



Restoration of fertility in a woman with giant prolactinoma in response to cabergoline treatment

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Summary

A 32-year-old woman presented with primary amenorrhoea, prolactin (PRL) level of 154 150 mIU/L and was diagnosed with a giant pituitary adenoma measuring maximum 6.2 cm. Cabergoline (CAB) treatment at a dose of 0.5 mg/week was prescribed to the patient. The treatment decreased the tumour size after 3 months (MRI scans of the brain) and brought back to normal the level of the PRL (345 mIU/L) after 6 months of CAB treatment. After 7 months of CAB treatment, menarche was achieved, and after 12 months, the patient became pregnant. She discontinued taking CAB at 4-week gestation. The pregnancy resulted in a missed miscarriage at 6–7 weeks; an abortion was conducted by the vacuum aspiration method. The MRI scans of the brain did not show any tumour enlargement. After 18 months from the start of the treatment the patient got pregnant for the second time. At 25-week gestation an MRI scan of the brain was conducted which did not show any increase in the tumour size. At 38 weeks the patient delivered a healthy full-term girl via C-section. The patient chose not to breastfeed and resumed CAB therapy after the delivery. During the treatment, the PRL level returned to the normal range and the menstrual cycle was restored. After 3 years the patient got pregnant for the third time. The patient did not receive CAB during the pregnancies; the examination did not show any tumour enlargement. Further MRI scans did not show any tumour growth. CAB therapy was effective in normalization of the PRL level, tumour shrinkage, menarche and pregnancy-induction which led to the birth of healthy children in a woman with primary amenorrhoea and a giant prolactinoma invading the skull base bones.

Learning points:

- Giant prolactinomas are very rarely found in women.
- Cabergoline therapy can be effective in the normalization of the PRL level, tumour shrinkage, menarche induction in a woman with primary amenorrhoea, and giant prolactinoma.
- Cabergoline therapy can be effective in pregnancy induction which leads to the birth of children in a woman with giant prolactinoma.
- Cabergoline discontinuation did not trigger tumour enlargement during pregnancy.



Background

Giant prolactinomas are a rare entity; they are mainly found in men, are locally aggressive, invading the cavernous sinuses and skull base bones, and extending to the nasal cavity, paranasal sinuses and nasopharynx (1, 2). Giant prolactinomas are very rarely found in women and are described mainly in postmenopausal women. Consequently, the present clinical case of a young woman with a giant prolactinoma with the restoration of fertility is of interest. At the present time the main method of treatment of prolactinomas, including giant prolactinomas, is dopamine agonist therapy, which is effective in achieving normalization of the PRL level and eyesight, reduction of the tumour volume in the majority of patients and restoration of fertility (3, 4, 5, 6). We present a woman with a giant prolactinoma. Despite the giant size of the tumour which invaded the skull base bones, high PRL level and primary amenorrhoea, cabergoline was effective in normalization of the PRL level, tumour shrinkage, menarche and pregnancy induction which led to the birth of children.

Case presentation

A patient aged 32 years was referred to N.N. Burdenko National Medical Research Centre of Neurosurgery in December, 2007 to receive surgical treatment.

The patient is married, has a high school education and was brought up in an orphanage.

Medical history: the patient presented with primary amenorrhoea. The patient did not consult doctors in connection with this disorder as she attributed it to the congenital impairment of her internal genital organs. The patient did not have a sex life and did not notice any discharge from her breasts. After the start of sexual activity at the age of 32 years, the patient sought medical help.

Results of physical, laboratory and instrumental examination: The patient is of normal build, demonstrates homogenous adipose tissue, height: 163 cm, weight: 64 kg, BMI: 24 kg/m² and demonstrates a female pattern of hair distribution. The breasts are symmetrical and normally developed. Nipples and areola are of normal shape. Lactorrhoea was not detected. An ophthalmological examination did not reveal any visual disturbances. Neither mental nor neurological disorders were revealed.

Investigation

A hormonal blood test (25/11/2007) showed an elevated serum PRL level up to 154 150 (normal range

(NR): 40–530) mIU/L, thyroid-stimulating hormone (TSH) – 1.09 (NR: 0.4–4.0) mIU/L, free T4 – 12.5 (NR: 10–22) pmol/L, cortisol – 458 (NR: 138–699) nmol/L, luteinizing hormone (LH) – 1.5 (NR: 1.9–12.5) mIU/L, follicle-stimulating hormone (FSH) – 5.7 (NR: 2.5–10.2) mIU/L, oestradiol – 35 (NR: 72–529) pmol/L. There was no evidence of hypothyroidism or secondary adrenal insufficiency.

A pelvic ultrasound revealed hypoplasia of the uterus (35×33×31 mm), and the endometrium measured 3 mm in thickness. The right ovary measured 29×25×21 mm, the left ovary measured 26×16×16 mm, the follicles were 5–8 mm in diameter, and peripherally arranged in both ovaries.

MRI scans of the brain revealed a giant pituitary tumour invading the sphenoidal sinus, both of the cavernous sinuses, the ethmoid sinus with significant multilobular intracranial extension. The maximum size of the adenoma is equal to 6.2 cm (Fig. 1A and B). The patient was diagnosed with an endo-supra-latero (S, D)-infraseellar giant prolactinoma, primary amenorrhea.

Treatment

Given the fact that the tumour is hormone producing, the patient was recommended CAB therapy at an initial dose of 0.25 mg twice a week, with a gradual increase of the dose under monthly control of the PRL level. After a month from the beginning of the treatment, the patient's PRL level reduced to 15 891 mIU/L. The dynamics of the PRL level are shown in Fig. 2.

An MRI scan of the brain conducted 3 months after the beginning of treatment showed a remarkable shrinkage of the suprasellar part of the tumour, formation of an empty sella with a residual tumour in the cavernous sinuses (Fig. 1C and D). After 6 months of treatment, the PRL level was brought back to normal (345 mIU/L) at a dose of CAB of 1 mg per week.

After 7 months the patient achieved menarche with further regular menses. After 12 months, MRI scans revealed almost complete tumour regression with the forming of an empty sella, a residual tumour (to 3–4 mm), in the cavernous sinuses (Fig. 1E and F). Further MRI scans carried out between 2007 and 2017 did not show any tumour enlargement.

The patient was advised to use contraception, but she neglected to follow the recommendations and got pregnant in December 2008. She discontinued taking CAB at 4 weeks gestation. Nevertheless, at 6–7 weeks of gestation the ultrasound investigation showed an

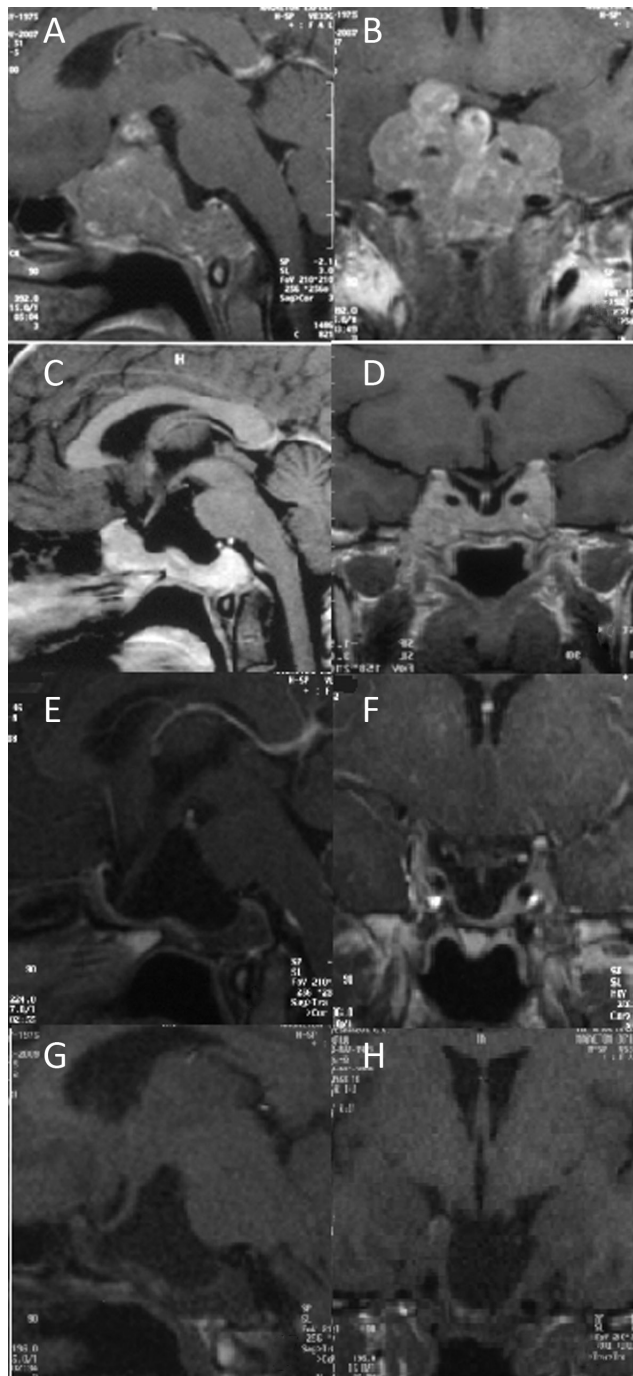


Figure 1

The dynamics of a giant prolactinoma in a 32-year-old woman (see the description in the text). (A and B) Before CAB treatment. (C and D) After 3 months of CAB treatment. (E and F) After 12 months of CAB treatment. (G and H) At 25 weeks gestation.

anembryonic pregnancy. At 11 weeks of gestation an abortion was conducted by the vacuum aspiration method. The abortive material was not investigated. The patient continued taking CAB at a dose of 1 mg per week.

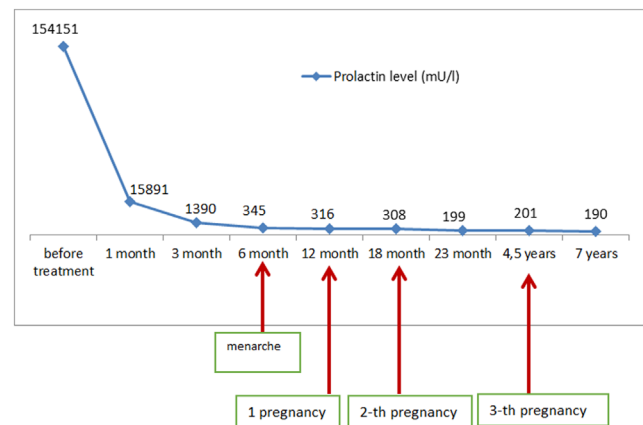


Figure 2

The dynamics of the PRL level in response to CAB treatment in a 32-year-old woman with a giant prolactinoma.

The menstrual cycle was restored 1.5 months after the abortion.

In June 2009 the patient got pregnant for the second time. She discontinued taking CAB at 4 weeks gestation. The patient's condition during the pregnancy was satisfactory. The patient underwent an ophthalmological examination once in 3 months, which did not show any visual field impairment. However, considering the possible growth of the tumour during the pregnancy, at 25 weeks of gestation an MRI scan of the brain was conducted that did not reveal any tumour enlargement. Still, a residual tumour (to 3–4 mm) remained in the cavernous sinuses; there was no tumour apoplexy. At 38 weeks the patient gave birth to a healthy girl (weight 3200 g, height 50 cm, Apgar score of 8/9), via C-section. The newborn baby did not have any signs of intrauterine growth retardation or abnormal development; the weight of the newborn was appropriate for the gestational age at the moment of birth. The postpartum period was uneventful. The patient chose not to breastfeed. CAB therapy was resumed (the PRL level was not measured) at a dose of 0.5 mg per week on the first day after the delivery because of the residual tumour in the cavernous sinuses (according to the MRI during pregnancy). After 2 months the PRL level returned to normal (199 mIU/L), and the menstrual cycle was restored 4 months after the delivery.

After 3 years the patient got pregnant for the 3rd time (CAB therapy was discontinued at the start of the pregnancy). At 38 weeks the patient gave birth to a healthy girl via C-section. MRI scans were not conducted during the pregnancy. The patient resumed CAB therapy at a dose of 0.5 mg per week after the delivery. The following MRI scans did not demonstrate any tumour enlargement.



Outcome and follow-up

It is worth pointing out that in the above mentioned rare case, despite the giant size of the tumour which invaded the skull base bones, the high PRL level and primary amenorrhoea, CAB therapy was effective in normalization of the PRL level, tumour shrinkage, menarche and pregnancy-induction which led to the birth of healthy children. A 10-year follow-up of this patient demonstrated stable positive dynamics of the clinical symptoms, normalization of the PRL level and absence of any tumour relapse in response to the exposure of low-dose CAB treatment.

Considering the clinical and biochemical remission of the patient in response to long-term CAB treatment, steady long-term normalization of the PRL level and no tumour growth on the MRI scan, the patient can discontinue CAB therapy after one further follow-up. In the case of a PRL increase CAB treatment should be continued.

Discussion

Hyperprolactinaemia is one of the main causes of infertility (7). The most frequent culprit of hyperprolactinaemia is prolactinomas – PRL-secreting pituitary tumours. Women in most of cases are diagnosed with pituitary microadenomas. Macroadenomas are a less frequent cause of hyperprolactinaemia in women. Tumours >4 cm in diameter are extremely rare in women. Only isolated cases of tumours >6 cm in diameter in women are reported (8). Particularly, among 18 patients with tumours of this size described in the investigation of Shimon I., there were only two women (9). The restoration of the gonadotrophic axis is shown in the majority of patients with macroprolactinomas in response to CAB treatment (10). However, the data on the restoration of the reproductive function in women with giant tumours goes practically unreported. Previously we conducted research on 63 patients with giant prolactinomas >6 cm in diameter, of whom only 18 were women. Eight of them aged 18–44 years (median: 39) received primary CAB treatment, however, in only three of them were the menses restored (11). CAB treatment in the majority of cases leads to the reduction of the PRL level in blood serum and the restoration of the ovulatory cycle in women with prolactinomas (12).

Nevertheless, the following problems can arise in cases of a giant prolactinoma:

1. Even PRL level normalization and tumour shrinkage do not always result in the restoration of the menstrual cycle, which is probably linked to the long-term pituitary compression with a giant tumour and pituitary cells atrophy, including the gonadotrophin-secreting cells. Given the aggressive character of the majority of giant prolactinomas and the risk of their growth, the prescription of oestrogen/gestagen therapy to patients with such tumours is restricted. The treatment can be recommended only in cases where it does not lead to a significant PRL level growth and tumour enlargement.
2. Giant prolactinomas can be completely or partially resistant to CAB therapy; surgical and/or radiological treatment of such tumours is accompanied by the increase of hypopituitarism (13).
3. A high oestrogen level in the blood during pregnancy can trigger the enlargement of prolactinomas. According to the European and Russian recommendations in diagnosing and treatment of hyperprolactinaemia, it is advised to discontinue dopamine agonists (DAs) at the start of pregnancy. It is recommended to resume DA therapy in case any clinical signs of tumour enlargement are present during the pregnancy (14, 15). Over 900 cases of patients' exposure to CAB during pregnancy have been reported, although in most of the described cases women discontinued CAB treatment at 3–4 weeks of gestation (12, 16). At the present moment there is no evidence of the increase of the number of spontaneous abortions, preterm deliveries, multifoetal pregnancies and congenital malformations in comparison with the normal population (16).
4. Transsphenoidal surgery during pregnancy can be an alternative method of treatment in cases where CAB therapy is ineffective, but it is much riskier than outside of pregnancy. However, considering the rare incidence of giant prolactinomas and absence of recommendations of pregnancy follow-up in women with such tumours, an individual approach is required.
5. Visual fields should be assessed periodically during gestation in women with macroadenomas. It is recommended to perform visual field assessment followed by MRI without gadolinium in pregnant women with prolactinomas who experience severe headaches and/or visual field changes. For patients who have macroadenomas and have not undergone prior pituitary surgery, it is prudent to undertake more frequent clinical examinations and visual field testing (15).
6. One of the frequently reported opinions in giant prolactinomas therapy is to prescribe high doses of CAB



at the beginning of the treatment with further gradual reduction of the dose (17). However, the CAB treatment of extensive and/or invasive macroprolactinomas can provoke complications such as the development of cerebrospinal fluid (CSF) rhinorrhoea (18). We start the treatment of patients with extensive and/or invasive macroprolactinomas, especially in cases of invasion in the structures of the base of the skull, with small CAB doses (0.5 mg per week), with a further increase of the dose. It can stave off the fast shrinkage of the tumour and prevent the risk of CSF rhinorrhoea development (10, 19, 20). Considering a fast normalization of the PRL level and substantial tumour shrinkage in the described case, there were no indications for increasing the CAB dose.

The case described in the present article shows a 32-year-old patient who did not have a menstrual cycle. The absence of galactorrhoea in the patient was probably linked to long-established hyperprolactinaemia and the lack of adequate levels of oestrogen and progesterone. A giant adenoma compressed the pituitary, but in spite of it, the pituitary function remained unimpaired. When the PRL level was stabilized the restoration of a gonadotrophin secretion was observed, which was accompanied by menarche after 7 months, and fertility restoration after a year of CAB therapy. However, the first pregnancy resulted in a missed miscarriage for unknown reasons. The two following pregnancies led to the birth of healthy children. CAB discontinuation did not trigger any tumour enlargement during the pregnancies.

Patient's perspective

Some women are unaware of the necessity to consult a doctor in the case of menstrual dysfunction, including amenorrhoea, in order to facilitate the early diagnostics of its causes. The treatment with cabergoline helped me to get pregnant and give birth to two healthy children.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written consent has been obtained from the patient.

Author contribution statement

L I Astaf'eva, B A Kadashev – purpose statement. Y G Sidneva – writing about methodology. P L Kalinin, G A Melnichenko – research design. S A Agadzhanian – research questions.

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