

CASE REPORT

Management of pituitary macroprolactinoma in a 27-year-old male patient from Taiwan

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Abstract: *Objectives:* The aim is to document the success of bromocriptine pharmacotherapy in a patient with gigantoprolactinoma.

Result: The management of the patient was not appropriate at the beginning, because he underwent an operative therapy after the ophthalmological examination and MR without previous internal — endocrinological examination and pharmacotherapy. The endocrinologist participated in the patient management later, after the unsuccessful operative and when the patient's status was characterized by hyperprolactinaemia 15 000 ug/l and by hypopituitarism. Bromocriptine therapy immediately at the beginning would enable the patient to avoid several surgical interventions and subsequent complications with a high probability.

Conclusion: The case report presents the failures at the beginning of diagnostic and therapeutic management of the patient with hyperprolactinaemia due to macroprolactinoma. It is both the example and the proof of irretrievability of general internal medicine, endocrinology and other internal disciplines in clinical practice. It confirms the integrating and coordinating function of the internal medicine specialist in clinical medicine (Tab. 1, Ref. 13). Full Text (Free, PDF) www.bmj.sk.

Key words: hyperprolactinaemia, prolactinomas, management.

Prolactinomas are the most frequent functionary adenohypophyseal tumors and the most common cause of hyperprolactinaemia. The goal in their treatment is the reduction of hyperprolactinaemia and tumor mass shrinkage with the possibility to improve neurogenic and ophthalmogenic symptoms. The therapy consists of three possibilities – pharmacotherapy with dopamine agonists, surgery treatment and radiotherapy. In the recent two decades, the dopamine agonist pharmacotherapy became the most preferred due to hyperprolactinaemia reduction and tumor shrink-

age without risks, which accompany surgery treatment and radiotherapy.

The patient described in this case report is from my clinical clerkship in Taiwan (Republic of China), organized by IFMSA (International Federation of Medical Students' Associations), at the Department of Metabolic and Endocrine Diseases in Veterans General Hospital Taipei. Here, in this very advanced hospital, the endocrinological examination and subsequent successful pharmacotherapy was started.

Hypophyseal tumors manifest by chronic cefalea, visual changes and visual field loss, signs of intracranial hypertension (vomitus, oedema papillae n. optici), focal neurogenic symptoms and hypopituitarism in case of hypophyseal tissue destruction. Functionary tumors have also additional symptoms caused by their excessive hormone production. Carcinomas of adenohypophysis are rare, on contrary, adenomas are frequent. Asymptomatic adenomas of various sizes and histological types are found in 5–27 % of all dissected pituitary glands. In clinical databases, prolactinomas create 60 % of diagnosed adenohypophyseal tumors (1, 2, 3, 4). Due to their multiform manifestation, doctors of various specializations can meet them (internal medicine, ophthalmology, neurology, gynaecology, urology and others). The problem is if they send the patient directly to neurosurgery where the patient undergoes the surgical treatment. Internal-endocrinological and internal-oncological diagnosis and treatment is neglected in the patient's management. But endocrinologist should be the main coordinator in the management of patient with hyperprolactinaemia and prolactinoma. Internal-endocrinological examination should be performed as the first one and the

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Dedicated to 90 anniversary of Medical Faculty of Comenius University in Bratislava and 35 anniversary of First Angiological Station in Slovakia establishment.

Tab. 1. Etiology of hyperprolactinaemia (13).

1. Pituitary diseases:	
Prolactinoma	Tricyclic antidepressants
Acromegaly	Methyldopa
Cushing's Disease	Metoclopramide
Non-functionary pituitary disorders	Verapamil
Lymphocyte hypophysitis	Kokain
2. Diseases of hypothalamus and infundibular stalk:	Fluoxetine
Craniopharyngeoma	Selective serotonin reuptake inhibitors
Meningeoma	Risperidone
Dysgerminoma and other tumors of hypothalamus	Domperidone etc.
Sarkoidosis	4. Neurogenic disorders:
Eosinophil granuloma	Lesions of thorax wall and spinal cord
Neuraxial irradiation damage	Stimulation of mammary gland, stress, sexual activity, food etc.
Vascular aneurysmas	5. Others:
Transsection or compression of infundibular stalk	Pregnancy
Lymphocyte hypophysitis	Hypothyreosis
3. Medicaments:	Renal insufficiency
Phenothiazine	Liver cirrhosis
Butyrophenone	Idiopathic hyperprolactinaemia

doctor should consider indication of pharmacotherapy, which is the treatment of choice in prolactinomas• treatment. The main title "Think twice before you cut" (old British saying) expresses the aim of this case report. The aim is to document the success of bromocriptine pharmacotherapy in a patient with gigantoprolactinoma, who underwent an unsuccessful surgical treatment without the consultation of endocrinologist at the beginning.

Case

In this case report we describe a 27-year-old male, 180 cm tall, 110 kg of weight, BMI 33,95, girth 120 cm, blood pressure 110/70 mmHg, pulse 75, 17 breaths per minute, axillary temperature 36.4 °C. Patient from the town of Pu-li noticed that he couldn't see as clear as usual in 2006 so he went to Ophthalmology Out-Patient Department in Pu-Li Veterans Hospital for examination. The ophthalmologist indicated MRI, which showed a tumor of size 5–6 cm, evaluated as prolactinoma. He referred the patient to China Medical University Hospital, to Neurosurgery Department in September 2006. Here, the patient underwent an operative treatment of macroprolactinoma. The patient was not examined by endocrinologist and did not take any medication (including dopamine agonists) before and after surgical treatment. Eight operations were performed, including open-skull procedure, and ventriculo-peritoneal shunt was set. But there was still a residual tumor mass, which couldn't be removed by this treatment. A visual field loss and somnolence appeared, which persists until now. Post-operative complications like diabetes insipidus centralis and wound infection were noted, and as the infection subsided, the patient was discharged. In March 2007 he was sent to Taichung Veterans General Hospital to deal with the residual tumor mass. Trans-sphenoidal operation was performed, but a complete tumor resection was impossible again.

At the end of the year 2007, the episode of nausea and vomiting was noted, with no blood containment. The patient went to Taichung Hospital, where gastric ulcer was revealed and medication of unknown type was prescribed. After two months of medication the symptoms subsided and he didn't take this medication more. In January 2008, itching of whole body appeared. The patient was scratching continuously, the scars were all over his body. Local and systemic therapy including steroids was prescribed but was not able to control the symptoms. The infectious etiology was excluded. In June 2008, the episodes of nausea and vomiting appeared again. At the beginning of July 2008, the patient came to Veterans General Hospital in Taipei, to Neurosurgery Department. Soon after that he was transferred to the Department of Metabolic and Endocrine Diseases for further evaluation and treatment. At admission, the patient was sleepy, with altered mental function, had a severe pruritus, and episodes of nausea with vomiting used to appear from time to time. He was very obese, with gynaecomastia and galactorrhoea. At the one eye, there was a complete amaurosis with ophthalmoplegia, at the second eye the visus partially remained. His prolactine level at admission was 15 000 ug/l (normal level in men is less than 15 ug/l). Pathological levels of other hormones were: cortisol 0.39 nmol/l (normal level at 8.00 a.m. is 110–717 nmol/l), ACTH <5 pg/ml (normal level at 8.00 a.m. is 8–25 pg/ml), TSH 0.015 mU/l (normal level is 0.4–4.0 mU/l), free T4 4.77 pmol/l (normal level is 10–26 pmol/l) and T3 0.189 nmol/l (normal level is 1.2–3.4 nmol/l). The examination of hormones showed a significant hyperprolactinaemia and hypopituitarism. The patient started to take bromocriptine therapy 2.5 mg three times a day, hydrocortisone 25 mg once a day and levotyroxine 0,1 mg once a day. The patient reacted very good to this treatment, after three weeks his prolactine level was 5000 ug/l, galactorrhoea, nausea and vomiting stopped and he was less sleepy. Pruritus, probably the re-

sult of hypopituitarism, cortisol deficit and subsequent Na^+/K^+ dysregulation (K^+ prevalence), subsided too. The improvement of visus was improbable due to an irreversible destruction of optic nerve. Neurosurgery doctor suggested to remove the residual tumor mass by trans-sphenoidal reoperation followed by Lexell gama knife therapy. Due to the successful bromocriptine treatment, this possibility was postponed, but not totally excluded in future. At the end of July 2008, the patient was discharged from Department of Metabolic and Endocrine Diseases set on bromocriptine and substitutional treatment. His therapy and health status will be monitored regularly. The next goal is the further reduction of prolactin level and tumor shrinkage.

Discussion

Prolactinomas are benign, rarely malignant tumors of lactotropic adenohypophyseal cells. Incidence of prolactin-secreting adenomas, which require therapy, is in our population 600–700 per million (5). Their prevalence is the biggest in the group of women around the age of forty. In men their prevalence is lower, but we can find more macroprolactinomas in this group. Prolactinomas are very rare in seniors and children. Prolactin in physiological conditions triggers milk secretion after delivery, inhibits the gonadotropins secretion and regulates the development of mammary gland in puberty and pregnancy. Prolactinoma cells produce this hormone in an excessive amount, which leads to hyperprolactinaemia. Physiological level of prolactin is 15 $\mu\text{g/l}$ in men and 20 $\mu\text{g/l}$ in women. Repeated elevation of prolactin level over 250 $\mu\text{g/l}$ is typical for prolactinomas, lower increase below this level can be found in various diseases and conditions, which must be excluded in the differential-diagnostic process (Tab. 1). Symptoms and signs of hyperprolactinaemia are infertility, hypogonadism, abdominal obesity, gynaecomastia, galactorrhoea, decrease of libido, impotence, osteoporosis and menstruation disorders, finally amenorrhoea. This specific symptom leads the women to medical check-up, so the prolactinomas in women are revealed earlier, usually as microprolactinomas. Diagnosis in men is in average ten years delayed, that is why incidence of macroprolactinomas is higher (6, 7, 8). Diagnosis of macroprolactinomas is based on anamnesis, physical examination and auxiliary examination methods, including adenohypophyseal hormonal profile (prolactin, ACTH, TSH, LH, FSH, STH) and hormones, which secretion is conducted by these adenohypophyseal hormones (cortisol, T3, T4, sexual hormones). Subsequently it is followed by MR or CT and perimeter examination. Unlike other hypophyseal tumors, in treatment of prolactinomas the method of choice is pharmacotherapy by dopamine agonists (bromocriptine, cabergoline, terguride, quinagolide). It is based on the fact that prolactin secretion is inhibited by dopamine, unlike other adenohypophyseal hormones, which secretion is inhibited by hypothalamic statins. Endocrinologist initiates the bromocriptine therapy and observes the patient's status during this treatment. If the patient responds good to this therapy, after several weeks, the decrease of prolactin level and hyperprolactinaemia-related symptoms improvement can be ob-

served. After several months, tumor shrinkage is detected. In case the patient's response to bromocriptine is not sufficient, another dopamine agonists are indicated, usually cabergoline. If this therapy fails, the prolactinoma is considered as pharmacotherapy-resistant. Approximately 20 % of macroprolactinomas and 5 % of microprolactinomas are partially resistant to dopamine agonists therapy, including cabergoline (5). Then neurosurgical treatment is indicated. Radiotherapy is the last method of choice, in case both pharmacotherapy and surgery treatment fail. Operative treatment without pharmacotherapy is not an appropriate alternative due to the recurrence of disease, incomplete tumor removing, risk of post-operative complications (hypopituitarism, diabetes insipidus centralis, infections) and uncertain prognosis. Pharmacotherapy can be stopped after several years, if there is a complete tumor mass reduction (no tumor tissue detected by MR) and if the prolactin level does not increase after finishing the therapy (6, 7, 9, 10). In case of relapse, the therapy is re-started. After six months after reaching the physiological prolactin level, we can expect the tumor mass reduction. The prolactinaemia becomes normal in 90 % of patients, tumor shrinkage occurs in 60 % of patients. After the prolactinaemia normalization, the prolactin level must be checked every six months, MR/CT check-up is performed after three months since prolactinaemia normalization and after tumor regression once per year. In macroprolactinomas also perimeter is examined between CT/MR check-ups (6, 7, 11, 12). As this patient comes from Taiwan and his disease history takes place here, a question of traditional Chinese medicine in his treatment is rising. Officially he did not undergo this kind of treatment. In Taiwan, unlike China mainland, traditional Chinese medicine has a supplementary role to western medicine in some kind of diseases and it is based on patient's decision if he/she wants to undergo it. Management of the patient described in the case report was not appropriate at the beginning, because he underwent an operative therapy after the ophthalmological examination and MR without previous internal-endocrinological examination and pharmacotherapy. Endocrinologist participated the management later, after the unsuccessful operative treatment and when the patient's status was characterized by hyperprolactinaemia 15 000 $\mu\text{g/l}$ and by hypopituitarism. Bromocriptine therapy immediately at the beginning of the management would enable the patient to avoid several surgical interventions and subsequent complications with a high probability.

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