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GONADOTROPH INCIDENTALOMAS AS A CAUSE OF OVARIAN FAILURE

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▪ ***Objective:*** to evaluate clinical significance of pituitary gonadotroph adenoma in the development of ovarian insufficiency.

Design: follow-up study.

Patients: seven observations of pituitary microadenomas in patients whose cause for treatment was prolonged amenorrhea. There was a dynamic decrease in the secretion of FSH, LH on the background of the normal concentration of prolactin. Performing magnetic resonance imaging (MRI) with contrast enhancement in all the patients revealed pituitary adenoma. Patients had no clinical signs of acromegaly or Cushing's disease, remained normal secretion of adrenocorticotroph hormone, cortisol, somatotroph hormone, which excluded the presence of adenoma of corticotrophs or somatotrophs.

Conclusion: the clinical manifestation of gonadotroph adenomas, dependent on the secretory efficacy of gonadotropins and/or their subunits, is diverse. It may be accompanied by persistent amenorrhea with psychosomatic disorders. If these symptoms are present, it is advisable to include an MRI with contrast enhancement in the examination algorithm. The diagnosis of a gonadotroph incidentaloma is suspected after exclusion of clinical and laboratory signs of prolactinoma, somatotroph, and corticotroph adenoma.

▪ **Keywords:** gonadotroph adenoma; pituitary incidentaloma; ovarian insufficiency; amenorrhea.

ГОНАДОТРОПНЫЕ АДЕНОМЫ КАК ПРИЧИНА ОВАРИАЛЬНОЙ НЕДОСТАТОЧНОСТИ

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▪ ***Цель*** — оценить клиническое значение гонадотропных аденом гипофиза в развитии овариальной недостаточности.

Под наблюдением находились шесть пациенток с длительной аменореей вследствие развития гонадотропной микроаденомы гипофиза.

Результаты исследования. Помимо аменореи пациенток объединяли жалобы на головные боли в анамнезе или в настоящее время, признаки психастении, депрессии, динамическое снижение секреции фолликулостимулирующего, лютеинизирующего гормонов на фоне нормальной секреции пролактина, снижение концентрации антимюллерова гормона и признаки снижения овариального резерва по данным ультразвукового исследования. В клинической картине также отмечена тенденция к одновременному снижению показателей тиреотропного гормона и свободного тироксина. По результатам магнитно-резонансной томографии с контрастным усилением у пациенток выявлена микроаденома гипофиза. У всех пациенток отсутствовали клинические признаки акромегалии или болезни Кушинга, оставалась нормальной секреция адренокортикотропного гормона, кортизола, соматотропного гормона, инсулиноподобного фактора роста-1, что исключало наличие аденомы кортикотрофов или соматотрофов.

Заключение. Клинические проявления гонадотропных аденом, зависимые от секреторной эффективности гонадотропинов и их субъединиц, разнообразны, включают в себя рецидивирующие кисты яичников, абдоминальный болевой синдром и метроррагии (периоды полового созревания и начала репродукции), стойкую аменорею с психосоматическими нарушениями. При наличии указанных симптомов в алгоритм обследования

целесообразно включать магнитно-резонансную томографию гипофиза с контрастным усилением. Пациенткам с гонадотропными аденомами показана заместительная гормональная терапия и диспансерное наблюдение с динамическим МРТ-контролем размеров опухоли (без роста аденомы кратность составляет 2–3 года).

▪ **Ключевые слова:** гонадотропная аденома гипофиза; гипогонадотрофный гипогонадизм; аменорея; инциденталома.

Introduction

Among the causes of amenorrhea, hypothalamic dysfunction with an undesirable inverse effect, hyperprolactinemia and ovarian failure are the most common. As a result of examinations of 262 patients, Reindollar et al (1986) revealed hypothalamic causes of amenorrhea in 35%, pituitary (mainly hyperprolactinemia) — in 17% of cases [1]. New information on the pathogenesis of hypothalamic, pituitary and other forms of amenorrhea has been presented [2, 3].

As for the pituitary causes, in addition to hyperprolactinemia, they include corticotroph and somatotroph adenomas, other tumors, genetic and other rare causes of hypopituitarism. However, pituitary incidentaloma has not, in fact, been announced as a cause of amenorrhea so far. The prevalence of pituitary adenomas is 94–77.6 per 100,000 cases [4]. They mainly include the formations noted above with the clinic of hyper production of hormones.

The remaining pituitary adenomas, as a rule, are considered to be non-functioning incidentalomas, "detected with the help of imaging technologies performed for reasons not related to the found formation."

The incidence rate of incidentalomas among all pituitary adenomas reaches 14.7–22.2 and even 30–35% [4, 5, 7]. It is believed that 80–90% of incidentalomas come from gonadotrophs [6], while formations from somatotrophs, lactotrophs and corticotrophs are much less common [8]. The clinical "silence" of gonadotroph adenomas is associated with their ineffective hormonal production.

According to the results of a histological examination of 506 surgically removed lesions of the pituitary gland, 422 were adenomas (83.4%). Incidentalomas were 42.4%, lactotroph adenomas were 16.6%, follicle-stimulating hormone (FSH) secreting — 8.8% and luteinizing hormone (LH) secreting — 0.5% [7]. On the whole, the frequency of gonadotroph adenomas (9.3%) corresponded to that of growth hormone (GH) secreting adenomas (9.2%) and exceeded the frequency of adrenocorticotroph adenomas (5.9%) and thyrotroph adenomas (1.7%).

Despite the fact that a significant proportion of pituitary adenomas originates from gonadotrophs, their clinical manifestation is the least studied and therefore they are most commonly referred to accidentally found formations.

Material and methods

The study included seven patients between the ages of 22 to 43 years old. The reason for the treatment of one of them was primary amenorrhea, for the rest of the patients — secondary amenorrhea.

In a patient with primary amenorrhea, repeated attempts at hormonal induction of menstruation, undertaken from the age of 17, ended with the refusal of further treatment due to the development of a severe psychotic state during bleeding.

In the second case, the menarche at 17 years old, a regular cycle lasted up to 21 years old, then amenorrhea, treatment with combined oral contraceptives (COCs) — up to 25 years old, discontinuation due to varicose vein diseaseand for the next 18 years — amenorrhea.

In the third case, a regular menstrual cycle is from the age of 12. At 19 the patient suffered from psychological stress with weight loss and the development of amenorrhea. Cyclic administration of progestogens was without effect. For the next 11 years amenorrhea has persisted, and the patient hasn't sought help.

In the fourth case, a regular menstrual cycle is from the age of 14.Two years after opsomenorrhea — amenorrhea developed. The patient was prescribed COCs. After of their cancellation amenorrhea returned.

In the fifth case, the menarche at 13 years old, the regular cycle with giving a normal birth — up to 30 years old. Then amenorrhea has developed (1.5 years).

In the sixth case, the menarche has come at the age of 15, immediately the state of

opsomenorrhea — amenorrhea. Ten years after a patient sought medical assistance, observation and treatment are irregular.

In the seventh case, the menarche has come at the age of 16, immediately the state of opso-amenorrhea. In this context, a patient had one abortion and two uncomplicated childbirths. Over the past year is a persistent amenorrhea.

The patients were examined using imaging technologies and laboratory diagnostic methods.

Results

All the patients had pronounced psycho-emotional symptoms: irritability, incredulity, anxiety, depression, sometimes aggressiveness and tearfulness. Two patients, diagnosed with the psychasthenia and depressive syndrome, were receiving antipsychotic medication, one of them was observed by a psychiatrist. Three patients indicated frequent headaches (in one case — from 13 years old, in the other case — after a traumatic brain injury). A decrease in the FSH and LH secretion was noted in all the patients (Table 1).

Two cases need some clarification. A gradual decrease in high gonadotropins between the ages of 18 to 24 years old (the first case) was observed in the patient against the background of severe estrogen and progesterone deficiency. She refused hormone replacement therapy (HRT).The same dynamics was observed in the second patient in the time period from 43 to 45 years old. The patient was undergoing hormone replacement therapy (HRT) with transdermal administration of estradiol (1 mg/day) and oral administration of progestogen (10 mg/day) in a cyclic mode.

Regardless of the absence of clinical signs of adenomas originating from other secretory cells, all the patients underwent additional examination. The concentration of prolactin remained normal or decreased due to previously prescribed cabergoline (in two cases). After the discontinuation of the drug, prolactin secretion was restored.

In addition to the absence of symptoms of Cushing's disease, the patients maintained normal production of corticotropin (ACTH) and total cortisol in the morning blood serum sample (2.4–3.1–3.7 pmol/L and 217–402 nmol/L, respectively). The secretion of growth hormone did not increase (0.23–0.58 μg/l).

At the same time, the secretion of free thyroxine, which is, as a rule, higher in the reproductive period, was at the lower limits of normal in most of the patients. In parallel, there was no increase in the secretion of thyroid stimulating hormone (TSH), whichis natural in such cases, as it remained in normally low limits (Table 1). In no case autoimmune damage to the thyroid gland was observed. The antibodies to thyroid peroxidase or thyroglobulin were within normal values. Ultrasound of the thyroid gland also showed no pathology.

Table 1 / Таблица 1

Results of a dynamic hormonal examination of patients with pituitary incidentalomas
Данные гормонального обследования в динамике наблюдения пациенток с аденомой гипофиза

Patients	FSH, mIU/ml	LH, mIU/ml	Prolactin, mIU/ml	AMG, ng/ml	TSH, μU/ml	Free T4, pmol/l
1	162.1; 116; 95.0	38.1; 20.0; 33.2	115.8; 175.0	0.28; 0.1	3.23; 2.78	11.7; 13.5
2	85.9; 17.6	21.1; 2.05	83.9; 222.90	0.18	1.98; 1.64	14.1; 13.2
3	11.1; 0; 0	1.58; 0; 0	243.7; 195.8; 97.9	5.8; 0.73	1.64; 0.66; 0.93; 0.82	10.7; 10.9; 10.6; 12.1
4	2.56; 0.08; 0.03	0.33; 0; 0	162.2; 181.9	7.2	0.83; 0.73; 0.67; 0.32	8.16; 11.7; 6.9; 2.7; 14.2
5	0.7; 3.42	0.43; 0.7	82.2; 76.9; 74.2	2.2; 1.08	1.95; 0.48	13.1; 8.2
6	4.3; 0.84; 0; 0	3.7; 0.23; 0; 0.02	397; 140	1.8	1.66; 1.53; 0.92; 0.78	15.0; 16.1; 16.8
7	1.2; 0.81	0.09; 1.1	180.2; 138.7	4.52; 7.84	0.974; 0.824	5.93; 12.02

In three cases, the first magnetic resonance imaging (MRI) scan did not reveal any pituitary adenomas. The diagnosis was made with repeated MRI 2–5 years after. It is not known whether the first study was performed with contrast enhancement or not. Repeated MRI with contrast enhancement in these patients and primary MRI in the rest revealed the presence of pituitary adenoma with a diameter of 0.35–0.5 mm. Dynamic control in the interval of one year — nine years in different patients did not show any growth in adenomas.

Discussion

Headaches, dizziness, nausea, vomiting, visual impairment in patients withgonadotropin adenomas were noted by Buurman H. et al., 2006. A high incidence of pituitary incidentalomas was detected at autopsy after suicide [10].

According to Shimon et al., 2001, gonadotroph incidentalomas contribute to the development of multiple follicular ovarian cysts due to the secretion of FSH, LH and/or their α and β subunits [11]. It is thought that this process is typical for both the period of reproduction and the period of premenopause [12]. Developing in childhood, gonadotropic adenomas induce premature puberty, early development of the mammary glands [13].

For girls with gonadotroph pituitary adenoma, the formation of ovarian cysts with abdominal pain and tension of the abdominal wall is common. In the process of regression of cysts, they experience episodes of bleeding associated with a decrease in estrogen concentration [14, 15, 16].

In women of reproductive age were noted endometrial hyperplasia, metrorrhagia, ovarian hyperstimulation syndrome with the development of massive cysts. The clinical picture can sometimes be similar to that with hyperstimulation with FSH drugs in cycles of assisted reproductive technologies [17].

However, with a low ovarian reserve observed in some patients, it is difficult to expect the development of ovarian cysts even in cases of high gonadotropin production. It seems that the formation of ovarian cysts should be more characteristic of puberty and early reproductive age, when the highest follicular consumption is noted.

Gonadotroph adenomas secrete FSH, α- and β-subunits of FSH, LH and β-subunit of LH with decreasing force [18, 19]. The ambiguous biosynthesis of gonadotropins is manifested by the diversity of their clinical picture. Given the hypoestrogenism or the fluctuating estrogen concentration, the hormonal response options may be mildly elevated, normal, or decreased levels of FSH. LH biosynthesis is also significantly reduced.

However, we did not find any information about the complete cessation of FSH and LH secretion in patients with pituitary gonadotropic adenoma. Meanwhile, the actual cessation of LH biosynthesis was noted in three cases, and FSH — in one case.

Observational analysis indicates that, in contrast to lactotroph, corticotroph and somatotroph adenomas, gonadotroph formations are more characterized by hypoproduction than hyperproduction of hormones. Even in cases of normal or high initial biosynthesis of FSH and LH, it decreases subsequently until the complete cessation. Initially high concentrations of gonadotropins associated with their overproduction by adenoma or with a reaction to ovarian insufficiency are later on reduced, despite low estrogen concentration.The concentrations of estradiol and progesterone in the patients, respectively, were 57.9–106.2 pmol/L and 2.6–3.5 nmol/L. A gradual decrease in the FSH and LH concentrations occurred both against the background of the preservation of amenorrhea, and against the background of HRT.

The impossibility to specify the time of the formation of incidentaloma does not allow us to answer the question of whether the hormonal production of gonadotroph cells changes due to the appearance of adenoma or even before its development.

By referring gonadotroph adenomas to incidentalomas, it is believed that they do not give specific clinical manifestations. This point of view does not seem entirely true. A possible increase in the biosynthesis of gonadotropins at the beginning of the formation of adenoma, inducing the constant formation of cysts at puberty and early reproductive age, depletes the ovarian reserve. This is evidenced by ultrasound data (decrease in ovarian volume and follicular expression) and by low levels of AMH in some patients aged 30–32 years or less (Table 2).

The result of the decrease in the secretion of gonadotropins and/or their α and β-subunits is oligomenorrhea — amenorrhea, anovulation and infertility. Therefore, the low secretion of gonadotropins, especially the decrease in secretion

Table 2 / Таблица 2

Pelvic ultrasound data at the time of the last examination of the patients with incidentaloma of the pituitary gland
Данные ультразвукового исследования на момент осмотра пациенток с длительной аменореей

Patients	Age at the first visit	BMI, kg/m^2	Uterine size, mm	Right ovary		Left ovary	
				Volume, cm^3	Follicles, number	Volume, cm^3	Follicles, number
1	22	20.8	22 × 16 × 22	1.15	1	2.1	0
2	43	24.3	28 × 14 × 29	1.10	0	0.13	0
3	30	18.5	33 × 30 × 28	3.57	7–8, d 4–5 mm	2.74	7–8, d 4–5 mm
4	23	18.6	34 × 29 × 30	2.25	3–4, d 4–5 mm	3.1	4–5, d 5–6 mm
5	32	20.0	51 × 34 × 48	2.6	8–10, d 3–4 mm	2.4	9–10, d 3–4 mm
6	30	15.7	50 × 41 × 35	5.7	9–10, d 6–8 mm	4.9	9–10, d 6–8 mm
7	33	20.9	50 × 37 × 50	7.43	10, d 4–5 mm	6.3	10–11, d 4–5 mm

in the dynamics of observation of the patients with the indicated pathology, makes us suspect the development of gonadotroph adenoma.

It is possible that with gonadotroph adenoma, the function of thyrotroph is also somewhat damaged. The inadequate response of thyrotroph to a low concentration of thyroxine in blood serum also does not exclude the influence of the total alpha α-subunit in FSH and TSH [20].

The results of the presented observation allow us to conclude that hypogonadotropic ovarian failure in patients with oligomenorrhea — amenorrhea, anovulation and infertility can be a consequence of gonadotroph adenoma.

Possible signs of gonadotroph adenoma:

– Incidences of stress, head injuries
– Signs of psychasthenia, depression
– Complaints of headaches in past medical history or at present
– Syndrome of abdominal pain, metrorrhagia during puberty
– Relapses of ovarian cysts (early reproductive age)
– Dynamic decrease in FSH, LH secretion
– A possible simultaneous decrease in TSH and free thyroxine
– When revealing pituitary adenoma (MRI with contrast enhancement):

- normal prolactin secretion
- lack of clinical signs of acromegaly, Cushing's disease
- normal secretion of ACTH and cortisol
- normal secretion of growth hormone and insulin-like growth factor-1

There is no information about the course of pregnancy when a gonadotroph adenoma is present. However, in general, microadenomas are not a contraindication to pregnancy and in such a case there is a chance of having a baby, but this chance is gradually disappearing with the growth of adenomas. Obviously, this chance should be used as early as possible in connection with the risk of depletion of the ovarian reserve. It is clear that induction of pregnancy in such a situation is possible only with the help of assisted reproductive technologies (ART).

Such patients require replacement therapy with natural estradiol preparations in a cyclic combination with intravaginal administration of progesterone or oral administration of its agonists. We believe that the use of COCs for patients with gonadotroph adenoma is contraindicated, since the progestogen effect of these drugs is aimed at suppressing the function of gonadotropes, which in these cases is already impaired.

In a prospective study, it was shown that HRT or even a refusal of treatment is more effective in terms of normalizing the cycle than the prescription of COCs [21]. It is advisable that patients visit a psychologist.

Incidentalomas originating from gonadotroph cells often express some subtypes of somatostatin

and dopamine receptors on cell membranes [8, 22]. Therefore, to control the growth of adenomas, some authors prescribe treatment with cabergoline, octreotide and GnRH agonists. The effectiveness of such treatment is not confirmed [23].

It seems that in cases of gonadotroph microadenomas, in addition to HRT, regular medical check-up (taking into account clinical symptoms, laboratory data) with dynamic MRI of the pituitary gland is sufficient.

Conclusion

With the accumulation of data, we have come to understanding that pituitary incidentalomas represent a heterogeneous group in which gonadotroph adenomas occupy a significant place. The clinical manifestation of these adenomas, depending on the secretory effectiveness of gonadotropins and their subunits, is diverse and includes the development of recurrent ovarian cysts, abdominal pain syndrome and metrorrhagia (puberty and the beginning of the reproductive period), the development of persistent amenorrhea with psychosomatic disorders and an asymptomatic course (incidentaloma). A sign of gonadotroph adenoma is hypogonadotropic amenorrhea with a dynamic decrease in the secretion of FSH and LH. In view of this, if was exclusion other probable causes of amenorrhea, pituitary MRI with contrast enhancement is indicated.

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