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Clinical and Radiological Characteristics of a Patient with a Pituitary Tumor of the Prolactinoma Type — Case Report

Charakterystyka kliniczna i radiologiczna pacjentki z guzem przysadki typu prolactinoma — opis przypadku

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Abstract

Introduction. Prolactinoma is a benign tumor of the anterior lobe of the pituitary gland. It is the most common type of pituitary adenoma. In terms of size, micro- and macroprolactinomas are distinguished. Prolactinoma is mostly a benign tumor (>98%). Symptoms in hyperprolactinemia are the result of excess hormone and mass effect. Symptoms of the mass effect include headaches, visual disturbances and dizziness. Excess prolactin leads to infertility and "amenorrhea — galactorrhea" syndrome.

Aim. To increase general understanding and awareness of the symptoms, causes, and treatments of patients diagnosed with prolactinomas.

Case Report. A 54-year-old female patient was admitted to the department for diagnosis due to left-sided headaches occurring for 6 years. Magnetic resonance imaging (MRI) of the pituitary gland was performed, which showed a 20×10×17.5 mm lesion. Blood tests showed high PRL values of 272.0 ng/ml (N<23.3 ng/ml). The patient was treated conservatively with cabergoline, achieving normalization of PRL levels and a reduction in tumor dimensions on follow-up MRI examination.

Discussion. Drug treatment of the patient with cabergoline led to normalization of prolactin levels and reduction in the size of the pituitary adenoma. Conservative treatment of hyperprolactinemia in the course of a prolactinoma adenoma is many years.

Conclusions. Pituitary adenomas of the prolactinoma type respond well to conservative treatment with dopamine agonists. Pituitary tumors should be considered in the differential diagnosis in cases of headaches, and if menstrual disorders or irregular menses are additionally present, it is necessary to complete the diagnosis for hyperprolactinemia.
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Key Words: hyperprolactinemia, menstrual disorders, pituitary tumor, prolactinoma

Streszczenie

Wstęp. Prolactinoma to łagodny guz przedniego płata przysadki mózgowej. Jest to najczęstszy rodzaj gruczolaka przysadki. Pod względem wielkości wyróżnia się mikro- i makroprolaktynoma. Prolactinoma jest w większości przypadków guzem łagodnym (>98%). Objawy w przebiegu hiperprolaktynemii są wynikiem nadmiaru hormonu i efektu masy. Objawy efektu masy to bóle głowy, zaburzenia widzenia, zawroty głowy. Nadmiar prolaktyny prowadzi do niepłodności i zespołu „brak miesiączki — mlekotok".

Cel. Zwiększenie ogólnego zrozumienia i świadomości w zakresie objawów, przyczyn i metod leczenia pacjentów, u których zdiagnozowano prolactinoma.

Opis przypadku. 54-letnia pacjentka została przyjęta na oddział w celu diagnostyki z powodu lewostronnych bólów głowy występujących od 6 lat. Wykonano rezonans magnetyczny (MRI) przysadki mózgowej, który wykazał zmianę w siodle tureckim o wymiarach 20×10×17,5 mm. Badania krwi wykazały wysokie wartości PRL wynoszące 272,0 ng/ml

(N<23,3 ng/ml). U pacjentki zastosowano leczenie zachowawcze kabergoliną uzyskując normalizację poziomu PRL i zmniejszenie wymiarów guza w kontrolnym badaniu MRI.
Dyskusja. Leczenie farmakologiczne pacjentki kabergoliną doprowadziło do normalizacji poziomu prolaktyny i zmniejszenia rozmiarów gruczolaka przysadki. Ponadto po 6 miesiącach leczenia uzyskano powrót miesiączek, co świadczy o tym iż przez wiele lat oś gonadalna była hamowana przez wysokie wartości PRL. Leczenie zachowawcze hiperprolaktynemii w przebiegu gruczolaka prolaktynoma jest wieloletnie.
Wnioski. Gruczolaki przysadki typu prolactinoma dobrze reagują na leczenie zachowawcze agonistami dopaminy. W przypadku bólów głowy należy w diagnostyce różnicowej uwzględnić guzy przysadki, a jeś1i dodatkowo występują zaburzenia miesiączkowania lub miesiączki nieregularne, konieczne jest uzupełnienie diagnostyki w kierunku hiperprolaktynemii. **(PNN 2024;13(2):78–84)**
Słowa kluczowe: hiperprolaktynemia, zaburzenia miesiączkowania, guz przysadki, prolaktynoma

Introduction

Prolactin (PRL) is a hormone produced by the anterior lobe of the pituitary gland. Assay-specific normal values of PRL are higher in women than in men and are generally lower than 25 µg/l. When the World Health Organization Standard 84/500 is used, 1 µg/l is equivalent to 21.2 mIU/l [1]. Prolactinoma is a benign tumor of the anterior lobe of the pituitary gland consisting exclusively of prolactin-producing cells. It is the most common type of pituitary adenoma. In terms of size, micro- and macroprolactinomas are distinguished. Prolactinomas are mostly benign tumors (>98%). Prolactin is the only pituitary hormone whose serum level can relate to tumor size [2]. Microprolactinoma (<1 cm) is associated with serum prolactin levels <200 ng/ml [3]. Macroprolactinoma is characterized by tumor size >1 cm in diameter in conjunction with serum prolactin levels >200 ng/ml. Prolactin inhibits the pulsatile secretion by the anterior lobe of the pituitary gonadotropic hormones, i.e. luteinizing hormone (LH) and folliculotropic hormone (FSH), and the ovulatory rise of LH, leading to the absence of ovulation. The estrogen-gonadotropin feedback loop is inhibited, so women have low estrogen levels and symptoms of hypoestrogenism. Hyperprolactinemia inhibits GnRH release, leading to a decrease in LH secretion. There may be a direct effect of PRL on the ovary and disruption of LH and FSH signaling, which inhibits estradiol and progesterone secretion, as well as follicle maturation [4].

Hyperprolactinemia is often accompanied by hirsutism or excessive hairiness and elevated levels of dehydroepiandrosterone sulfate (DHEAS). Symptoms in hyperprolactinemia are the result of excess hormone and mass effect. Symptoms of the mass effect include headaches, visual disturbances and dizziness. Excess prolactin leads to infertility and "no menstruation — galactorrhea" syndrome. Galactorrhea can be transient and usually does not go away on its own. For women, the main symptoms of hyperprolactinemia are primarily menstrual disorders in the form of irregular periods, absence of menstruation or lack of ovulation. Gonadal dysfunction depends primarily on the effect of prolactin on the pituitary-gonadal axis, so the return of a normal monthly cycle occurs when prolactin levels are reduced. Additional symptoms in women include anxiety, increased nervous tension and depression. For men, the main symptoms are hypogonadism, impotence and infertility, while galactorrhea is rare. An early symptom is decreased libido. The diagnosis of prolactinoma in men comes late, when symptoms associated with enlargement of the sella turcica are already present. Testosterone levels are low and gonadotropins are still normal. Prolactinomas usually grow slowly, and PRL levels are proportional to tumor size. However, one should be aware of pseudoprolactinomas, which are tumors that lead to hyperprolactinemia due to their location. The cause of the increase in PRL in this case is not a pituitary adenoma, but impaired transport of dopamine from the hypothalamus, which physiologically inhibits PRL. In cases of prolactinoma, prolactin levels are significantly elevated. In the case of lower values, diagnosis for other causes is necessary (Table 1).

In order to exclude endocrine function of the adenoma, other pituitary hormones should be evaluated (TSH — thyroid stimulating hormone, ACTH — adrenocorticotropic hormone, hGH — human growth hormon, FSH — follicle stimulating hormone, LH — luteinizing hormone). In addition, it is advisable to consider the presence of macroprolactin in the differential diagnosis.

The primary imaging test is pituitary magnetic resonance (MRI) revealing the tumor mass. Prolactinomas are pituitary tumors in which conservative treatment is possible. The goal of treatment is a reduction in PRL levels and reduce the size of the tumor with improvement of pressure effects (especially visual disturbances) and prevention of tumor expansion and restoration of gonadal function. The main disadvantage of pharmacological treatment of prolactinomas with DA is that it must be continued for life in most patients [3]. Berinder and co-authors studied a group of 50 patients in 2020 treated with cabergoline achieving a decrease in PRL levels in almost 80% of patients treated with dopamine agonists and a reduction in tumor size. PRL levels should be monitored every 3–6 months for the first year and

Table 1. The table shows the factors that increase PRL concentrations

Physiological factors	Other	Pathological factors
Pregnancy and baby nutrition	TRH	Pituitary tumors
Stimulation of the nipples	VIP	Hypothalamic damage
Neonatal period	Estrogens	Radiotherapy
Stress	Dopamine antagonists (metoclopramide, phenothiazine, haloperidol, reserpine, opioids)	Spinal cord injury
Physical activity		Hypothyroidism
Sleep	MAO inhibitors	Chronic kidney disease
	Cimetidine (i.v.)	Severe liver disease
	Verapamil	
	Liquorice	

every 6–12 months thereafter [5]. The drugs of choice are dopamine agonists (bromocriptine, pergolide, cabergoline) or quinagolide. Bromocriptine was the first dopamine agonist introduced for the treatment of prolactinoma. It should be taken mainly in the evening due to its side effects, nausea,vomiting, drowsiness and headaches. It can also cause constipation and a drop in blood pressure. Quinagolide is administered once a day, while cabergoline is administered 1–2 times a week. The latter two drugs are usually well tolerated. Discontinuation of treatment leads to recurrence or an increase in PRL levels and tumor progression.

Cabergoline is the most effective drug used in the treatment of prolactinomas. It reduces PRL levels, shrinks the tumor and effectively restores gonadal function. Side effects of cabergoline are rare, but nausea and orthostatic hypotension can occur, as with other dopamine agonists [6]. Both cabergoline and bromocriptine are ergot derivatives. Chinagolide is a dopamine agonist that is not an ergot derivative. Its side effects are similar to bromocriptine, but are rare [7].

Pah and his co-authors have shown that cabergoline is more effective and better tolerated than bromocriptine. However, there are more data on the safety of the latter drug during pregnancy, so bromocriptine remains the drug of choice in women with hyperprolactinemia who wish to become pregnant [8].

Surgical treatment is required for large tumors showing rapid growth with visual deterioration, refractory to drug treatment, and for pseudoprolactinomas. Vision loss can occur if an untreated prolactinoma grows pressing on the optic nerve junction, affecting peripheral vision [3].

To increase general understanding and awareness of the symptoms, causes, and treatments of patients diagnosed with prolactinomas.

Case Description

We present the case of a 54-year-old woman who had been experiencing severe headaches for the past 6 years, and at the age of 44 developed loss of menstruation. The patient consented to present her case report. The patient was admitted to the department to expand the diagnosis due to long term headaches. In addition, the patient had a history of hypothyroidism treated with L-thyroxine and had not had menstrual periods for 10 years, which was diagnosed as premature menopause. An MRI of the head was performed, which showed a pituitary gland of the brain with dimensions 11.5×4×8 mm — AP×CC×ML (dimenstion in anterioposterior (AP), mediolateral (ML) and craniocaudal (CC) directions) left sided, not thickened. The posterior lobe of the pituitary is preserved in the correct location. To confirm the pituitary tumor, an MRI of the pituitary gland was performed, which showed a lesion in the sella turcica showed invasion into the right cavernous sinus. The tumor measured 20×10×17.5 mm and had traversed the pituitary gland to the left and occupied 50% of the right internal carotid artery (RICA). Laboratory examination showed the presence of high prolactin values — 272 ng/ml (N<23.0 ng/ml). Due to the patient's headaches, CT angiography of the head was performed. There was no pathological enhancement or loss of contrast in the arteries of the circle of Willis and their main branches. No vascular malformations were visualized. On the right side, the topography of the cavernous sinus and partially of the sella turcica confirmed a tumor mass with soft tissue shading, which showed enhancement after intravenous administration of contrast agent. The patient was consulted ophthalmologically — no visual field abnormalities were found. The solid lesion mass did not compress the optic nerve junction. The patient's baseline blood tests showed no abnormalities (Table 2).

In order to diagnose the endocrine function of the pituitary tumor, evaluation of other pituitary hormones was ordered. The following pituitary hormones were determined: gonadotropins: (luteinizing hormone (LH), folliculotropic hormone (FSH), growth hormone (GH), prolactin (PRL), adrenocorticotropic hormone (ACTH), thyrotropic hormone (TSH)) and the evaluation of peripheral hormones: cortisol, free T4 (fT4), free T3 (fT3) estrogen, IGF-1 (insulin-like growth factor 1). Blood tests showed high PRL values of 272.0 ng/ml (N<23.3 ng/ml). Due to the patient's treatment for

Table 2. Laboratory tests of our patient before the inclusion of cabergoline treatment:

Laboratory test	Laboratory results
Electrolytes	Na — 142.0 mmol/l (N: 136–145 mmol/l) K — 3.93 mmol/l (N: 3.5–5.1)
Glucose	4.71 mmol/l (N: 3.9–5.5 mmol/l)
Morphology	Leukocytes 6.4 tys/µl (N: 3.98–10.04 tys/µl) Erythrocytes 4.1 mln/µl (N: 3.93–5.22 mln/µl) Hemoglobin 12.8 g/dl (N: 11.2–15.7 g/dl) Hematocrit 37% (N: 34.1–44.9%) MCV 90 fl (N: 79.4–94.8 fl) MCH 31 pg (N: 25.6–32.2 pg) MCHC 34.5 g/dl (N: 32.2–35.5 g/dl) RDW-SD 42 fl (N: 36.4–46.3) RDW-CV 13% (N: 11.7–14.4%) Platelets 222 tys/µl (N: 150–400 tys/µl) MPV 10.40 fl (N: 9.4–12.5) PDW 11fl (N: 9.8–16.2 fl) P-LCR 28 (N: 19.1–46.6) PCT 0.2% (N: 0.17–0.35%)
GFR	>90 ml/min/1.73 m² (N: >90 ml/min/1.73 m²)
Creatinine	59.10 umol/l (N: 50.4–98.1 umol/l)
Urinalysis	Result: Transparent texture Color: Straw Specific gravity: 1.016 kg/l (N: 1.015–1.03 kg/l) PH 6.0 Glucose: none Ketones: absent Urobilinogen: normal Bilirubin: absent Protein: none Nitrites: absent Ervtrocytes: detected Leukocytes: not detected
Liver tests ASP ALT	 20 U/l (N: 5–34 U/l) 25 U/l (N: 0–55 U/l)
GGTP	33 U/l (N: 9–36 U/l)

Table 3. Results of the patient's hormonal tests before the inclusion of cabergoline treatment:

Laboratory test	Laboratory results
PRL (N: 4.79–23.3 ng/ml)	272.0 ng/dl
Serum cortisol at 8 am (N: 6.2–19.4 µg/dl)	12.11 µg/dl
ACTH (N: 7.20–63.30 pg/ml)	15.40 pg/ml
IGF1 (N: <248 ng/ml)	145.00 ng/ml
GH (N: 0.0–8.0) ng/ml	1.49 ng/ml
TSH (N: 0.27–4.2 µIU/ml)	3.4 µIU/ml
FT4 (N: 0.93–1.71 ng/dl)	1.23 ng/dl
FT3 (N: 2.04–4.4 pg/ml)	3.17 pg/ml
anti TPO (N: 0.0–34.0 IU/ml)	9.03 IU/ml
anti TG (N: 0.0–115.0 IU/ml)	24.20 IU/ml

many years of primary hypothyroidism with L-thyroxine, antithyroid antibodies (anti-TPO, anti-TG) were additionally determined (Table 3).

The patient was consulted neurosurgically, but due to the nature of the tumor, conservative treatment was decided. Treatment with cabergoline at a dose of 0.5 mg once a week was initiated. After 3 and 9 months, the effectiveness of the treatment was evaluated, noting a significant decrease in PRL concentrations (Table 4).

Table 4. Results of our patient's prolactin (PRL) levels during the following months of cabergoline treatment:

Result	Before treatment	3 months after inclusion of the drug	9 months after inclusion of the drug
PRL (N: 4.7–23.3 ng/ml)	272 ng/ml	5.84 ng/ml	7.0 ng/ml

Another MRI imaging study of the pituitary gland was performed after 6 and 12 months of cabergoline treatment, finding a reduction in tumor size (Table 5).

Table 5. Pituitary adenoma dimensions before and after 6 and 12 months of taking cabergoline. Results of tumor dimensions in anterioposterior (AP), mediolateral (ML) and craniocaudal (CC) directions

Before starting treatment with cabergoline	After 6 months of cabergoline treatment	After 12 months of cabergoline treatment
AP×ML×CC 17.5×20×10 mm	AP×ML×CC 16×17×9.5 mm	AP×ML×CC 15×16×9 mm

The patient had an initial MRI of the head with contrast (Figure 1), a follow-up MRI of the pituitary gland after 6 months without contrast for technical reasons (Figure 2), and another MRI of the pituitary gland with contrast after 12 months (Figure 3). The imaging results are shown in the figures below. Tumour mass indicated with a green arrow.

After normalization of prolactin levels, the function of the hypothalamic-gonadal axis and menstruation returned, indicating that this axis had been inhibited for many years by high PRL values.

After normalisation of prolactin levels, hypothalamicgonadal axis function and menstruation

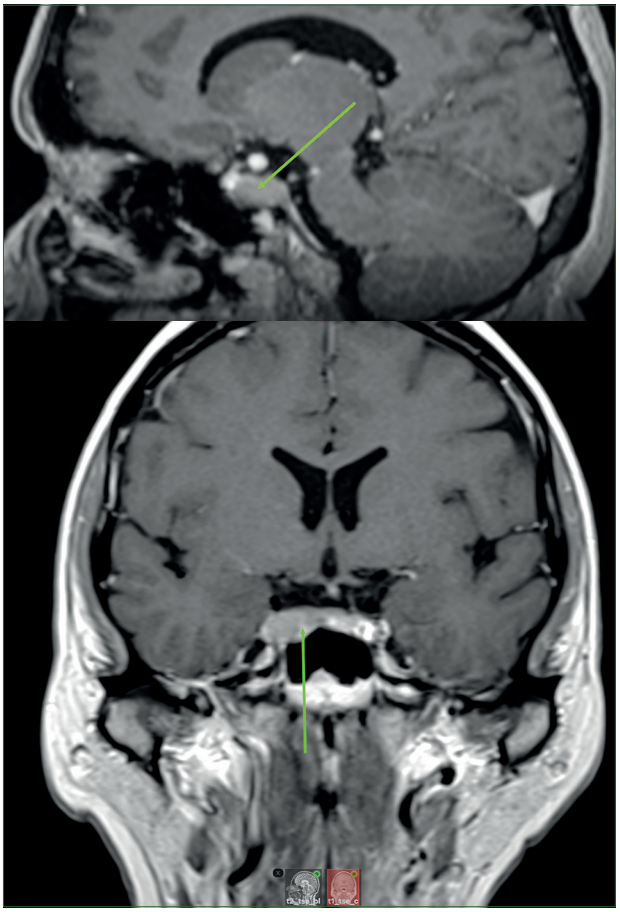

Figure 1. Before treatment

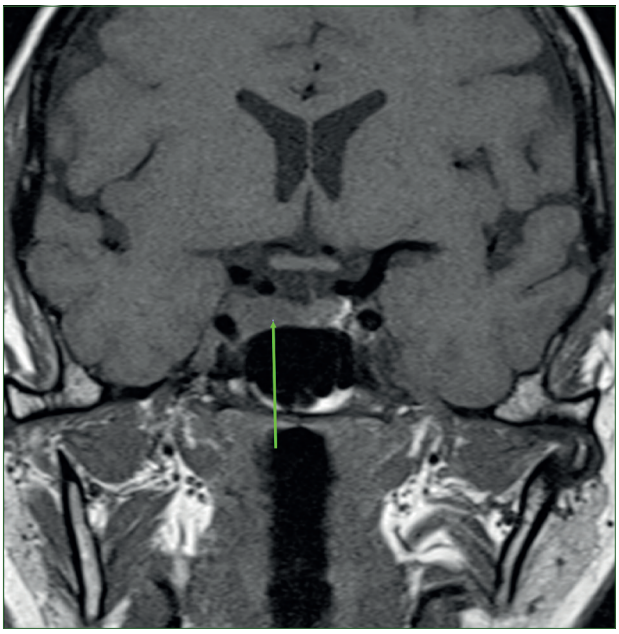

Figure 2. NMR 6 months after treatment

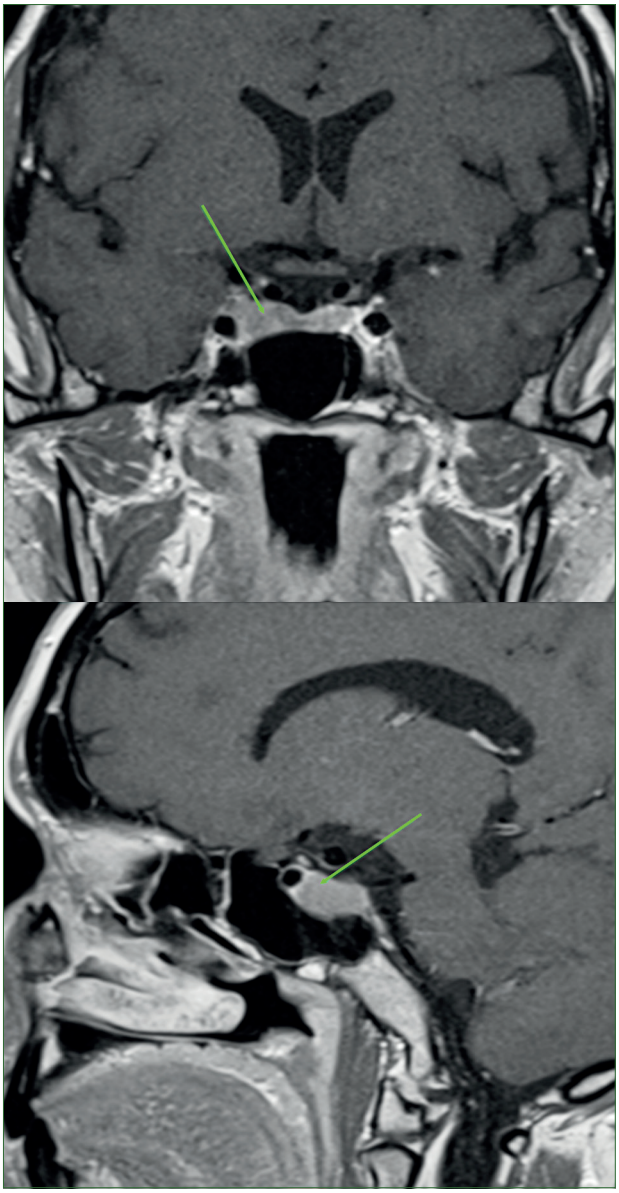

Figure 3. NMR 12 months after treatment

returned, indicating that this axis had been inhibited for many years by high prolactin levels (Table 6). A few months after the normalisation of PRL, FSH values increased (46.73 mIU/ml), indicating the development of menopause appropriate at this age.

Table 6. Results of hormonal tests of the pituitary-gonadal axis of our patient after 6 months of cabergoline treatment:

Hormones		
LH	FSH	Estradiol
follicular phase: 2.40–12.60 ovulation phase: 14.0–95.6 luteal phase: 1.00–11.40 post-menopause: 7.7–58.5	follicular phase: 3.50–12.50 ovulation phase: 4.70–21.50 luteal phase: 1.70–7.70 post-menopause: 25.8–134.8	follicular phase: 3.50–12.50 ovulation phase: 60.4–533 luteal phase: 60.4–232 post-menopause: 0–138
3.37 mIU/ml	6.18 mIU/ml	28.5 pg/ml

The patient's treatment will be multi-year under the control of blood PRL concentrations and imaging studies in the form of pituitary MRI every 6–12 months.

Discussion

Our case shows that pituitary tumors should be considered in the diagnosis of unexplained headaches and absence of menstruation. Prolactinoma is an adenoma that produces a good response in terms of a decrease in tumor size and PRL concentrations in response to conservative treatment with dopamine analogs, which was also achieved in our patient's case. The decrease in PRL concentrations caused the pituitary-gonadal axis to start functioning again and menstruation returned. Pharmacological treatment of the patient with cabergoline has good therapeutic effects, which is also confirmed by the results of other authors. The effects of cabergoline treatment according to Fukuhara and co-authors are highly effective in normalizing serum PRL levels and reducing tumor size. In patients treated with cabergoline, 83% achieved normalized PRL levels; 72% had their menstrual cycle restored, and only 3% discontinued treatment due to side effects. Of those treated with bromocriptine, 59% achieved normalization of PRL; 52% regained their menstrual cycle, and 12% discontinued treatment due to side effects [9]. No side effects of the treatment were observed. A study by N. Tritos also concluded that cabergoline treatment was first-line therapy for prolactinomas [10]. Conservative treatment of hyperprolactinemia in the course of prolactinoma is perennial, and discontinuation of medication may cause a renewed increase in prolactin and progression of tumor [11]. It is therefore necessary to instruct the patient that treatment will continue for many years.

Conclusions

In the case of co-occurring symptoms in the form of headaches, dizziness, sometimes visual disturbances and menstrual disorders, it should be remembered that one of the causes of the above-mentioned symptoms may be a pituitary tumor secreting PRL. These tumors give a very good response to treatment with dopamine analogs, so it is not necessary to refer the patient immediately for neurosurgical treatment. It should be remembered that any neurosurgical intervention carries the risk of complications in the form of hypopituitarism or diabetes insipidus.

It is important to monitor the results of treatment by evaluating PRL levels in the blood, as well as assessing tumor size using MRI imaging. However, a meta-analysis by Zou et al. showed a very low rate of prolactinoma recurrence after DA withdrawal [12].

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References

[1] Melmed S., Casanueva F.F., Hoffman A.R. et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(2):273–288.
[2] Igaz P. (Ed.), *Practical Clinical Endocrinology*. Springer, 2021.
[3] Yatavelli R.K.R., Bhusal K. *Prolactinoma* (updated July 31, 2023). Retrieved January 10, 2024, from https://www.ncbi.nlm.nih.gov/books/NBK459347/
[4] Owen K., Turner H., Wass J. (Eds.), *Oxford Handbook of Endocrinology and Diabetes* (4th ed.). OUP, Oxford 2022.
[5] Berinder K., Stackenäs I., Akre O., Hirschberg A.L., Hulting A.L. Hyperprolactinaemia in 271 women: up to three decades of clinical follow-up. *Clin Endocrinol (Oxf)*. 2005;63(4):450–455.
[6] Cho E.H., Lee S.A., Chung J.Y. et al. Efficacy and safety of cabergoline as first line treatment for invasive giant prolactinoma. *J Korean Med Sci*. 2009;24(5):874–878.
[7] New drugs: Quinagolide. *Aust Prescr*. 2005;28(6):156–158.
[8] Mah P.M., Webster J. Hyperprolactinemia: etiology, diagnosis, and management. *Semin Reprod Med*. 2002;20(4):365–374.
[9] Fukuhara N., Nishiyama M., Iwasaki Y. Update in Pathogenesis, Diagnosis, and Therapy of Prolactinoma. *Cancers (Basel)*. 2022;14(15):3604.

[10] Tritos N.A., Miller K.K. Diagnosis and Management of Pituitary Adenomas: A Review. *JAMA*. 2023;329(16): 1386–1398.
[11] Shimon I. Giant Prolactinomas. *Neuroendocrinology*. 2019;109(1):51–56.
[12] Zou Y., Li D., Gu J. et al. The recurrence of prolactinoma after withdrawal of dopamine agonist: a systematic review and meta-analysis. *BMC Endocr Disord*. 2021;21(1):225.

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