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PITUITARY ADENOMA DUE TO PRIMARY HYPOTHYROIDIS AS A FACTOR OF MALE INFERTILITY

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Infertility, defined as the inability to conceive after at least 1 year of unprotected sexual intercourse, affects about 15% of couples, and it is particularly common in developing countries [1,2,3]. Male and female partners alone are responsible for 20–30% of cases, respectively, but contribute to 50% of cases overall [1]. Several endocrine and metabolic diseases are involved in male infertility, such as hypogonadism, diabetes, obesity and adrenal dysfunction [7,8,9,10,11]. Beyond these conditions, thyroid dysfunction may affect male fertility too, albeit this is not widely investigated. Noteworthy, congenital hypothyroidism does not cause impaired development of male reproductive system [11,12,13], although, on the other hand, if not properly treated with replacement therapy, it causes delayed sexual maturation [11,12,13,14], and the treatment of hypo- and hyperthyroidism is associated with an improvement in testis function, but evidence is scarce [15, 16,17,18].There is a close link between thyroid function and female fertility: physiologically, pregnancy has a significant effect on the thyroid gland, and thyroid dysfunction has long been associated with female infertility with both obstetric and fetal outcomes being well established. On the other hand, the impact of thyroid function on the male reproductive system is debated, and a role for thyroid hormones in influencing Sertoli and Leydig cells as well as spermatogenesis has been proposed [4,5,6]. In the practice of an endocrinologist, manifest hypothyroidism is quite rare, in which clinical manifestations of hypofunction of the thyroid gland (TG) are diagnosed against the background of a decrease in thyroid hormones, in particular, the levels of free thyroxine (T4f), free triiodothyronine (T3f) and increased levels of thyroid-stimulating hormone in the blood hormone (TSH). As for the prevalence in countries with iodine deficiency, this pathology ranges from 1% to 2%. Hypothyroidism is approximately ten times more common in women than in men. The lack of adequate hormone replacement therapy can lead to some complications, one of which is hypertrophy of thyroid-stimulating cells with the development of pituitary adenoma with the development of panhypopituitarism (decreased functions of other tropic hormones), which occurs as a result of damage to pituitary tissue by an enlarging tumor. There is an opinion that manifest hypothyroidism is associated with hypoandrogenemia in men. However, the question of how the parameters of spermograms change, as well as the levels of gonadotropic hormones in men with infertility, in patients with manifest hypothyroidism, has currently been studied little. The work presented below describes a case of the development of pituitary adenoma due to primary hypothyroidism against the background of chronic autoimmune thyroiditis, a feature of which is the presence of infertility in the patient.

Case presentation: A 30-year-old man, applied to the local clinic with complaints of general weakness, headache, depressed mood, cold intolerance, dry skin, reproductive and sexual disorders, in recent days, he developed a headache. Additionally, his relatives also supplemented that he suffered from hypomnesis and hypophrenia.On examination: height 169 cm, body weight 70 kg, body mass index 24.8 kg/m2. Hereditary history is not burdened. The

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patient underwent an ultrasound examination of the thyroid gland, determination of blood levels of thyroid-stimulating hormone, free thyroxine and free triiodothyronine, as well as analysis of spermogram parameters in accordance with WHO norm criteria and the content of free testosterone (Tsf), luteinizing hormone (LH), follicle-stimulating hormone (FSH) hormones and prolactin (PRL) in the blood serum.

Results and discussion: Color Doppler ultrasound showed a diffuse goiter. During the examination, for the first time, an increase in the concentration of TSH was revealed - 19.63 mIU/ml (normal 0.39–4.20) in combination with a reduced content of free fractions T3f - 1.7 pmol/l (normal 2.5–5.8) and T4f 5.6 pmol /l (normal 10-25) increase in the content of antibodies to thyroid peroxidase (TPO) - 1102 IU/ml (normal 0-5.6 IU/ml) and the serum prolactin (PRL) level was slightly elevated - 577.6 ng/ml (normal 60-560). In order to clarify the causes of headaches that were difficult to relieve with analgesics, an Magnetic resonance imaging (MRI) study of the pituitary gland with contrast was performed and a pituitary macroadenoma (17 × 12 × 18 mm) with supra-, para-, infrasellar distribution was verified. The patient was examined by an ophthalmologist: no evidence of chiasmatic syndrome was received. This formation, due to the mass effect, affected the function of gonadotropic hormones and led to a decrease in their function LH-0.8 mIU/ml (normal 1.5-9.0), FSH-0.33 mIU/ml (normal 0.8-25), No changes in other tropic hormones were detected. Primary dysfunction of the thyroid gland and hypofunction of gonadotropic hormones and increased prolactin in a patient with infertility led to a significant decrease in testosterone levels (Tsf-5.6 ng/ml (normal 9-38)), which indicates the presence of hypoandrogenemia. In this patient, testicular volumes did not differ from normal values. At the same time, the concentration of sperm per milliliter of ejaculate was below the world health organization WHO norm. However, the average value of this spermogram parameter was significantly less. The average percentage of motile and viable forms of sperm in a patient with primary manifest hypothyroidism was significantly less than the lower limit of WHO standards (21%). Such changes in spermogram parameters indicate the formation of oligozoospermia in the examined patient.

Based on the totality of data, a diagnosis of “primary hypothyroidism against the background of chronic autoimmune thyroiditis, a complication of pituitary adenoma with secondary infertility” was made. A microscopical tumorectomy was performed. Postoperatively, the hormone levels were gradually improved. Histopathological examination showed a plurihormonal pituitary adenoma. Thyroid hormone replacement therapy (thyroxine at a dose of 50 mcg/day with a gradual increase in the dose of the drug to 100 mcg/day) was prescribed after microsurgery. During the follow-up period of 2 months, there was no recurrence, and the symptoms were completely relieved. Now, patients orally take thyroxine 100 μg/day, and there are no signs of recurrence of related symptoms. replacement therapy with levothyroxine sodium was prescribed. After 6 months of adequate hormone replacement therapy, when studying hormone levels during therapy, they were within normal limits, testosterone levels were at the lower limit. There was a significant shift in the spermogram parameters and the number of motile sperm (40%). The patient was recommended to be monitored by an endocrinologist and urologist at his place of residence.

Discussion. In 1985, Scheithauer et al performed histopathological and immunocytological examinations of pituitary glands in the autopsy of 64 patients with long-standing primary hypothyroidism, and they noted pituitary enlargement in 91% cases, pituitary tumorous hyperplasia in 12% cases, and pituitary adenoma in 18.7% cases.[19]The authors also proposed

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that pituitary tumorous hyperplasia might represent an intermediate stage between enlargement and adenoma. Pituitary hyperplasia refers to non-neoplastic growth or enlargement of pituitary gland cells without qualitative changes in cell biology, which include physiological, pathological, syndrome-related (such as Addison disease, Klinefelter syndrome, and Turner syndrome) and idiopathic subtypes.[20] Pituitary hyperplasia caused by primary hypothyroidism is due to the loss of thyroxine feedback inhibition to the hypothalamus, which can induce the overproduction of TRH and hyperplasia of lactotrophs. Moreover, patients with pituitary hyperplasia or pituitary adenoma may as well be asymptomatic. Noteworthily, pituitary hyperplasia has no histopathological atypia or pathologic mitosis, and hormone replacement therapy can be effective.[21-24] However, pituitary adenoma is a benign neoplasm originating from anterior pituitary cells with necrosis and/or cystic changes.[25,26] We speculate that pituitary adenoma shares similar pathogenetic mechanisms with pituitary tumorous hyperplasia: long-term stimulation by TRH and loss of thyroxine feedback inhibition. Pituitary gland cells are adenomatous hyperplasia. Pituitary adenomas exhibit a typical structural disorder, cell necrosis, and cystic changes. Immunohistochemistry showed that more than two hormones were positive. Most patients require surgery, postoperative combined hormone therapy.

In the current study, we also noted hyperprolactinemia in these two cases. According to literature, pituitary adenomas secondary to primary hypothyroidism are usually associated with elevated PRL levels. In 1989, Ahmed et al reported five cases of pituitary enlargement secondary to primary hypothyroidism, in which endocrinological examination showed both elevated TSH and PRL; the hormone levels returned to normal following thyroid hormone replacement therapy, indicating the hyperplasia of TSH- and PRL-secreting cells is reversible, and thus the authors considered this condition as ‘pseudo-prolactinoma syndrome’.[27] The PRL levels in patients with hypothyroidism usually range from 1680 mIU/mL to 2120 mIU/mL, which are lower than those in patients with prolactinoma. The pathogenesis of hyperprolactinemia in hypothyroidism remains unclear; the mainstream hypothesis is that TRH can not only activate the TSH-secreting cells but also stimulate the PRL-secreting cells, and the enlarged pituitary gland compresses the pituitary stalk affecting the hypophysioportal circulation and resulting in reduced dopamine (an antagonist against the PRL releasing hormone).

Pituitary hyperplasia caused by primary hypothyroidism responds well to thyroid hormone replacement therapy.[28-30,24] It is worth noting that repeated detection of serum T3, T4, and TSH should be performed 3 months after replacement therapy. If the results showed that TSH level decreased partly, but thyroid function did not improve significantly, long-term increased secretion of pituitary TSH adenoma should be considered, microsurgical resection via a transsphenoidal approach could be ordered. If the optic nerve or optic chiasm were pressed by the adenoma, microsurgery should be chosen first, to relieve the pressure, and thyroxine tablet substitute therapy should be taken after surgery.[31]In the current study, both patients showed no endocrinological improvement following administration of long-term oral thyroxin while the thyroid hormone levels were improved after surgery combined with oral thyroxin. Especially, for the cases with optic chiasma compression, surgical resection of the adenoma is necessary for visual restoration. Thus, the differential diagnosis between pituitary adenoma and pituitary hyperplasia is crucial, and microsurgical resection via a transsphenoidal approach should be reserved for decompression of the optic chiasm or pathological diagnosis, in the case of a pituitary mass not responding to, or worsening on, thyroid hormone replacement therapy.

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Pituitary adenoma secondary to primary hypothyroidism is an extremely rare disorder, and the neurosurgeons should be aware of this entity as it is usually underdiagnosed. Surgical resection combined with thyroid hormone replacement therapy should be highlighted, which can lead to a favorable prognosis.

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