cycle disorder [4].

In men, manifestations of hyperprolactinemia can be various sexual disorders in a form of decreased libido independently of testosterone levels, impotence, erectile dysfunction, oligo-azoospermia which lead to infertility, gynecomastia, galactorrhea (rare) and also low bone mass as a result of prolonged hypogonadism [3,5]. At the same time in a large series with 1370 participants presenting with erectile dysfunction, hyperprolactinemia was present only in 1.5% [6].

Hyperprolactinemia is more common in women. The prevalence of hyperprolactinemia ranges from 0.4% in an unselected normal adult population to as high as 9 to 17% in women with reproductive disorders. Its prevalence was found to be as high as 17% among women with polycystic ovary syndrome [7]. In each case, the clinical manifestations due to hyperprolactinemia differ in a certain variety, and in some patients the clinical signs of this hormonal disorder are generally nonspecific. The latter point may be the cause of untimely establishment of a correct diagnosis, as well as diagnostic errors. Thus, it is relevant to analyze the variants of clinical manifestations of hyperprolactinemia, taking into account literature data and our own experience.

Clinical manifestations of hyperprolactinemia and their analysis.

Galactorrhea and breast diseases in hyperprolactinemia

One of the most characteristic manifestations of hyperprolactinemia in women is galactorrhea, because the breast is a target organ for PRL. Galactorrhea is milk production from the breast unrelated to pregnancy or lactation. Milk production one year after cessation of breastfeeding is non-lactational and is considered as galactorrhea. According to various authors, galactorrhea is diagnosed in 20-80% of cases of hyperprolactinemia [8]. The absence of this symptom in some patients is due to the fact that a necessary condition for the development of galactorrhea is an elevated level of PRL on the background of sufficient levels of estrogen in the blood. It is important to note that the degree of galactorrhea does not always correlate with the level of PRL and the duration of the disease [9]. In 50% of women with secretions of milk-like fluid from the nipples PRL may be normal and, conversely, in 60% of cases of hyperprolactinemia galactorrhea may be absent [10]. The galactorrhea is usually bilateral and can be white or rarely green. It must be remembered that bloody discharge from the nipples can be a sign of breast tumors. So, it needs further workup in oncological direction. A Sudan IV stain for fat droplets can confirm whether the discharge is milk or not [11,12].

Some women can have non-puerperal galactorrhea along with regular menstrual cycles and normal PRL levels. This so-called “idiopathic galactorrhea” is estimated to be present in up to 40-50% of all women with non-puerperal galactorrhea [3]. In contrast, the finding of galactorrhea in men is highly suggestive of a prolactinoma and is reported in ~10% of cases in such patients [2,13].

Hyperprolactinemia can be detected in 30% of women with galactorrhea or infertility, in 10–25% of women with secondary amenorrhea or oligomenorrhea and in 75% of those with both amenorrhea and galactorrhea [14]. This should be taken into account by gynecologists when working with patients with menstrual disorders.
Hyperprolactinemia also plays a leading role in the pathogenesis of disharmonic breast diseases. An increased level of PRL leads to hypergastrinemia, enlarges the number of estradiol receptors in the breast tissue, enhances sensitivity to the action of estradiol, accelerates the growth of epithelial cells in the mammary gland, having a direct stimulating effect on the development of proliferative processes in them. This forces patients to come to an appointment with a mammologist, the examination plan of whom should include a mandatory study of the level of PRL. It has also been proven that hyperprolactinemia can have a carcinogenic effect on breast tissue [15].

Prolactinoma as a cause of hyperprolactinemia.

Among the causes of hyperprolactinemia, a special place is occupied by the presence of hormonally active pituitary tumor, which produces PRL. This tumor is the most common of all possible variants of pituitary adenoma and accounts for about 40% of cases [16]. Approximately 90% of pituitary tumors are microadenomas (less than 10 mm in diameter) [17]. Prolactinoma is less common in men than in women, typically presenting as an incidental finding on a brain computed tomography scan or magnetic resonance imaging (MRI), or with symptoms of tumor mass effect. This is most evident as a complaint of headache, visual field defects, external ophthalmoplegia [18]. In premenopausal women, signs and symptoms of hyperprolactinemia predominate, whereas in men, tumoral effects are more important [5]. By the time of diagnosis in men, approximately 60% have macroprolactinomas.

In patients harboring macroprolactinomas, more rare tumor mass effect symptoms include cerebrospinal fluid rhinorrhea, hydrocephalus, and seizures. Such symptoms force patients to visit doctors of different specialties (otolaryngologist, neurologist, psychiatrist etc.), and only high experience of them helps to make correct diagnosis and prescribe an appropriate treatment.

Hypopituitarism beyond hypogonadism can occur if there is compression of the pituitary stalk or destruction of normal pituitary tissue [1,2,19,20]. Such a variant of the disease manifestation is quite clearly demonstrated by our own clinical observation, which is given below.

Clinical observation demonstrated symptoms of hypogonadism and mass effects of the macroadenoma in man.

Patient P., male, 58 years old. Due to short-term loss of consciousness, hyperprolactinemia was detected on the background of pituitary macroadenoma, after which the patient's hearing deteriorated and a "veil" appeared in front of his left eye. These symptoms were manifestations of the mass effect of a pituitary tumor measuring 18.3 * 12.0 * 15.4 mm. Noteworthy was the level of PRL - 112.17 ng / ml (at a rate of 5-25 ng / ml), which, according to the literature, is not very typical for macroprolactinoma, namely - too low [17,21]. Meanwhile, the question of the relationship between the level of PRL and the size of the prolactinoma remains debatable. In addition to the above symptoms, the patient suffered from erectile dysfunction as a manifestation of hypogonadotropic hyperprolactinemic hypogonadism, which he regarded as "age-related". It should also be noted that in this clinical case, compression of structures adjacent to the tumor also led to the development of secondary adrenal and thyroid insufficiency, which had been confirmed in this case by the results of relevant hormonal studies and required hormonal replacement therapy. Note that for some time the patient was disturbed by some possible manifestations of hyperprolactinemia. However, erectile dysfunction and recurrent headaches were not considered by the patient as a reason to visit a doctor but were perceived as "natural" symptoms of aging. As a result of the prescribed suppressive treatment with cabergoline along with hormonal replacement therapy with levothyroxine and prednisone the patient's state of health improved significantly. Headaches became very rare, there was no visual changes, in 6 months of such treatment positive dynamics of the tumor size was noted. But unfortunately, there was no effect of therapy on erectile dysfunction. It is possible that with timely access to a doctor (for example, an andrologist for erectile dysfunction or a neurologist for headaches), timely diagnosis and adequate treatment would lead to better results.

Thus, prolactinomas in men are usually large and invasive, presenting with signs and symptoms of hypogonadism and mass effects, including visual disturbances. Increased PRL level is associated with low testosterone, sometimes with anemia, metabolic syndrome and if long-standing also osteoporosis.

Prolactinomas in women.

Unlike men, women have hyperprolactinemia diagnosed, usually at the stage of microadenoma or even without the detection of organic pathology of the pituitary gland according to MRI. This is due to the manifestation of a number of fairly pronounced symptoms, some of which have been listed above.

The relationship of hyperprolactinemia with oligo-amenorrhea and irregular menstrual cycles has been well-known. Effekhari N. with co-authors found out that among patients with vaginal bleeding of unknown cause, hyperprolactinemia was present in more than 50% of cases and in 46% it was associated with galactorrhea [22].

An illustration of the above from our own clinical practice is the case history of patient D., woman, 23 years old, who consulted a gynecologist about recurrent menorrhagia. MRI of the pituitary gland revealed a microadenoma 5 * 6 mm in size. Evidence that uterine bleeding was associated with an increase in PRL is that it stopped after normalization of hormone levels on the background of suppressive therapy with dopamine agonists.

Hair loss in patients with hyperprolactinemia.

One of the symptoms that occur in patients with hyperprolactinemia is hair loss, the appearance of which forces patients to come to a dermatologist or trichologist. This symptom is more common in women, possibly due to the fact that women pay attention to it more often than men.

Recently, many studies concentrated on exploring new functions of PRL, and now PRL is recognized as playing a role in the hair growth [23]. The effect of PRL on hair growth has been extensively studied in mammals [24]. In human scalp skin, PRL and PRL receptors were identified for the first time in 2006 by Foitzik et al. The protein luteotropin was found in a thin layer of keratinocytes, while PRL receptors were found in the outer root sheath and in the proximal part of the inner root sheath, as
well as in the matrix keratinocytes. The mechanism by which PRL directly regulates hair growth is due to its inhibitory effect on hair shaft elongation and premature induction of the catagen phase. In addition, luteotropin also plays a significant role in the proliferation and apoptosis of keratinocytes in hair follicles by decreasing the number of Ki-67-positive cells and increasing the quantity of TUNEL + cells [23]. The luteotropic hormone seems to increase the level of free testosterone and dehydroepiandrosterone sulfate, decreasing at the same time the level of serum testosterone-estradiol-binding globulin [25].

Speaking of hair loss, it should be borne in mind that this symptom is quite characteristic of uncompensated hypothyroidism and often allows this diagnosis. At the same time, a combination of hypothyroidism and hyperprolactinemia is not uncommon. It is connected with physiological regulation of PRL secretion. It is controlled by hypothalamic PRL inhibitor factor, other factors like vasoactive inhibitory peptide and also thyroid releasing hormone which cause to increase PRL secretion [26]. So, in patients with primary hypothyroidism, increased levels of thyroid releasing hormone according to the negative feedback can lead to rise PRL levels. In this case, there is a clear algorithm for patient management. First, hypothyroidism is compensated, and then the level of PRL is assessed again on the background of normal thyroid stimulating hormone [12]. We will illustrate this scenario with the medical history of patient X, 23 years old, who consulted a trichologist with complaints of hair loss. The examination revealed hyperprolactinemia of 35.97 ng/ml in connection with which the patient was referred to an endocrinologist, who, along with hyperprolactinemia, diagnosed hypothyroidism. After compensation of hypothyroidism with hormone replacement therapy with levothyroxine, the level of PRL also returned to reference values, indicating the secondary nature of hyperprolactinemia. Over time, against the background of adequate treatment of hypothyroidism, hair loss stopped.

**Peculiarities of the course of hyperprolactinemia.**

The heterogeneity of clinical manifestations of hyperprolactinemia lies not only in the variety of manifestations of the disease, but also in the peculiarities of the course. To illustrate, we present the clinical case of a 42-year-old woman M., who received dopamine agonist therapy for microprolactinoma for 15 years. The course of the disease was aggravated by the development of secondary dopamine resistance, which was manifested by the inability to maintain normal levels of PRL on the background of the maximum tolerated dose of the drug (2 mg of cabergoline per week). Due to the fact that the treatment was not effective because of the development of secondary resistance to the dopamine agonists and the patient felt better when she was not receiving dopamine agonists which can be explained by side effects of the drugs, patient refused any therapy on her own. Along with changes in different receptors in tissues, described in the literary sources [12], we consider prolonged inadequate therapy with dopamine agonists as one of the possible mechanisms of resistance to dopamine agonists in our patient. In control measurements, the level of PRL ranged from 75.6 to 51.1 ng/ml. After about 3 years without therapy on the background of hyperprolactinemia, the patient became pregnant and gave birth to a healthy girl in time.

The unusualness of this clinical case is due to the fact that the main features of pregnancy in untreated patients with hyperprolactinemia are the frequent threat of abortion (about 32%), which in more than half of cases ends in involuntary termination. In addition, reproductive losses in pregnant women who did not receive suppressive therapy with dopamine agonists before conception are significantly higher than in those whose pregnancies occurred with appropriate treatment [27]. In addition, it should be noted that pregnancy, which is accompanied by hyperprolactinemia because of pituitary adenoma, can lead to an increase in tumor size. Thus, tumor growth due to pregnancy was identified in 2.5% of 800 macroprolactinomas, 18% of 288 macroprolactinomas without previous surgery or radiotherapy and 4.7% of 148 macroprolactinomas submitted to surgery and/or radiotherapy [28]. It is unclear whether tumor growth is secondary to the high estrogen levels or to dopamine agonists withdrawal due to pregnancy.

**Osteopenia in patients with hyperprolactinemia.**

Hyperprolactinemic patients have high bone turnover, impairing bone mineral density and leading to skeletal fragility [29]. Along with it hypogonadotropic hypogonadism associated with persistent high PRL level may be a cause of secondary osteoporosis [30-32]. In some studies subjects with hyperprolactinemia and low bone density do not demonstrate increased fractures [33]. Other authors report a higher prevalence of vertebral fractures in particular in postmenopausal women with untreated prolactinomas, compared to patients treated with dopamine agonists [34]. Simultaneously there is a lack of evidence that normalization of PRL levels improves bone mineral density or reduces the risk of fractures [35]. A retrospective cohort study has shown that the prevalence of bone impairment is significantly higher in men with prolactinomas than in women. Impaired bone mineral density reflects the severity of long-term hyperprolactinemia and associated hypogonadism [30,36]. Treatment of hyperprolactinemic patients with osteopenia and osteoporosis is carried out according to generally accepted standards. However, without treatment of the underlying disease and reduction of PRL levels, the standard accepted method of managing osteoporosis, in our opinion, will be ineffective.

**Hyperprolactinemia in children.**

In children the clinical manifestations of hyperprolactinemia vary mainly according to gender, age of onset, PRL levels and pituitary tumor size if it is present. According to the literature, headache is the commonest complaint in case of prolactinoma in children [37]. In adolescents it is more common to have menstruation related problems, including primary amenorrhea than galactorrhea [38,39].

**Conclusion.**

So, doctors of various specialties may suspect hyperprolactinemia. Thus, gynecologists are approached by women with complaints of menstrual irregularities and / or infertility. Patients of andrologists often complain of erectile
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Резюме
Статья посвящена особенностям клинической картины гиперпролактинемии, которая частично может определяться как полом, так и возрастом пациентов. Наряду с общеизвестными «классическими» проявлениями синдрома гиперпролактинемии, такими, как клинические признаки гипогонадизма и механического давления опухоли гипофиза на расположенные рядом анатомические структуры, приводятся другие, плохо известные широкому кругу практикующих врачей. К менее распространенным вариантам проявления гиперпролактинемии относят развитие гипопитуитаризма, остеопороза или остеопении, аlopeции. Анализ литературных данных иллюстрирован клиническими примерами из собственной практики. Отмечается, что выраженная гетерогенность клинических проявлений гиперпролактинемии, определяет необходимость выработки преемственности и согласованности между врачами разных специальностей для своевременной диагностики и адекватного лечения данной патологии.

Ключевые слова: гиперпролактинемия, клинические проявления, гипогонадизм, алоpecia, галакторея, пролактинома.