The efficacy of dopamine agonist therapy in a giant prolactinoma

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Prolactinomas are the most common hormone secreting pituitary adenomas. Patients with prolactinomas generally have a benign prognosis. An algorithm is currently available for managing of this disease. Giant prolactinoma larger than 40 mm with severe invasive growth account for about 2—3% of the prolactin-secreting pituitary adenomas and evidence about management of such patients is limited. This case illustrates progress of a giant prolactin-secreting pituitary adenoma up to 70 mm in young male with a family history of prolactinomas in the absence of the adequate therapy for 8 years after initial diagnosis. After evaluation, it was decided to prescribe medical treatment. Cabergoline therapy started after evaluation appeared to be effective and had lead to significant decrease of serum prolactin level and shrinkage of pituitary adenoma. Described case emphasize the crucial role of identification of hyperprolactinemia among young patients on early stages of the disease. Our observation implies that treatment with dopamine agonists might be effective even in cases with giant prolactinomas.

Keywords: case report, giant prolactinoma, hypopituitarism, cabergoline.

Prolactinomas are the most common hormone-active pituitary adenomas (30 cases per 100,000 population) [1]. Prolactinomas are classified according to their size as microadenomas (<10 mm), which are more common among women, and macroadenomas (>10 mm) with almost the same incidence in men and women [1]. In the overwhelming majority of cases, the size of hormone-secreting pituitary adenomas varies in the range of 10—40 mm, with their prognosis being quite favorable, and a precise algorithm for managing this category of patients being developed to date [2—5].

Giant prolactinomas, which include formations larger than 40 mm in size, are quite rare and account for about 2—3% of all prolactin-secreting formations of the chiasmo-sellar region (CHO). Therefore, this issue has been poorly studied. The available articles are rare and mostly descriptive in nature [6]. The results of a series of cohort studies, including groups of patients with prolactinomas of 40 to 60 mm in size, can be found in the scientific literature [7—11]. The cases of prolactinomas with a diameter of more than 60 mm that are characterized by invasive growth and represent a serious clinical problem are practically absent [6]. Here we present a case of a giant pituitary prolactinoma with analysis of the literature devoted to the specifics of management and outcome of the disease in the corresponding population of patients.

Case study

A 36 year old man complained of persistent intense headache in the right temporal region, a progressive decrease in vision, mainly on the right side, and decreased libido.

The first complaints of headache appeared at the age of 28. For this reason, brain MRI was performed, which revealed microadenoma of the pituitary gland (44×44×29 mm in size) with extrasellar growth, chiasmal compression, and involvement of the right cavernous sinus. Examination revealed an increase in the blood level of prolactin to 202.8 ng/ml (reference range, 4.0—15.2). The patient was recommended for transcranial adenomectomy followed by radiotherapy, which he refused. The patient neither sought medical help nor received any treatment during the next 8 months. An increase in the intensity of headaches and a progressive decrease in vision served as an indication for second MRI of the chiasmo-sellar region 8 years after the onset of the disease. The repeated examination showed pituitary adenoma of 65×52×70 mm in size with extrasellar growth and in-
volvement of the right cavernous sinus, siphons of both internal carotid arteries, subtotal obturation of the suprachiasmal cisterns; prolapse of the tumor components into the right half of the basilar sinus and the ethmoidal labyrinth was noted with dislocation of the median brain structures to the left by 5 mm. Blood prolactin level was 15466.0 ng/ml (reference range, 4.9—25.4), macroprolactin level was 1.1%. In order to clarify the diagnosis and select a further treatment approach, the patient was hospitalized in the endocrinology department of the FSBI «V.A. Almazov National Medical Research Centre» of the Ministry of Health of the Russian Federation in January 2016.

Results of physical, laboratory and instrumental examination

Physical examination results are as follows: height, 177 cm; body weight, 98 kg; BMI, 31.3 kg/m²; waist circumference, 110 cm. Scant hair growth in androgen-dependent regions was noted; there were no data suggestive of gynecomastia and galactorrhea. Arterial blood pressure was 135/80 mm Hg and 130/80 mm Hg in sitting and upright positions, respectively. Examination by an ophthalmologist revealed partial atrophy of the OU optic nerve and hemianopsia of the lower quadrant of OU. Blood level of prolactin (dilution test) was 17090.0 ng/ml (reference range, 4.0—15.2). Taking into account the presence of a giant pituitary adenoma in the patient, function of the anterior lobe of the pituitary gland was assessed in the hospital. Basal blood cortisol level was 327.6 nmol/l in the morning (reference range, 171.0—536.0). To exclude adrenal insufficiency, insulin hypoglycemia test was performed (rapid-acting insulin, 0.2 U/kg body weight). In association with hypoglycemia (2.2 mmol/l), there was no adequate increase in the cortisol level. The maximum level of cortisol was 479.2 nmol/l, which indicated adrenal insufficiency. The level of hormones were as follows: TSH, 1.5 mIU/l (reference range, 0.4—4.0); free T4, 11.4 pmol/l (reference range, 11.5—23.0); FSH, 3.3 IU/l (reference range, 1.5—7.0); LH, 0.3 IU/l (reference range, 1.0—9.0); total testosterone, 2.5 nmol/l (reference range, 8.0—32.0); IGF-1, 197.3 ng/ml (reference range, 113.0—269.0). The T- and Z-scores in the lumbar spine and the proximal femur were within the normal range, as demonstrated by X-ray densitometry.

Taking into account the onset of the disease at the age of 28, prolactinoma in the younger sister and urolithiasis in the elder and middle sisters of the patient, an examination was conducted to exclude MEN1 syndrome. The serum level of parathyroid hormone was 79.4 pg/ml (reference range, 12.0—88.0), total calcium level was 2.5 mmol/l (reference range, 2.2—2.6), phosphorus level was 1.3 mmol/l (reference range, 0.9—1.4). No pathological changes were detected on ultrasound examination of the parathyroid glands and the abdominal cavity. Molecular genetic analysis revealed no data suggestive of MEN, AIP, FIPA hereditary syndromes.

Thus, the diagnosis of a giant prolactin-secreting pituitary adenoma, secondary adrenal insufficiency, hypogonadotropic hypogonadism, and secondary hypothyroidism was established. There were no convincing laboratory and instrumental data suggestive of MEN1 syndrome. There were no indications for urgent neurosurgical intervention. Therapy with dopamine agonists was initiated: cabergoline with a starting dose of 0.25 mg twice a week followed by a dose increase to 1.0 mg per week; replacement therapy with L-thyroxine at a dose of 50 µg daily was prescribed; glucocorticoids were recommended in urgent situations. During the first few weeks after onset of the treatment, the patient noted episodes of vomiting, which subsequently regressed.

One and a half months after initiation of cabergoline therapy, a positive trend was observed in the form of reduced headache severity and improved OD vision. A laboratory examination showed a decrease in the level of prolactin up to 10849.0 ng/ml. In connection with replacement therapy with levothyroxine, the TSH level was 1.6 mIU/l, free T4 level was 18.1 pmol/l, total testosterone level was 4.1 nmol/l.

A positive trend in the form of a further decrease in the level of prolactin was maintained against gradual increase in cabergoline dose (fig. 1). Cabergoline administration at a dose of 3.0 mg per week resulted in reduction of the prolactin level to 198.1 ng/ml. The drug dose was then increased to 4.0 mg per week. Despite a significant decrease in the prolactin level, laboratory signs of hypogonadism (total testosterone, 3.5 nmol/l) remained unchanged after 6 and 9 months. Taking into account the literature data indicating a long period of restoration of normal prolactin level in patients with giant prolactinomas (up to 20 months) and maintenance of hypogonadism in one third of the patients against biochemical remission of the disease [6], the patient was recommended replacement therapy with testosterone agents.

Six months after initiation of the therapy with dopamine agonists, the patient reported a decrease in headache and a significant improvement in the overall well-being. According to the brain MRI, there was a positive trend in the form of a decreased size of the formation to 53×50×35 mm (fig. 2).

Discussion

The described clinical case illustrates a course of a giant prolactinoma in a male with the disease onset at the age of 28, which corresponds to the epidemiological data, according to which prolactin-secreting adenomas of the pituitary gland over 40 mm in size are found in the reproductive age (20—50 years) with a male/female ratio of 9:1 [7].

According to the cohort study characterizing a population of patients with prolactinomas larger than 60 mm in size [6], the most frequent complaints on the first visit to a doctor were: headache, decreased visual acuity, erec-
tile dysfunction, and decreased libido. Galactorrhea and gynecomastia were significantly less common and occurred in only 1 (6%) of 16 men. Our patient had similar complaints. Among disorders of the anterior pituitary gland function described in men with prolactinomas larger than 60 mm in size, hypogonadotropic hypogonadism was found in 100% of the patients, secondary hypothyroidism appeared in 43%, secondary adrenal insufficiency was found in 25%, and growth hormone deficiency occurred in 18% of the patients [6]. Our patient had hypogonadotropic hypogonadism, secondary hypothyroidism, and secondary adrenal insufficiency.

The lack of an adequate treatment led to the progressive growth of prolactinoma from 44 to 70 mm in size for the period of 8 years. It is known that surgical treatment with transsphenoidal or transcranial access and radiotherapy are not relevant in macroprolactinomas [2, 4, 12—14]. Usually, surgery is indicated for patients with the signs of severe chiasmal compression or in case of ineffectiveness/intolerance of dopamine agonist therapy. In a

Fig. 1. Dynamics of the changes in serum prolactin level against cabergoline therapy.

Fig. 2. Change in the size of pituitary formation 6 months after cabergoline therapy.
study by I. Shimon et al., surgical intervention was performed in 50% of patients and did not lead to the disease remission in any of the cases [6]. Complications of the surgical treatment were ophthalmoplegia and the development of panhypopituitarism, including diabetes insipidus. It should be noted that, in some cases, when therapy with dopamine agonists was found to be ineffective, cabergoline therapy against cyto reduction led to normalization of prolactin level in patients. The role of radiation therapy in prolactinomas is currently limited. Normalization of prolactin level is observed in about one third of the patients who underwent radiation therapy; the period of restoration of normal prolactin level can take up to 20 years [14]. Side effects of radiation therapy are panhypopituitarism, injured cranial nerves and, rarely, the development of secondary tumors [14]. In accordance with modern recommendations, radiation therapy is an emergency approach in patients with aggressive and/or malignant prolactinomas, in whom medical and surgical treatment has proved to be ineffective [2].

The use of chemotherapy in the treatment of macroprolactinomas resistant to the therapy with dopamine agonists, is also limited. Single studies have been published on a decrease in the level of prolactin and tumor size against therapy with an alkylating drug temozolomide [15, 16]. Suggestions have been made that temozolomide is more effective as a second-line therapy in patients with invasive prolactinomas compared to radiation therapy [15]. However, the use of the drug is limited by the lack of evidence, the development of side effects and selective sensitivity to its effect depending on the expression of methylguanine-DNA methyltransferase in tumor cells [2].

According to the literature data, administration of dopamine agonists allows achieving biochemical remission of the disease in 90% of patients with microprolactinomas, in 70—80% of patients with macroprolactinomas and in about 60% of patients with giant pituitary prolactinomas [3, 17, 18]. In the study by I. Shimon et al., the efficacy of cabergoline therapy in patients with prolactinomas larger than 60 mm in size was 61%; such therapy led to a significant decrease in the level of prolactin in patients who did not achieve remission. The mean time of remission induction was 20 months, while cabergoline dose was increased to 4.0 mg per week, and the dynamic monitoring of the patient’s condition still continues to this day.

Conclusion

Our description is consistent with the literature data, according to which, despite the invasive growth, giant prolactinomas demonstrate a good response to the drug therapy with cabergoline. Dopamine agonists are helpful in reducing the formation size and compression of the surrounding structures, they allow significant reduction in prolactin level until biochemical remission is achieved. Surgical treatment is indicated in case of resistance to the therapy with dopamine agonists and in acute situations (severe chiasmal compression, liquorrea, and apoplexy of the pituitary gland). Timely selection of an adequate management approach in the form of cabergoline administration with subsequent titration of the drug dose, alongside with surgical intervention in appropriate indications, allow achieving favorable outcomes in this severe category of patients.

ADDITIONAL INFORMATION

Consent of the patient. The patient voluntarily signed an informed consent for publication of his personal medical information in the journal “Problems of Endocrinology”.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.


