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Could hormonal remission in prolactinomas be achieved with surgery? Our experience

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Objective. To determine the factors that lead to sustained hormonal remission in patients with pituitary adenomas.

Material and methods. In this study, retrospective analysis of 33 patients with pituitary adenomas with no prior DA treatment was performed. Ten (30.3%) patients experienced microprolactinomas, 19 (57.6%) — macroprolactinomas, 4 (12.1%) — giant prolactinomas. All patients underwent endoscopic endonasal transsphenoidal surgery. Plasma PRL levels were obtained before surgery, and then 1 day, 1 week, 1 month, 3 months later and every 6th month after surgery. MRI monitoring was performed before surgery and then 3 and 12 months later, and then annually.

Results. Average preoperative plasma PRL serum levels for all patients with no preoperative DA treatment were 530 ng/mL (ranging 65–1440 ng/mL). Cavernous sinus invasion (Knosp 3, Knosp 4) was observed in 16 (48.4%) cases. Depending on cavernous sinus invasion, hormonal remission with no DA therapy after surgery was achieved in Knosp 0–2 — in 16 (94.1%) cases, Knosp 3 — in 4 (44.4%) cases. In cases of Knosp 4 biochemical remission was not achieved in all 7 (100%) patients. Only with further DA therapy biochemical remission was achieved. The biochemical remission was achieved in 10 (100%) cases of microadenomas, in 7 (58.3%) cases of macroadenomas after surgery with no DA therapy. Remission of endocrine symptoms was achieved in 18 (81.8%) cases with no DA therapy after surgery. The follow-up was up to 3 years.

Conclusions. Biochemical remission could be surgically achieved in 100% of cases with microprolactinomas. In cases of macroprolactinomas the adenoma size (up to 24 mm) has an important role in achieving biochemical remission. Cavernous sinus invasion (Knosp 0–2) is a prognostic factor. The ophthalmic disturbances regression in macro and giant pituitary adenomas was found to be achieved much faster in surgical management rather than using DA.

Key words: *pituitary adenoma; endoscopic surgery; prolactinomas; hormonal remission*

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Чи можливо досягти гормональної ремісії пролактином хірургічно? Наш досвід

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Відділення ендоскопічної та краніофаціальної нейрохірургії з групою ад'ювантних методів лікування, Інститут нейрохірургії ім. акад. А.П. Ромоданова НАМН України, Київ, Україна

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Мета: визначити чинники, котрі призводять до стійкої гормональної ремісії у хворих з аденомами гіпофіза (АГ).

Матеріали і методи. Проведено ретроспективний аналіз результатів лікування 33 хворих з АГ. МікроАГ виявлено у 10 (30,3%) хворих, макроАГ – у 19 (57,6%), гігантські АГ – у 4 (12,1%). Усім пацієнтам проведено хірургічне лікування з використанням ендоскопічної ендоназальної методики. Рівень пролактину в крові визначали до операції, наступної доби після операції, через 1 тиж і 3 міс після операції, а потім кожні 6 міс. Магнітно-резонансну томографію гіпофіза із внутрішньовенним контрастуванням виконували через 3 і 12 міс після операції, а потім щорічно.

Результати. Середній доопераційний рівень пролактину в крові без доопераційної терапії агоністами дофаміну (АД) становив 530 нг/мл (від 65 до 1440 нг/мл). Інвазію кавернозного синуса (Knosp 3, Knosp 4) виявлено у 16 (48,4%) спостереженнях. Залежно від інвазії кавернозного синуса гормональної ремісії без АД-терапії після операції досягнуто в 16 (94,1%) випадках Knosp 0-2, у 4 (44,4%) – Knosp 3. У всіх пацієнтів з Knosp 4 біохімічної ремісії не досягнуто. Це вдалося лише після АД-терапії.

Біохімічної ремісії досягнуто в 10 (100 %) випадках мікроАГ та в 7 (58,3 %) – макроАГ після операції без АД-терапії. Регрес ендокринологічних виявів досягнутий у 18 (81,8 %) спостереженнях. Катамнез – до 3 років.

Висновки. Біохімічна ремісія може бути досягнута в 100 % випадків при мікроАГ. При макроАГ важливу роль в досягненні біохімічної ремісії відіграє розмір АГ (до 24 мм), а також інвазія кавернозного синуса. Відзначено, що регрес офтальмологічних порушень при макро- і гігантських АГ досягається значно швидше хірургічно, ніж після терапії АД.

Ключові слова: *аденома гіпофіза; ендоскопічна хірургія; пролактиноми; гормональна ремісія*

Український нейрохірургічний журнал. 2018;(4):51-56

Возможно ли достичь гормональную ремиссию пролактином хирургически? Наш опыт

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Цель: определить факторы, приводящие к стойкой гормональной ремиссии у больных с аденомой гипофиза (АГ).

Материалы и методы. Проведен ретроспективный анализ результатов лечения 33 пациентов с аденомами гипофиза. МикроАГ выявлены у 10 (30,3 %) больных, макроАГ – у 19 (57,6 %), гигантские АГ – у 4 (12,1 %). Всем пациентам проведено хирургическое лечение с использованием эндоскопической эндоназальной методики. Уровень пролактина в крови определяли до операции, на следующий день после операции, через 1 нед и 3 мес, а затем каждые 6 мес. Магнитно-резонансную томографию гипофиза с внутривенным контрастированием выполняли через 3 и 12 мес после операции, а затем ежегодно.

Результаты. Средний дооперационный уровень пролактина в крови без дооперационной терапии агонистами дофамина (АД) составил 530 нг/мл (от 65 до 1440 нг/мл). Инвазия кавернозного синуса (Knosp 3, Knosp 4) выявлена в 16 (48,4 %) наблюдениях. В зависимости от инвазии кавернозного синуса гормональная ремиссия без АД-терапии после операции достигнута в 16 (94,1 %) случаях при Knosp 0-2, в 4 (44,4 %) – при Knosp 3. У всех пациентов с Knosp 4 биохимическая ремиссия не достигнута. Это удалось только после АД-терапии. В 10 (100 %) случаях – микроАГ и 7 (58,3 %) – макроАГ после операции была достигнута биохимическая ремиссия без АД-терапии. Регресс эндокринологических проявлений достигнут в 18 (81,8 %) наблюдениях. Катамнез – до 3 лет.

Выводы. Биохимическая ремиссия может быть достигнута в 100 % случаев при микроАГ. При макроАГ важную роль в достижении биохимической ремиссии играет размер АГ (до 24 мм), а также инвазия кавернозного синуса. Отмечено, что регресс офтальмологических нарушений при макроАГ и гигантских АГ достигается значительно быстрее хирургически, чем после терапии АД.

Ключевые слова: *аденома гипофиза; эндоскопическая хирургия; пролактиномы; гормональная ремиссия*

Украинский нейрохирургический журнал. 2018;(4):51-56

Introduction

Prolactinomas (PRL) are the most common benign hormonal pituitary tumors (PA) in adults [1, 2]. They account for about 45 % of all pituitary tumors [3]. The earliest manifestation is the secondary amenorrhea and galactorrhea [4], and this happens in women in 75 % cases [5].

Microprolactinomas (< 10 mm in diameter) are more common in women than in men. Symptoms of microprolactinomas in women come up right at the disease onset and manifest with amenorrhea and galactorrhea. Meanwhile6 in men symptoms might come later with impotence and decreased libido. Macroprolactinomas (≥ 10 mm in diameter) are more frequent in men and may present with a tumor mass effect manifesting with visual disturbances, visual field defects. Giant prolactinomas are not often, its prevalence is 0.5–4.4 % of all pituitary cases [6–9]. Very high prolactin (PRL) serum level is revealed in giant PA. Nowadays microprolactinomas are more often diagnosed than it was before. Since the beginning of 1970s, dopamine agonists (DA) were recognized as an effective medical treatment of macroprolactinomas [10, 11]. Bromocriptine, an ergot derivative that binds to and stimulates dopamine (D2) receptors on lactotrophic cells, represents the initial treatment. It has proved to be effective in suppressing PRL secretion, reducing prolactinoma size and restoring gonadal function in many patients [12–14]. In the collaborative European multicenter study on 459 women with prolactinomas, normoprolactinemia was achieved in 59 %

This article contains some figures that are displayed in color online but in black and white in the print edition

when using bromocriptine [15]. The recent studies showed that normal PRL level can be achieved in 80–90% when using DA therapy. Relevant systemic side effects, including vomiting, nausea, dizziness, headache have been reported in about one third of patients treated with DAs [16, 17].

Patients and methods

This study included 33 patients who underwent primary pituitary surgery for prolactinomas with no prior DA treatment (19 females, 14 males; age ranged 20–67 years). Ten (30.3%) patients experienced microprolactinomas, 19 (57.6%) — macroprolactinomas, 4 (12.1%) persons — giant prolactinomas. According to cavernous sinus invasion, patients were divided into 2 groups: without cavernous sinus invasion (Knosp 0–2) — 17 (51.5%), with cavernous sinus invasion (Knosp 3–4) — 16 (48.5%) cases ***(see Table)***. Endoscopic endonasal transsphenoidal (EET) surgery was performed by single neurosurgeon. Plasma PRL levels were obtained before surgery, and then on the 1st day, one week, one month, three months later and then every 6th month after surgery. Catamnesis 5 years of MRI monitoring was performed before surgery and then 3 and 12 months later, then annually.

Preoperative work-up

All patients had a fasting PRL serum level. Besides, we evaluated anterior pituitary functions. Plasma PRL levels were obtained before surgery, and then on the 1st day, 1st week, 1st month, 3rd month and every 6th month after surgery.

All patients were consulted by ophthalmologist for visual field defects, sight accuracy was checked.

Magnetic resonance imaging (MRI) of the sellar region was performed with gadolinium to all the patients. MRI was performed before surgery and then 3, 6 and 12 months later, then annually after surgery. High-resolution paranasal sinus computed tomography (CT) sections were obtained and reconstructed in a three-dimensional fashion. Cavernous sinus invasion was evaluated by MRI and/or during the surgery.

Surgical technique

All patients underwent endoscopic endonasal trassphenoidal surgery using binostril (4-hand) technique. A patient was in supine position. The head was positioned with slight rotation towards the surgeon and about 20° inclination to align paraseptal corridor to facilitate endoscopic exposure. We used 0° or 30° angle (Karl Storz, Tuttlingen, Germany) for binostril endoscopic approach. Inside the sphenoid sinus bony landmarks were defined such as: sella turcica, optic protuberance, carotid protuberances, opticocarotid recess, tuberculum sella. Sella turcica was opened widely, from one cavernous sinus to the other, which ensured the maximum exposure of the sella turcica and its contents (tumor, pituitary gland). EET technique allows visualize the pituitary gland, identify the tumor and a safe tumor dissection from surrounding anatomically important structures (medial wall of cavernous sinus, pituitary gland, pituitary stalk) was performed. After tumor removal, sella turcica reconstruction was performed in respect to CSF leak, using multilayer technique (inlay of fascia lata and outlay + nasoseptal flap) or free grafts (fat + bone or fascia lata + bone).

Baseline characteristics of 33 patients with PRL pituitary adenomas

Variables	Patients (n = 33)
Sex, F/M	19/14
Age, years	20–67
Microadenoma (%)	10 (30.3)
Macroadenoma (%)	19 (57.6)
Giant adenoma	4 (12.1)
Cavernous sinus invasion (%)	16 (48.5)
Long-term follow-up	
Remission	
Microadenoma (%)	10 (100)
Macroadenoma	10 (52.6)
• Size less then 24 mm (%)	8 (88.9)
• Size more then 25 mm (%)	2 (20)
Giant adenomas (%)	0
Recurrence (%)	4 (12.1)

Results

Median preoperative plasma PRL serum level for all patients with no preoperative DA treatment was 530 ng/mL (ranging, 65–1440 ng/mL). In case of microprolactinomas, median preoperative PRL plasma level was 573.1 ng/mL (ranging 65–1440 ng/mL). TTH was decreased in 7 (21%) cases. Cortisol level was decreased in 14 (42.4%) cases.

Cavernous sinus invasion was observed in 16 (48.4%) cases confirmed by MRI and during surgery. Seventy-six percent of female patients complained about amenorrhea and/or infertility, and 5 (35.7%) male patients had symptoms including decreased libido and/or impotence. Galactorrhea appeared in 7 (21.2%) female patients. In 9 cases symptoms included visual disturbances.

The biochemical remission was achieved in 10 (100%) cases of microadenomas, in 7 (58.3%) cases of macroadenomas after surgery with no DA therapy. Follow-up lasted to 3 years. Hypopituitary syndrome was observed in 14 (42.4%) cases. Cavernous sinus invasion has a significant effect on further hormonal remission [18]. Depending on cavernous sinus invasion, hormonal remission with no DA therapy after surgery was achieved in Knosp 0–2 in 16 (94.1%) cases, Knosp 3 — in 4 (44.4%) cases. In cases of Knosp 4 biochemical remission was not achieved at all 7 (100%) patients. Only with further DA therapy biochemical remission was achieved.

Endocrinological remission was achieved in 18 (81.8%) cases with no DA therapy after surgery. Hormonal disorders were not present in 6 (18.2%) cases.

Visual improvement was observed in all (100%) cases after surgery.

Postoperative complications such as CSF leak, meningitis, additional oculomotor disorder or visual impairment have not been established. No mortality.

Discussion

Among all the hormone-active pituitary adenomas, prolactinomas are the most common. As recent studies show, high levels of PRL are observed both in micro and macroadenomas [18–22]. Giant prolactinomas are characterized by extremely high PRL level in plasma, which can be up to 10.000 ng/ml. In our series, the average PRL serum level was 530 ng/ml, ranging 65–1440

ng/ml. In case of microadenomas, the mean prolactin level was 573.1 ng/ml, ranging 65–1440 ng/ml. For macroadenomas mean PRL serum level was 442.6 ng/ml, ranging 236–850 ng/ml. In case of giant pituitary adenomas, the average PRL level was 525.2 ng/ml, ranging 426–1036 ng/ml. Drug therapy decreased PRL level to normal in 40–100 % cases. Menses normalized in 77 %, sexual function restored in men by 60–100 %, visual disturbances regressed in 67–84 % [2, 17, 18, 20, 23, 24]. DA therapy has number of side effects. It is known that DA affects the pituitary D2 receptors that inhibit the activity of adenylyl cyclase and, as a result, suppress gene transcription and prolactin secretion. However, DAs have a significant effect on other dopamine, serotonin androgenic receptors, which leads to severe neurological disorders such as postural hypotension or dyskinesia, psychosis, or mania, which provoke compulsive states [25–27]. Patients with pituitary microadenomas were offered for medication therapy for several years with a possible biochemical remission of 40–100 % [17], or EET surgery over the micro and macroprolactinomas (tumor should be removed in capsule). This allows biochemical and clinical remission to be achieved within a short period of time. Macroadenomas would give recurrence over 6-month period in more than 40 % cases. We noticed that starting from 25 mm would likely to recure. Meanwhile, adenomas, which size is less than 24 mm, would give 88.9 % remission in catamnesis up to 4 years, but giant pituitary adenomas are always to cured. There are several features that leads to recurrence, one is the tumor size, and the other is cavernous sinus invasion [18, 24, 28]. Cavernous sinus invasion significantly influents the remission rate; p = 0.003. In case of cavernous sinus invasion, we have PRL remission in Knosp 0–2 in 16 (94.1 %) cases, Knosp 3–4 — in 44.4 % ***(Fig. 1)***. In Knosp 4 invasion all patients experienced recurrence.

Also, there was relation between hormonal remission and tumor size (p = 0.000). Biochemical remission after surgery was achieved in all 10 (100 %) cases with microadenomas, in 9 cases (88.9 %) with macroadenomas, which size is less than 24 mm, with no use of DA ***(Fig. 2)***.

Indications for surgery were: ophthalmic disorders, hypopituitary syndrome, patient's choice for surgery to avoid DA therapy with their consequences. In order to have total removal with capsule, to control the hormone level, the removal of the tumor should be radical. The surgery option was proposed only in cases of microadenomas and adenomas up to 18 mm. It is known that prolactinomas decrease in size by 50 % just on medication therapy, but fear to have visual deterioration or pituitary function decrease over this period of time is high.

We offer prolactinoma surgery vs DA therapy in order to avoid the latter. It was patient's conscious choice to have 100 % microadenoma removal with 100 % success biochemical remission, rather than 40–100 % in medication DA therapy with all following consequences.

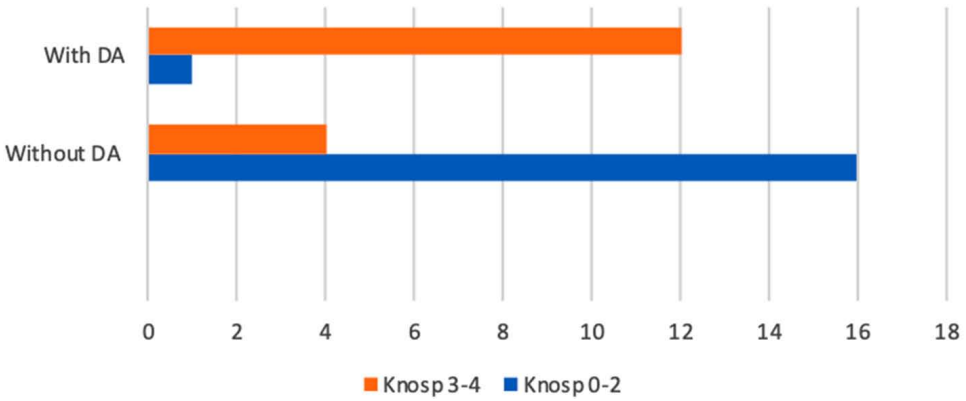


Fig. 1. Hormonal remission rate after EETsurgery

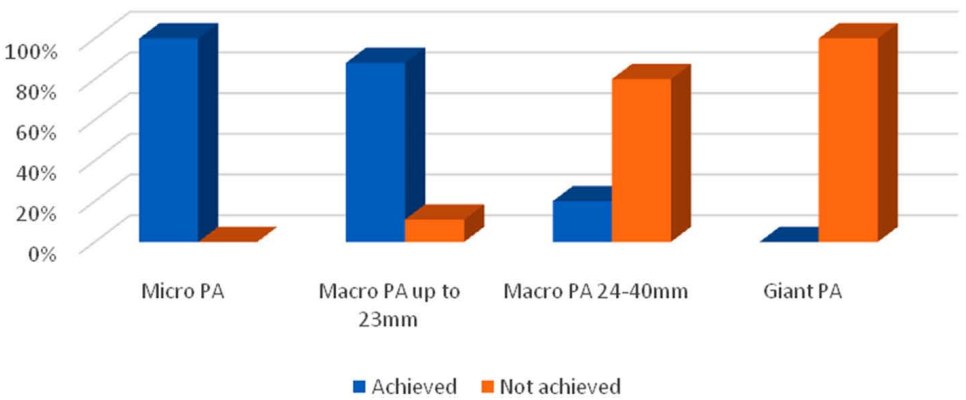
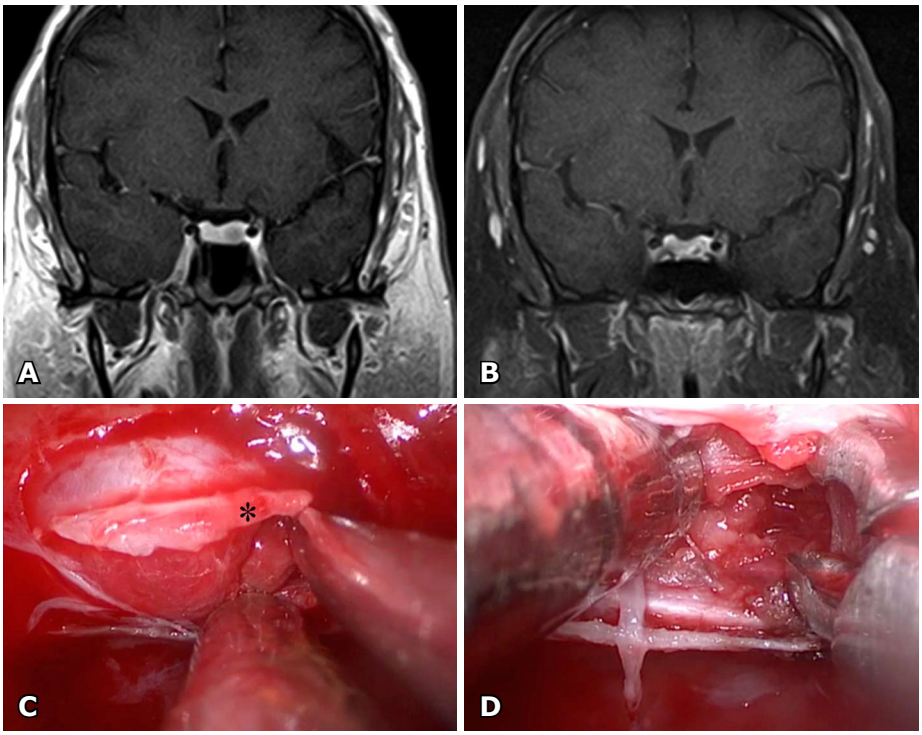
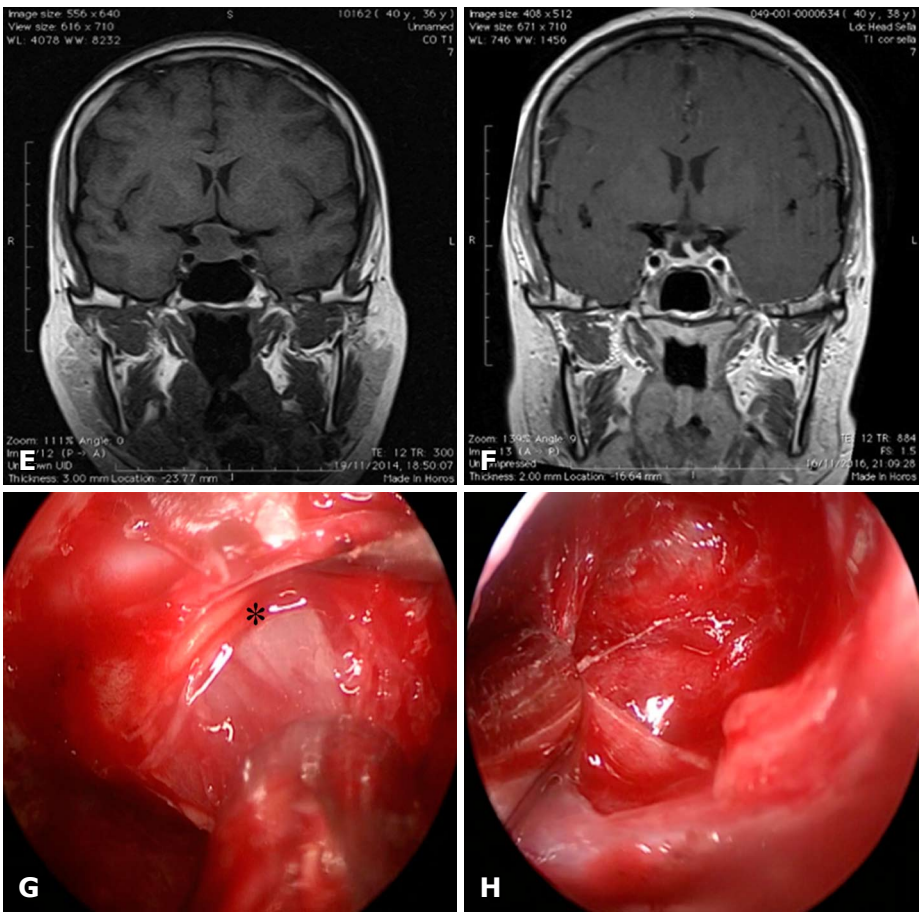


Fig. 2. Hormonal remission depending on the tumor size

Clinical cases



Case 1. Women 30 years old, presenting with amenorrhea, galactorrhea. Preoperative T_1-weighted image with dynamic Gd contrast (A) demonstrated hypointensive lesion $7 \times 5 \times 6$ mm. PRL level was 1164 ng/ml. Endoscopic endonasal resection of microadenoma was offered. Intraoperative images are presented (C, D). Image C shows intraoperative endoscopic view of pituitary adenoma (*) and pituitary gland left hand side from macroprolactinoma. Image D shows intraoperative endoscopic view after microprolactinoma total removal. The Image B demonstrates coronal and sagittal postoperative T_1-weighted image with dynamic Gd contrast after surgery. Following surgery, the patient's prolactin level returned to normal one. Patient got pregnant 3 months after surgery. Catamnenis 2 years. No DA after surgery.



Case 2. Women 37 years old, presenting with dysmenorrhea, galactorrhea. Preoperative T_1- and T_2-weighted images (E) demonstrate hypertensive lesion with suprasellar extension $13 \times 18 \times 17$ mm, Knosp 1. PRL level was 850 ng/ml. Patient underwent EET resection over macroadenoma. Intraoperative images are presented (G, H). The image G shows intraoperative endoscopic view of macroprolactinoma (*). Image H shows intraoperative endoscopic view after macroprolactinoma total removal. Postoperative MRI with dynamic Gd contrast (F) showed total resection of the tumor with suprasellar cistern decompression. Prolactin level returned to normal one within 3 months. No DA therapy after surgery. Catamnenis 4 years.

Conclusions

Biochemical remission could be achieved surgically, especially in microprolactinomas, in 100 % cases.

Biochemical remission might be achieved surgically in macroprolactinomas with size up to 24 mm (88.9 %); cavernous sinus invasion (Knosp 0–2) is a prognostic factor.

Ophthalmic symptoms regression is achieved in 100 % patients, faster in comparison to DA therapy.

Menses normalized in 100 % cases of microprolactinomas and in 86 % in macroadenomas with size up to 24 mm.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

The written informed consent was obtained from each patient or appropriate family member before the surgery.

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