Hyperprolactinemia – looking at diagnostic and clinical problems

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Abstract

Hyperprolactinemia is a common problem in clinical diagnoses and prolactin determination is a basic element of diagnostic procedures in many endocrinopathies, including reproductive disorders. Knowledge about physiological, pathological or iatrogenic factors affecting the secretion of prolactin is a prerequisite for the proper interpretation of the results of its determinations and the implementation of possible treatment. The article presents the current knowledge on the diagnostic value of the prolactin determination methods useful in clinical practice as well as the primary care physician.

Key words:

prolactin, diagnosis, hyperprolactinaemia, macroprolactin, prolactinoma

Definition of hyperprolactinemia

Hyperprolactinaemia is characterized by the elevated levels of prolactin (PRL) in the blood serum of men and women. It is diagnosed after at least two-time measurements of PRL concentration in blood serum. The upper limit of normal for women is the value of 20 ng/ml (400mU/l) and 15ng/ml (300mU/l) for men [1]. PRL secretion is defined by the physiological increase at night during sleep, with the secretion peak between 3 and 5 am. Hyperprolactinaemia is not a disease but a symptom associated with many diseases and endocrine disorders.

Causes of hyperprolactinemia

Hyperprolactinemia is caused by physiological and pathological factors. In physiological conditions, the PRL secretion is regulated by dopamine produced by hypothalamus. It inhibits the synthesis and secretion of PRL acting through dopaminergic receptors of type 2 (D2) in the pituitary gland. The physiological concentration of PRL increases during pregnancy (approx. 10-times) and lactation. The increased secretion occurs also during sexual climax (teasing nipples and cervix) as well as during consumption of meals rich in protein and insulin-induced hypoglycemia states. Many scientific reports confirm the impact of stress on elevated levels of PRL in blood serum. Iatrogenic hyperprolactinemia (drug-induced) is caused by drugs widely used in medical practice. Most often these are antidepressants: imipramine, amitriptyline, neuroleptics: haloperidol, chlorpromazine, antiemetics: metoclopramide, domperidone, cisapride, drugs used to treat high blood pressure: methyldopa, reserpine, clonidine [2,3]. Hyperprolactinemia is recognized while the diagnostic process of such diseases as: hypothyroidism, kidney and liver failure.

The pathological factors which directly lead to the increase in PRL concentration are tumors of the pituitary gland-prolactinoma. There are microprolactinoma, when the diameter does not exceed 10 mm, and macroprolactinoma when diameter measures more than 10 mm. The PRL concentration in blood serum most frequently correlates with the size of the tumor. In women, in the majority of cases the microprolactinoma is diagnosed (95%). In men, macroprolaktinoma (90%) is observed most often. Generally, prolactinoma occurs in women at the reproductive age. Over the age of 50, prolactinoma is diagnosed in both sexes equally [4]. The factors inhibiting the secretion of PRL are: vitamin B6, endothelin-1, TGF-β1, acetylcholine, norepinephrine. The factors which strongly stimulate the secretion of PRL are: TRH, estrogen, oxytocin. What is more, the subject literature mentions a lot more stimulating substances: vasoactive intestinal peptide (VIP), epidermal growth factor, fibroblast growth factor, angiotensin II, vasopressin, serotonin [5,6].

Diagnostics

PRL is a polypeptide which occurs in the form of three immunoreactive varieties. The monomeric form – "small" prolactin constitutes 85% of PRL secreted into blood, the dimeric form of prolactin referred as "big" is 10-15% and the polymeric form – "big big" prolactin constitutes 1–2%. The so-called "small" prolactin shows the greatest bioavailability. Macroprolactin is a complex of PRL with autologous immunoglobulin G-anti-PRL-IgG. This embodiment of PRL is not biologically active because due to its large molecule, the access to the receptor is difficult, yet, it is detected in laboratory tests giving false positive results. It is assumed that macroprolactinemia occurs in 10-26% of patients with idiopathic hyperprolactinemia [7]. In these cases, the characteristic symptoms of the increased PRL concentration are not observed and the magnetic resonance (MR) of the pituitary gland is negative. Thus, the test with the use of 25% polyethylene glycol (PEG) is recommended to precipitate PRL [8]. The difficulties with the interpretation of laboratory results in some cases arise from the presence of macroprolactin and also the rhythm of PRL secretion. It is assumed that PRL is secreted perpetually throughout a woman's cycle. However, there are reports in which it is stated that PRL secretion increases slightly in the middle of the cycle [5]. Therefore, it is recommended to perform PRL tests in the follicular phase, late in the morning. Before the test, an examined patient should refrain from physical exertion, sexual intercourse and a substantial meal. Some authors recommend performing at least two tests of PRL in blood serum or the 24-hour assessment of PRL secretion rhythm. This procedure involves a patient's stay in hospital and higher costs. The metoclopramide test is also questionable. In the case of normal or slightly higher PRL concentrations, the test is not recommended even in the case of infertility diagnostics. The metoclopramide test is reserved for differentiation of organic and functional hyperprolactinemia. In healthy patients, metoclopramide (10 mg) will cause the increase of PRL up to 100 ng/ml or PRL will be less than 600% of the initial concentration [9]. The lack of PRL concentration

increase with the high baseline concentration leads to organic hyperprolactinemia diagnosis. Most frequently, the PRL increase in the metoclopramide test is over 6-times higher in comparison with the baseline PRL levels, only at times slightly above the normal concentration. In this case, the functional hyperprolactinemia is diagnosed.

Influence on the reproductive functions

Hyperprolactinemia is often observed in the group of women treated for infertility. Literature reports that this problem affects one in three patients treated due to inability to become pregnant [10]. Hyperprolactinemia is usually accompanied by hypogonadism with the secondary amenorrhea, irregular menstruation, luteal phase deficiency, anovulatory cycles. Other symptoms that may suggest elevated levels of PRL in blood serum are: galactorrhoea, mastopathy, mastalgia, menstrual tension syndrome, weight gain, osteopenia. Hyperprolactinemia also affects the sexual sphere of both sexes. In women it may result in reduced libido, impaired phase of agitation, difficulty with lubrication and may be responsible for dyspareunia and abnormal orgasm [11]. In men hyperprolactinemia is responsible for reduced libido and erectile dysfunction [11,12]. High concentrations of PRL in the blood serum of men reduce sperm parameters. Spermiogram disorders manifest themselves in oligospermia, decrease in sperm motility, decreased volume of ejaculate and even testicular hypotrophy [13].

Hyperprolactinemia affects the reproductive functions primarily due to the fact that the excess of PRL inhibits the secretion of GnRH. In consequence, this leads to the reduction of the frequency and amplitude of pulses of luteotropic hormone (LH) and follicle stimulating hormone (FSH). In the studies of Brown et al. it was found that in a mouse model hyperprolactinemia inhibits the secretion of kisspeptin protein which stimulates the synthesis and secretion of gonadotropin-releasing hormone [14]. The abolition of positive feedback between estrogen and gonadotropins (necessary for the occurrence of ovulatory cycles) was found in patients with hyperprolactinemia. In addition, PRL acts on the synthesis of endogenous sex hormones which play a key role in the processes of reproduction. Hyperprolactinemia hinders estrogen production via inhibition of aromatase activity and the expression of hydroxysteroid dehydrogenase 3β-enzymes (3β-HSD) involved in the synthesis of progesterone [15].

Hyperprolactinemia is also observed in the endocrine diseases which cause infertility. Hyperprolactinemia is diagnosed in one-third of patients with polycystic ovary syndrome (PCOS) [1]. Hypothyroidism is also accompanied by the secondary hyperprolactinemia.

Therapeutic management

Therapeutic management aims to reduce the PRL levels to the standard values or to reduce the concentration of PRL to the values which determine the resolution of symptoms, reduction in tumor size or return of fertility. To perform the effective treatment, the type of hyperprolactinemia should be identified. Initially, the physiological increase in the PRL concentration which takes place during pregnancy or lactation should be excluded. To identify drug-induced hyperprolactinemia, a proper medical history should be prepared. The assessment of liver, kidney and thyroid functions will exclude or confirm secondary hyperprolactinemia associated with hypothyroidism or hepatic or renal impairment. PRL values above 200-250 ng/ml suggest a pituitary adenoma.

Hyperprolactinemia treatment includes medication and/or surgeries. In pharmacological treatment the dopamine agonists are used: bromocriptine, cabergoline, quinagolide, pergolide. Pharmacological treatment may be prior to surgery to reduce the tumor mass [16]. Bromocriptine is a first-line drug for the treatment of hyperprolactinemia. When taken daily during the meal, usually in the evening, it gives a considerable decrease in PRL concentration after just a few days. Clinically, we are observing the return of regular ovulatory cycles in approx. 80-90% of treated patients. Yet, bromocriptine therapy is burdened with numerous side effects: nausea, vomiting, orthostatic hypotension, psychomotor agitation,

allergies changes [17]. The subject literature reports on alternative use of bromocriptine vaginally to prevent the symptoms from the gastrointestinal tract [17,18]. Bromocriptine is a drug widely used with the most known and documented safety profile in case of the coexistence of early pregnancy during pharmacotherapy. Approximately 6,000 pregnancies have been described so far in which the fetus was exposed to the drug and there was no increase in fetal abnormalities and obstetric complications [19]. Resistance to bromocriptine occurs when after 3 months of treatment at a dose of 15 mg/day normalization of blood PRL is not obtained [20].

Cabergoline is a drug of a newer generation giving less side effects. Comfortable in its application, it can be implemented in patients with severe side effects or resistant to bromocriptine. Having compared the efficacy of bromocriptine and cabergoline, a statistically significantly higher rate of pregnancies during treatment with cabergoline was demonstrated (72 vs.52%) [21]. Yet, there is much less pregnancies exposed on cabergoline described in the literature. The reports show that there was no increase in the percentage of obstetric complications, but there are reports of frequent pathologies of heart valves in fetuses [22,23]. Quinagolide has fewer side effects than bromocriptine and drug resistance is observed less frequently. Yet, it is not recommended in patients treated for infertility. Pregnancies during short-term use of the drug with increased rates of miscarriages and fetal abnormalities are described in the literature [24]. In patients planning pregnancy, bromocriptine is recommended, yet after the confirmation of pregnancy the drug should be withdrawn [24]. Pharmacological treatment is also used in micro- and macroprolactinoma. It usually brings the expected normalization of PRL levels or their significant decrease. The duration of treatment should be adjusted individually. Usually after 2-3 years of treatment it can be discontinued and if the PRL levels stay within the standard values, the therapy can be terminated [24].

The surgical treatment is conducted in the case of ineffective pharmacological treatment due to drug poor tolerability or resistance to dopamine antagonists. Nowadays, the surgery of adenoma removal is performed via the sphenoid sinus access. The surgeries are connected with the high recurrence rate and in the case of large macroprolactinoma only a non-radical surgery can be conducted. The surgeries are very effective for microprolactinomas and small macroprolactinomas located in sella turcica.

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