DOI: 10.23888/PAVLOVJ2018261117-132

АКРОМЕГАЛИЯ И КОМОРБИДНЫЕ СОСТОЯНИЯ. НОВЫЕ ВОЗМОЖНОСТИ ДИАГНОСТИКИ И ЛЕЧЕНИЯ
(обзор литературы)

© А.Ю. Жулидова, И.И. Дубинина

Рязанский государственный медицинский университет им. акад. И.П. Павлова,
Рязань, Россия

На основании данных, опубликованных в отечественной и зарубежной литературе, проведен анализ клинико-гормональных особенностей, современных методов лечения акромегалии в сочетании с полиэндокринопатией (сахарный диабет, диффузный, узловой зоб, гипокортицизм) и кардиоваскулярной патологией. Согласно различным исследованиям, снижение качества и продолжительности жизни больных связано с развитием значительных изменений со стороны эндокринной системы в связи с контринсулярным и стимулирующим действием соматотропного гормона и инсулиноподобного фактора роста 1 на органы и ткани. Развитие вторичного сахарного диабета выявляется у 16-46% больных, узловых образований щитовидной железы у 30-70%, вторичной надпочечниковой недостаточности − у 11-20% пациентов. Наиболее частой причиной акромегалии является активная опухоль гипофиза – соматотропинома, в редких случаях гиперпродукция соматотропного гормона происходит из нейроэндокринных клеток, расположенных эндо- или экстракраниально. Благодаря успехам нейроэндокринологии существенно улучшилась тактика ведения пациентов. Цель лечения акромегалии − достижение клинической и биохимической ремиссии заболевания. В настоящее время имеются три основных метода лечения акромегалии: хирургический (эндоназальная транссфеноидальная аденомэктомия), медикаментозный, лучевая терапия и стереотаксическая радиохирургия (кибер-нож). Дифференцированное и комбинированное использование современных лекарственных средств в виде монотерапии, а также в сочетании с хирургическим и лучевым лечением, способствует достижению как клинической, так и гормональной ремиссии акромегалии, обеспечивая тем самым повышение качества и продолжительности жизни пациентов.

В настоящем обзоре литературных данных приводятся современные представления об этиологии, патогенезе, клинических особенностях, современных методах диагностики и лечения этого заболевания.

Ключевые слова: *акромегалия, полиэндокринопатия, транссфеноидальная аденомэктомия, аналоги соматостатина, агонисты дофаминовых рецепторов.*

DOI: 10.23888/PAVLOVJ2018261117-132

ACROMEGALY AND COMORBID CONDITIONS. NEW POSSIBILITIES OF DIAGNOSIS AND TREATMENT (literature review)

A.U. Zhulidova, I.I. Dubinina

Ryazan State Medical University, Ryazan, Russian Federation

Based on the data published in Russian and foreign reference sources, an analysis of clinical-hormonal peculiarities, modern methods of treatment of acromegaly combined with polyendocrinopathies (diabetes mellitus, diffuse and nodular goiter, hypocorticoidism) and cardiovascular diseases was conducted. According to different authors, a decline in the quality and duration of life of patients is associated with significant changes in the endocrine system caused by contrainsular and stimulating effect of somatotropic hormone (STH) and insulin-like growth factor 1 (IGF-1) on organs and tissues. Secondary diabetes mellitus was identified in 16-46% of patients, nodular goiter in 30-70%, secondary adrenal insufficiency in 11-20% of patients. The most common cause of acromegaly is an active pituitary tumor – somatotropinoma, rarely STH is overproduced by neuroendocrine cells, located endo- and extracranially. Recent achievements in neuroendocrinology provided significant improvement of management of patients. The aim of treatment for acromegaly is to achieve clinical and biochemical remission of the disease. At present three basic methods of treatment for acromegaly are used: surgical (endonasal transsphenoidal adenomectomy), drug therapy, radiation therapy and stereotactic radiosurgery (cyber knife). Differential and combined use of modern medical drugs in the form of monotherapy and in a combination with surgical and radiation treatment permits to achieve both clinical and hormonal remission of acromegaly improving in this way the quality and duration of life of patients. In the given review of literature modern concepts of etiology, pathogenesis, clinical peculiarities, modern methods of diagnosis and treatment of this disease are presented.

Keywords: *acromegaly, polyendocrinopathy, transsphenoidal adenomectomy, somatostatin analogues, dopamine receptor agonists.*

Acromegaly is a severe neuroendocrine disease caused by overproduction of somatotropic hormone (somatotropin, STH), and of insulin-like growth factors (IGF-1, IGF-2) in individuals with completed physiological growth. The disease is characterized by disproportional periosteal pathological growth of bones, cartilages, internal organs, soft tissues, and also by disorders in the morphological and functional condition of the cardiovascular system, peripheral glands, metabolism. The time interval between appearance of

DOI: 10.23888/PAVLOVJ2018261117-132

the first symptoms of the disease and making the diagnosis is 5-15 years. In the previous century incidence of acromegaly ranged from 40 to 60 cases per 1 mln of individuals. Belgian research of 2006 gives higher figures – more than 100 cases per 1 million [1]. According to data of Moscow register of 2016, 506 patients with acromegaly are under regular medical check-up, 138 (27%) men and 368 (73%) – women. Within three years 195 patients with acromegaly were identified, 139 women and 46 men, of the average age 46 years. The onset of the disease occurs in the 3^{d}-4^{th} decade of life – the most productive years in the working population. In 144 (26%) patients the disease began at the age of 50-69 years, in 103 (20%) – at the age of 40-49 and in 99 (19%) – at the age of 60-69. The ratio of micro/macroadenomas was 1.0:1.4 [2].

The leading cause of sporadic forms of gigantism and acromegaly is pituitary adenoma (somatotropinoma) with autonomous excessive secretion of STH or of its active forms [3]. Adenomas are monoclonal tumors resulting from somatic mutation of GSP-protein (GSP-oncogen) responsible for dimerization of alpha- and beta-subunits of receptor G-proteins which, being normally stimulated by somatoliberin, activate adenylate cyclase and stimulate intracellular production of cAMP required for increase in the functional activity and mitotic activity of somatotrophs [4,5]. Mutation and structural alteration of receptor proteins cause permanent activation of adenylate cyclase with frustration of its natural inhibition with the result of excessive accumulation of cAMP in the cytosol that becomes the direct cause of uncontrollable proliferation of somatotropic cells with enhanced secretion of STH. In 20-25% of cases mixed pituitary adenomas are identified which, besides STH, produce prolactin, thyrotropic hormone (TTH), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH), alpha-subunit. Very rarely (in 2% of cases) the cause of acromegaly is an ectopic tumor that arises from neuroendocrine cells and may be located endocranially (tumor of pharyngeal and sphenoidal sinus) or extracranially (tumor of lungs, mediastinum, pancreas, gonads, intestine) [5,6].

Clinical symptoms of acromegaly are defined by compressive effect of somatotopinoma on the surrounding tissues (headache, hypopituitarism, narrowing of fields of vision, hydrocephaly, hypothalamic disorders), and by numerous systemic manifestations of long-term production of STH and IGF-1 (insulin-like growth factor-1) [6].

The speed of growth of somatotropinoma, its hormonal activity and character of complication at the onset of the disease are largely determined by the age of a patient. In young patients the clinical picture is characterized by complications associated with mass-effect (neurological, vision disorders, partial pituitary insufficiency) with the extent of evidence directly proportional to the volume of tumorous tissue. In patients of middle age at the beginning of the disease metabolic and multiorgan disorders dominate that can be attributed to late diagnosis, age-related

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changes, duration of the active stage [1,4,6]. There are noted a characteristic enlargement of the facial traits (cheek bones, superciliary arches), prognathism, hypertrophy of soft tissues (lips, nose, ears). Progressing expansion of the circumference of the head, enlargement of feet, bones, thickening of fingers are noted. Expansion of nasal sinuses and enlargement of the vocal cords determines a thick deep voice [5,7]. A common complication of acromegaly is acromegalic cardiomyopathy affecting patients of any age and characterized by disorders in the cardiac rhythm, hypertrophy of the myocardium of the left ventricle (HMLV). Unless hormonal disorders in acromegaly are timely corrected, cardiomyopathy leads to diastolic cardiac failure [7,8]. Development of arterial hypertension in patients is associated with insulin resistance, retention of sodium, water, exaggerated vessel tone, reduced production of atrial natriuretic peptide [8,9]. According to some authors, the extent of elevation of arterial pressure correlates rather with the duration of the disease and the age of patient than with the level of growth hormone [9,10]. Damage to the central and peripheral nervous system is caused by aggressive growth of somatotropinoma and compression of peripheral nervous trunks by edematous soft tissues and bone formations [10,11]. Elevation of the intracranial pressure and compression of the diaphragm of *sella turcica* by the tumor provokes persisting headaches [11]. A common complication of acromegaly is secondary diabetes mellitus. According to the results of modern research, the incidence of early disorders of carbohydrate metabolism in acromegaly ranges from 16% to 46% [11,12]. Pathogenesis of secondary diabetes mellitus in acromegaly consists in a complex of changes associated, on the one hand, with development of hepatic and peripheral insulin resistance, and on the other hand with hyperinsulinemia [12]. Diabetes mellitus in patients with acromegaly may be considered an additional risk factor for atherogenic dyslipidemia, hyperfibrinogenemia and platelet dysfunctions in the form of reduction of disaggregation properties and enhancement of release reactions [13].

A study of structural and functional condition of the thyroid may reveal its enlargement with or without nodular structures in 35-70% of cases. Structural changes in the thyroid are induced by direct influence of IGF-1. Histological examination shows predominating signs of the proliferating colloid goiter. Other signs are autoimmune thyroiditis, toxic goiter, papillary cystoadenoma. Structural changes in the gland mainly develop with the underlying euthyroidism. Hypothyroidism develops in case of formation of multiple nodules, especially with the underlying autoimmune thyroiditis (primary hypothyroidism), and also in case of compression of thyrotrophs by somatotropinoma leading to reduction in TTH production (secondary hypothyroisim). Rarely these conditions coexist. Thyrotoxicosis in acromegaly is not common (2-10% of cases). Rare cases of secondary thyrotoxicosis are reported which result from overproduction of TTH by mixed adenoma of pituitary [4,14].

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In about 11-20% of cases disorders in the adrenal functions are noted. In most cases secondary adrenal insufficiency is identified that results either from compression of corticotrophs by growing somatotropinoma, or develops in postoperative period after removal of adenoma [4,15].

With the presence of characteristic complaints and clinical (external) signs of acromegaly, complex laboratory-instrumental examination is required to confirm the diagnosis and determine further treatment approach [15,16]. At present, the main laboratory diagnostic method is measuring the levels of growth hormone and IGF-1 in blood [1,2,16]. Normal concentration of STH in healthy individuals is 5-10 ng/ml, while in remission of acromegaly it should not exceed 2.5 ng/ml [16]. The gold standard of laboratory diagnosis of acromegaly is oral glucose tolerance test (OGTT). It was found that intake of 75 g of glucose leads to reduction in the STH to the minimal detectable level in 94% of healthy individuals. After intake of glucose solution, blood is taken in a fasting patient every 30 minutes within 2 hours. The test is considered positive if the level of STH does not fall below 1 ng/ml (2.7 mUn/l). Such reaction is observed in the majority of patients in the active stage of acromegaly. Moreover, more than 40% of patients with acromegaly show a paradoxical increase in STH level in response to increase in glucose level [5,15,17]. In the opinion of many authors, the best diagnostic criterion that confirms overproduction of STH is the level of IGF-1 in blood plasma. The advantages of this marker are as follows: a high level of IGF-1 gives a typical clinical picture of acromegaly; the value of IGF-1 reflects the average value of STH on the previous day; IGF-1 does not show any significant variations within a short period of time; even a slightly elevated level of STH is reflected by a high level of IGF-1 [15,17].

It should be taken into account that the level of IGF-1 depends on the gender, age and dietary habits. It may probably change (up to the normal age- and gender-related norm) in case of any disorder in nutrition, hepatic insufficiency and starvation. Besides determination of STH and IGF-1, other laboratory markers of acromegaly are the level of somatoliberin in blood, test with thyroliberin and somatoliberin, the level of STH in 24-hour urine and also in blood of inferior cavernous sinuses, the level of IGF-1-binding protein-3. In real clinical practice these laboratory diagnostic methods are practically out of use [3-5,15,17].

By the international consensus the main criteria are determined for exclusion of acromegaly: STH level <1 ng/ml, IGF-1 corresponding to the age-related norm, minimal level of STH after OGTT <0,4 ng/ml, the average integrated STH for 24 hours <2,5 ng/ml [18]. The main method of radiodiagnosis of tumors of the pituitary is magnetic resonance imaging (MRI) [5,18]. It gives information about location, structure, spread of the pathological process and permits to carry out a successive control of treatment with no limitation of number of examinations [19]. The most promising direction of further development of

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MRI diagnosis is dynamic MRI diagnosis with bolus injection of a contrast substance. According to some authors, dynamic contrast MRI possesses significant advantages over ordinary contrast MRI, since it permits not only to detect accumulation of contrast substance in tumor, but also to determine the dynamics of this pathological process and to identify quantitative-temporal parameters of the accumulation [19,20].

Medical treatment of acromegaly suggests use of modern means of surgical, medicinal or radiation control of growth and secretory activity of pituitary adenoma taking into account the extent of mass-effect, peculiarities of clinical course and somatic conditions of patients [21]. The first line treatment of microadenomas and intrasellar macroadenomas is transsphenoidal adenomectomy [20,21].

Surgical method is also indicated in case of appearance of mass-effect of the growing tumor, evident cranialgia, progressing disturbances in vision. After surgical removal of adenoma, complete hormonal remission (with optimization of the level of IGF-1 in blood) is observed in 70-80% of cases, after removal of macroadenoma remission is achieved only in 40-60% of patients. A large size of adenoma makes it technically difficult to achieve clinico-biochemical remission because of invasive growth of tumor into surrounding structures. In 43% of cases growth continues and in 2-3% recurrent course is noted [22,26]. Transcranial method is used when use of transsphenoidal method is impossible. Transsphenoidal approach is divided into microsurgical (with use of a microscope) and endoscopic. There also exists a method of microscopic removal of pituitary adenomas with auxiliary endoscopic control. Advantages of modern endoscopy (optimal illumination, phenomenon of endomicroscopy and lateral viewing) permit intraoperative determination of the boundaries of adenoma and identification of location and size of the remaining non-removed parts of the tumor. Currently in real clinical practice 3-D endoscopes are already in use with different levels of signal transmission (binocular frame structures, transmission of 3-D image with computerized processing in 3-D mode, systems emulating true 3-D images) [23,24,25]. Lateral view of endoscope permits to remove adenoma from the optimal side avoiding damaging brain structures and the contents of cavernous sinuses. In case of intraoperative liquorrhea, the method permits its verification and management [23,26].

In modern surgery in general and in neurology in particular, a tendency is observed to maximal possible use of minimally invasive surgery. Introduction and subsequent perfection of the transshenoidal approach permitted to significantly reduce the number of postoperative complications. Despite the fact that development of technologies, surgeon's experience, knowledge of anatomy permit to avoid many potential complications of surgical interventions, the risk of vessel damages should not be completely excluded. It is especially important in view of the increasing number of surgeries on different formations in the sellar area [24-26].

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Recently, effective pharmaceutical drugs are being actively introduced into the world pharmacological practice facilitating normalization of a disturbed hormonal function. They include non-selective and selective agonists of dopamine receptors, of somatostatin analogues (SA) and blockers of STH receptors. All these promising medical drugs possess advantages and indications to use [27]. Use of SA is the primary medical treatment of acromegaly [27,28]. Drugs of this group directly realize their effect through type 2 and 5 somatostatin receptors with the result of reduction of secretory activity of STH-producing adenoma [27-29]. Currently in Russian Federation the following medical drugs of SA group are registered [27-29]:

A.Octreotide-containing drugs:

1. fast-acting forms for subcutaneous introduction – Sandostatin, Octreotide (50, 100 and 300 μg/ml).

2. long-acting forms for intramuscular introduction – Sandostatin LAR, Octreotide-Depo, Octreotide-Long at doses (10, 20 and 30, 40 mg once in 28 days).

B. Lanreotide-containing long-acting form – Somatuline Autogel (120 mg once in 4–8 weeks subcutaneously).

According to data of Moscow region register, initial treatment with SA at a dose 20 mg resulted in a complete remission (that is, achievement of the target biochemical hormonal values) in 23 of 79 (29.1%) patients, in another 10 (12.7%) patients at least one target parameter (STH or IGF-1) was achieved [30].

The most well-known original drug of the group of octreotide-containing somatostatin analogues is Octreotide-Depo (Long) prolonged effect of which is due to incorporation of the active substance (octreotide) into microspheres consisting of a specific poly-DL-lactid-coglycolide-glucose polymer providing slow release of the medical drug from intramuscular storages [27,28,30]. After a certain time the introduced microspheres undergo biodegradation by hydrolysis. At a dose of the medical drug 10-40 mg the therapeutic concentration of Octreotide-Depo in blood remains unchanged within 28 days. Another original long-acting medical preparation of SA registered in Russian Federation is Somatuline Autogel 120 mg with the active substance lanreotide. Incorporation of D-tryptophan into the structure of the drug improves its stability, and of D-alanine improves selectivity of action of the molecule. Somatuline Autogel is an oversaturated aqueous solution of lanreotide with formation of gel. Advantages of the drug include the absence of pharmacological carrier, prolonged effect (up to 56 days) due to slow diffusion of crystals from the subcutaneous storage, uniform pharmacokinetic effect without any initial spikes of increased concentrations, ready for use pharmaceutical form, small volume of introduction, method of introduction – subcutaneous. Another positive side of Somatuline Autogel is a possibility (according to indications) to prolong intervals between injections up to 8 weeks, which undoubtedly improves the extent of liberty and quality of life of pa-

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tients. In the 70-80s the leading drug in pharmacotherapy of acromegaly was a stimulator of dopaminergic receptors – a semisynthetic ergot alkaloid – bromocriptine – which induced a paradoxical reduction of STH in about 40-50% of patients [27,28,31]. Currently it is replaced with selective long-acting D2-agonists of dopamine (quinagolide and cabergoline). Cabergoline at a dose 1.0-3.5 mg a week reliably reduces IGF-1 in 60-70% of patients, with complete normalization of this parameter in 30-50% of cases. Reduction in size of somatotropinoma was noted in 55% of cases. Cabergoline still retains its proven effectiveness in acromegaly, but, despite this, the result of its clinical use is insignificant: remission was seen only in 10% of cases [30,31]. According to the modern recommendations, cabergoline may be indicated for treatment of acromegaly in patients who prefer only peroral drugs, who refused from surgery, after incomplete adenomectomy – in a combination of hyperprolactemia and not high levels of STH and IGF-1, and also in combined therapy of patients taking maximal doses of SA [32].

In 2000 a principally new medical drug was introduced for treatment of acromegaly – pegvisomant (*somavert, Pfizer Inc.*) which is a genetically engineered analogue of endogenous STH with 9 mutations, antagonist of growth hormone receptors. One of the most important effects of pegvisomant is the ability to normalize different metabolic disorders that almost always exist in patients with acromegaly and are the main cause of their disability and death. Recent research conducted by a group of Italian scientists proved that treatment with pegvisomant within 18 months results in a significant regress of manifestations of acromegalic cardiomyopathy and increases tolerance to physical loads. This conclusion is based on the results of a dynamic study of different hemodynamic parameters using radionucleotide angiography at rest and after physical load. Pegvisomant normalizes lipid metabolism as well as levels of leptin and parameters of bone remodeling [33].

The third method of treatment for acromegaly is radiation therapy. There exist two main kinds of radiation therapy: conventional fraction radiation therapy and stereotactic radiosurgery [3,5,34]. Stereotactic radiosurgery includes: gamma knife, cyber knife and linear accelerator using high-energy photons. Some centers use proton particles for stereotactic radiosurgery [1,35]. Its main difference from fraction radiotherapy is the possibility to direct a one-time high dose through a narrow focused beam to a distinctly limited zone (area) which significantly reduces the number of complications and improves the effectiveness of the given type of radiotherapy [35]. In irradiation with gamma knife method, gamma rays emitted from 201 sources containing radioactive cobalt-60, are concentrated on a narrow field. Remission comes in 2 to 7 years. Radiotherapy may be used as an additional method of treatment after conducted neurosurgical treatment (sometimes after repeated treatment), in case of insufficient sensitivity to somatostatin analogues and in high proliferation index Ki-67 [1,4,35-37].

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Conclusion

Thus, modern diagnostic methods (magnetic resonance imaging of pituitary, determination of somatotropic hormone and insulin-like growth factors in blood) permit maximally early identification of acromegaly. The main methods of treatment (endonasal transsphenoidal adenomectomy, primary and secondary medicinal therapy, stereotactic radiosurgery improve the quality and duration of patients' life. Effectiveness of therapy is guaranteed by a long period of maintenance of normal concentrations of somatotropic hormone and insulin-like growth factors which is confirmed by international research.

Литература

1. Дедов И.И., Молитвословова Н.Н., Рожинская Л.Я., и др. Федеральные клинические рекомендации по клинике, диагностике, дифференциальной диагностике и методам лечения акромегалии // Проблемы эндокринологии. 2013. Т. 59, №6. С. 4-18.

2. Анциферов М.Б., Алексеева Т.М., Пронин В.С. Московский регистр больных акромегалией: отдаленные результаты наблюдения // Фарматека. 2016. Т. 16, №329. С. 62-66.

3. Благосклонная Я.В., Шляхто Е.В., Бабенко А.Ю. Эндокринология: учебник для медицинских вузов. 2-е изд. СПб: СпецЛит; 2007.

4. Дедов И.И., Молитвославова Н.Н., Марова Е.И. Акромегалия: патогенез, клиника, диагностика, дифференциальная диагностика, методы лечения: пособие для врачей. Тверь: Триада; 2003.

5. Потемкин В.В., Пронин В.С. Гипофизарный гигантизм и акромегалия. В кн.: Потемкин В.В., ред. Эндокринология: руководство для врачей. М.: МИА, 2013.

6. Дедов И.И., Мельниченко Г.А. Эндокринология: национальное руководство. М.: ГЭОТАР-Медиа, 2013.

7. Пронин В.С. Диагностические и прогностические факторы, определяющие особенности клинического течения и тактику лечения акромегалии: дис. … докт. мед. наук. М., 2011. Доступно по: http://medical-diss.com/medicina/diagnosticheskie-i-prognosticheskie-faktory-opredelyayuschie-osobennosti-klinicheskogo-techeniya-i-taktiku-lecheniya-akro-1. Ссылка активна на 1 февраля 2018.

8. Иловайская И.А. Кардиологические осложнения акромегалии // Фарматека. 2009. №10. С. 25-31.

9. Егорова Н.А., Халимов Ю.Ш., Никифоров В.С., и др. Взаимосвязь показателей суточного мониторирования артериального давления и гормональной активности со структурно-функциональными характеристиками миокарда у больных акромегалией в зависимости от наличия артериальной гипертензии // Артериальная гипертензия. 2011. Т.17, №2. С. 141-145.

DOI: 10.23888/PAVLOVJ2018261117-132

10. Завьялова Ю.В., Боровиков Н.Н., Занозина О.В. Анализ суточного мониторирования артериального давления у больных с соматотропиномой // Архивъ внутренней медицины. 2014. Т. 3, №17. С. 52-54.

11. Древаль А.В., Триголосова И.В., Виноградова А.В., и др. Нарушения углеводного обмена при акромегалии: пособие для врачей. М., 2012.

12. Триголосова И.В., Виноградова А.В., Круглякова М.В. Сахарный диабет при нейроэндокринных заболеваниях // Альманах клинической медицины. 2014. № 32. С. 89-96.

13. Петрик Г.Г., Павлищук С.А. Влияние хронической гипергликемии на параметры белкового, липидного обменов и тромбоцитарно-коагуляционного гемостаза при акромегалии // Ожирение и метаболизм. 2011. №4. С. 24-27.

14. Молитвословова Н.Н., Петеркова В.А. Гормон роста и щитовидная железа. Доступно по: https://www.rostmaster.ru/lib/gormonrost/gormonrost-0013.shtml. Ссылка активна на 26 января 2018.

15. Молитвословова Н.Н. Акромегалия. В кн.: Дедов И.И., ред. Клиническая нейроэндокринология. М.: УП-Принт, 2011. С. 137-169.

16. Holdaway I.M., Bolland M.J., Gamble G.D. A meta-analysis of the effect of lowering seruv levels of GH and IGF-1 on mortality in acromegaly // Eur. J. Endocrinol. 2008. Vol. 159. P. 89-95. doi:10.1530/EJE-08-0267.

17. Melmed S., Casanueva F.F., Cavagnini F. Consensus Guidelines for Acromegaly Management // J. Clin. Endocr. Metab. 2002. Vol. 87, №9. P. 4054-4058. doi: 10.1210/jc.2002-011841.

18. Giustina A., Casanueva F.F., Cavagnini F. Diagnosis and treatment of acromegaly complications // J. Endocrinol. investigation. 2003. Vol. 26, №12. P. 1242-1247.

19. Яковлев С.А. Роль динамической контрастной МРТ в комплексной лучевой диагностике и дифференциальной диагностике объемных образований головного мозга, расположенных по средней линии. Дис. … канд. мед. наук. Санкт-Петербург, 2009. Доступно по: http://medical-diss.com /medicina/rol-dinamicheskoy-kontrastnoy-mrt-v-komplek snoy-luchevoy-diagnostike-i-differentsial noy-diagnostike-obemnyh-obrazovaniy-g. Ссылка активна на 15 января 2018.

20. Лобанов И.А., Лавренюк А.Н., Никитин Д.Н. Магнитно-резонансная диагностика аденом гипофиза // Медицинский альманах. 2011. №1. С. 104-107.

21. Katznelson L., Atkinson J.L.D., Cook D.M., et al. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly // Endocrine practice. 2011. Vol. 17, №4. P. 1-44.

22. Lenzi J., Lapadula G., Damico T. Evaluation of trans-sphenoidal surgery in pituitary GH-secreting micro- and macro-adenomas: a comparison between microsurgical and endoscopic approach // J. Neurosurg. Sci. 2015. Vol. 59, №1. P. 8-11.

23. Сытый В.П., Гончар А.А., Сытый Ю.В. Аденомы гипофиза: история, распространенность, клиника, диагностика, лече-

DOI: 10.23888/PAVLOVJ2018261117-132

ние // Проблемы здоровья и экологии. 2010. Т. 3, №25. С. 41-50.

24. Молитвословова Н.Н., Марова Е.И., Юшков П.В. Хирургическое лечение акромегалии: клинико-морфологические особенности соматотропином, определяющие послеоперационный прогноз. В кн.: Высокие медицинские технологии в эндокринологии: 5-й Всероссийский конгресс по эндокринологии. М., 2006. С. 411.

25. Азизян В.Н., Григорьев А.Ю., Иващенко О.В., и др. Интраоперационное кровоизлияние в аденому гипофиза как причина ремиссии акромегалии // Эндокринная хирургия. 2011. №1. С. 39-44.

26. Григорьев А.Ю., Азизян В.Н.; Дедов И.И., Кузнецов Н.С., ред. Эндоскопическая хирургия аденом гипофиза: практическое руководство для врачей. М.: УП Принт, 2011.

27. Ациферов М.Б., Пронин В.С., Алексеева Т.М., и др. Настоящее и будущее фармакотерапии акромегалии // Фарматека. 2012. №16. С. 20-28.

28. Мельниченко Г.А., Пронин В.С. Современные схемы фармакотерапии акромегалии // Врач. 2008. №8. С. 9-13.

29. Shimon I., Yan X., Taylor J.E. Somatostatin receptor (SSTR) subtype-selective analogues differentially suppress in vitro growth hormone and prolactin in human pituitary adenomas. Novel potential therapy for functional pituitary tumors // J. Clin. Invest. 1997. Vol. 100. P. 2386-2392.

30. Марова Е.И., Мельниченко Г.А., Молитвословова Н.Н. Клиническая эффективность аналога соматостатина длительного действия Октреотида-депо у больных акромегалией // Фарматека. 2007. №11. С. 66-69.

31. Vilar L., Czepielewsk M.A., Naves L.A., et. al. Substantial shrinkage of adenomas cosecreting growth hormone and prolactin with use of cabergoline therapy // Endocr. Pract. 2007. Vol. 13, №4. P. 396-402.

32. Cozzi R., Attanasio R., Lodrini S. Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status // Clin. Endocrinol. 2004. Vol. 61. P. 209-215.

33. Молитвословова Н.Н. Акромегалия: современные достижения в диагностике и лечении // Проблемы эндокринологии. 2011. №1. С. 46-59.

34. Дедов И.И., Мельниченко Г.А., Липатенкова А.К. Современная нейроэндо-кринология // Вестник РАМН. 2012. №8. С. 7-13.

35. Марова Е.И., Авакян М.Р., Подлящук Е.Л. Результаты дистанционной гамма-терапии у больных с акромегалией // Проблемы эндокринологии. 1991. Т. 37, №1. С. 22-25.

36. Ильичева В.Н., Ушаков Б.Н. Влияние ионизирующего излучения на энергетический обмен в различных отделах коры головного мозга // Российский медико-биологический вестник имени академика И.П. Павлова. 2013. №1. С. 30-36. doi: 10.17816/PAVLOVJ2013130-36.

37. Титова Л.Ю., Аристархов В.Г., Аристархов Р.В., Пузин Д.А. О влиянии инфракрасной лазерной терапии на тире-

DOI: 10.23888/PAVLOVJ2018261117-132

оидный гормональный статус у женщин при нарушении менструальной функции // Наука молодых (Eruditio Juvenium). 2017. №2. С. 291-297. doi:10.23888/HMJ20172 291-297.

References

1. Dedov II, Molitvoslovova NN, Roghin-skaya LY, et. al. Federal'nye klinicheskie rekomendacii po klinike, diagnostike, differencial'noj diagnostike i metodam lechenija acromegalii. *Problems of endocrinology*. 2013; 59(6):4-18. (In Russ).

2. Antsiferov MB, Alekseeva TM, Pronin VS. Moskovskiy registr bol'nykh akromegaliey: otdalennye rezul'taty nablyudeniya. *Farmateka*. 2016; 16(329):62-6. (In Russ).

3. Blagosklonnaya YaV, Shlyakhto EV, Babenko AYu. *Endokrinologiya: uchebnik dlya meditsinskikh vuzov*. 2nd ed. Saint-Petersburg: SpecLit; 2007. (In Russ).

4. Dedov II, Melnichenko GA, Marova EI. *Akromegaliya: patogenez, klinika, diagnostika, differentsial'naya diagnostika, metody lecheniya: posobie dlya vrachey*. Tver': Triada; 2003. (In Russ).

5. Potemkin VV, Pronin VS. Gipofizarnyy gigantizm i akromegaliya. In: Potemkin VV, editor. *Endokrinologiya: rukovodstvo dlya vrachey*. Moscow: MIA; 2013. (In Russ).

6. Dedov II, Mel'nichenko GA. *Endokrinologiya: natsional'noe rukovodstvo*. Moscow: GEOTAR-Media; 2013. (In Russ).

7. Pronin VS. *Diagnosticheskie i prognosticheskie faktory, opredelyayushchie osobennosti klinicheskogo techeniya i taktiku lecheniya akromegalii* [dissertation]. Moscow; 2011. Available at: http://medical-diss.com/medicina/diagnosticheskie-i-prognosticheskie-faktory-opredelyayuschie-osobennosti-klinicheskogo-techeniya-i-taktiku-leche-niya-akro-1. Accessed: 1 Feb 2018. (In Russ).

8. Ilovayskaya IA. Kardiologicheskie oslozhneniya akromegalii. *Farmateka*. 2009; 10:25-31. (In Russ).

9. Egorova NA, Khalimov YuSh, Niki forov VS, et al. Vzaimosvyaz' pokazateley sutochnogo monitorirovaniya arterial'nogo davleniya i gormonal'noy aktivnosti so strukturno-funktsional'nymi kharakteristikami miokarda u bol'nykh akromegaliey v zavisi-mosti ot nalichiya arterial'noy gipertenzii *Arterial Hypertension*. 2011; 17(2):141-5. (In Russ).

10. Zav'yalova YuV, Borovikov NN, Zanozina OV. Analiz sutochnogo monitorirovaniya arterial'nogo davleniya u bol'nykh s somatotropinomoy. *Arkhiv" vnutrenney meditsiny*. 2014; 3(17): 52-4. (In Russ).

11. Dreval' AV, Trigolosova IV, Vinogradova AV, et al. *Narusheniya uglevodnogo obmena pri akromegalii: posobie dlya vrachey*. Moscow; 2012. (In Russ).

12. Trigolosova IV, Vinogradova AV, Kruglyakova MV. Sakharnyy diabet pri neyroendokrinnykh zabolevaniyakh. *Almanac of clinical medcine*. 2014;32:89-96. (In Russ).

13. Petrik GG, Pavlishchuk SA. Vliyanie khronicheskoy giperglikemii na pa-rametry belkovogo, lipidnogo obmenov i trombotsitarno-koagulyatsionnogo gemostaza pri akromegalii. *Obesity and metabolism*. 2011; 4:24-7. (In Russ).

14. Molitvoslovova NN, Peterkova VA. *Gormon rosta i shchitovidnaya zheleza*. Available at: https://www.rostmaster.ru/lib/gormonrost/gormonrost-0013.shtml. Accessed 26 Jan 2018. (In Russ).

15. Molitvoslovova NN. Akromegaliya. In: Dedov II, editor. *Klinicheskaya neyroendokrinologiya.* Moscow: UP-Print; 2011. P. 137-69. (In Russ).

16. Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering seruv levels of GH and IGF-1 on mortality in acromegaly. *Eur. J. Endocrinol.* 2008;159:89-95. doi:10.1530/EJE-08-0267.

17. Melmed S, Casanueva FF, Cavagnini F. Consensus Guidelines for Acromegaly Management. *J. Clin. Endocr. Metab.* 2002; 87:4054-8. doi: 10.1210/jc.2002-011841.

18. Giustina A, Casanueva FF, Cavagnini F. Diagnosis and treatment of acromegaly complications. *J. Endocrinol. Investigation.* 2003; 26(12):1242-7.

19. Yakovlev SA. *Rol' dinamicheskoy kontrastnoy MRT v kompleksnoy luchevoy diagnostike i differentsial'noy diagnostike ob"emnykh obrazovaniy golovnogo mozga, raspolozhennykh po sredney linii* [dissertation]. Saint-Petersburg; 2009. Avaiable at: http://medical-diss.com/medicina/rol-dinamicheskoy-kontrastnoy-mrt-v-kompleksnoy-luchevoy-diagnostike-i-differentsialnoy-diagnostike-obemnyh-obrazovaniy-g. Accessed 15 Jan 2018. (In Russ).

20. Lobanov IA, Lavrenyuk AN, Nikitin DN. Magnitno-rezonansnaya diagnostika adenom gipofiza. *Meditsinskiy al'manakh.* 2011; 1:104-7. (In Russ).

21. Katznelson L, Atkinson JLD, Cook DM, et al. Medical guidelines for clinical practice for the diagnosis and treatment of acromegaly. *Endocrine practice.* 2011; 17(4):1-44.

22. Lenzi J, Lapadula G, Damico T. Evaluation of trans-sphenoidal surgery in pituitary GH-secreting micro- and macroadenomas: a comparison between microsurgical and endoscopic approach. *J. Neurosurg Sci.* 2015; 59(1):8-11.

23. Sytyy VP, Gonchar AA, Sytyy YuV. Adenomy gipofiza: istoriya, rasprostranennost', klinika, diagnostika, lechenie. *Problemy zdorov'ya i ekologii.* 2010; 3(25):41-50. (In Russ).

24. Molitvoslovova NN, Marova EI, Yushkov PV. Khirurgicheskoe lechenie akromegalii: kliniko-morfologicheskie oso-bennosti somatotropinom, opredelyayushchie posleoperatsionnyy prognoz. *In:* Vysokie meditsinskie tekhnologii v endokrinologii: 5-y Vserossiyskiy kongress po endokrinologii. Moscow; 2006. P. 411. (In Russ).

25. Azizyan VN, Grigor'ev AYu, Ivashchenko OB, et.al. Intraoperatsionnoe krovoizliyanie v adenomu gipofiza kak prichina remissii akromegalii *Endocrine surgery.* 2011; 1:39-44. (In Russ).

26. Grigor'ev AYu, Azizyan VN, Dedov II. *Endoskopicheskaya khirurgiya adenom gipofiza:* prakticheskoe rukovodstvo dlya vrachey. Moscow; 2011. (In Russ).

27. Atsiferov MB, Pronin VS, Alekseeva TM, et. al. Nastoyashchee i budushchee farmakoterapii akromegalii. *Farmateka.* 2012; 16:20-8. (In Russ).

DOI: 10.23888/PAVLOVJ2018261117-132

28. Mel'nichenko GA, Pronin VS. Sovremennye skhemy farmakoterapii akromegalii. *Vrach.* 2008;8:9-13. (In Russ).

29. Shimon I, Yan X, Taylor JE. Somatostatin receptor (SSTR) subtype-selective analogueues differentially suppress in vitro growth hormone and prolactin in human pituitary adenomas. Novel potential therapy for functional pituitary tumors. *J Clin. Invest.* 1997; 100:2386-92.

30. Marova EI, Mel'nichenko GA, Molitvoslovova NN. Klinicheskaya effektivnost' analoguea somatostatina dlitel'nogo deystviya Oktreotida-depo u bol'nykh akromegaliey. *Farmateka.* 2007;11:66-9. (In Russ).

31. Vilar L, Czepielewsk MA, Naves LA, et al. Substantial shrinkage of adenomas cosecreting growth hormone and prolactin with use of cabergoline therapy. *Endocr Pract.* 2007;13(4);396-402.

32. Cozzi R, Attanasio R, Lodrini S. Cabergoline addition to depot somatostatin analogueues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. *Clin Endocrinol.* 2004;61:209-15.

33. Marova EI, Mel'nichenko GA, Molitvoslovova NN. Klinicheskaya effektivnost' analoguea somatostatina dlitel'nogo deystviya Oktreotida-depo u bol'nykh akro-megaliey. *Problems of endocrinology.* 2011; 1:46-59. (In Russ).

34. Marova EI, Mel'nichenko GA, Molitvoslovova NN. Klinicheskaya effektivnost' analoguea somatostatina dlitel'nogo deystviya Oktreotida-depo u bol'nykh akromegaliey. *Vestnik RAMN*. 2012; 8:7-13. (In Russ).

35. Marova EI, Avakyan MR, Podlyashchuk EL. Rezul'taty distantsionnoy gamma-terapii u bol'nykh s akromegaliey. *Problems of endocrinology.* 1991; 37(1):22-5. (In Russ).

36. Ilicheva VN, Ushakov BN. Effects of ionizing radiation on the energy exchange in different cerebral cortex. *Rossijskiy mediko-biologicheskiy vestnik imeni akademika I.P. Pavlova.* 2013; 21(1):30-6. (In Russ). doi: 10.17816/PAVLOVJ2013130-36.

37. Titova L.Ju., Aristarhov V.G., Aristarhov R.V., Puzin D.A. Laser therapy in the treatment of infertility and menstrual function against the background of autoimmune thyroiditis. *Nauka molodykh (Eruditio Juvenium).* 2017;5(2):291-7. (In Russ). doi:10.23888/HMJ20172291-297.

DOI: 10.23888/PAVLOVJ2018261117-132

Дополнительная информация
[Additional Info]

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, о которых необходимо сообщить, в связи с публикацией данной статьи. [**Conflict of interests**. The authors declare no actual and potential conflict of interests which should be stated in connection with publication of the article.]

Информация об авторах
[Authors Info]

Жулидова А.Ю. – очный аспирант кафедры факультетской терапии с курсами эндокринологии, клинической фармакологии и профессиональных болезней ФГБОУ ВО РязГМУ Минздрава России, г. Рязань, Российская Федерация. [**Zhulidova A.U.** – PhD Student of the Department of Faculty Therapy with a Course of Endocrinology, Clinical Pharmacology and Occupational Diseases, Ryazan State Medical University, Ryazan, Russian Federation.]
SPIN 2012-8600,
ORCID ID 0000-0003-1381-1884,
Researcher ID C-8079-2018.
E-mail: anya.zhulidova@yandex.ru

Дубинина И.И. – д.м.н., профессор, профессор кафедры факультетской терапии с курсами эндокринологии, клинической фармакологии и профессиональных болезней ФГБОУ ВО РязГМУ Минздрава России. г. Рязань, Российская Федерация. [**Dubinina I.I.** – MD, Grand PhD, Professor of the Department of Faculty Therapy with a Course of Endocrinology, Clinical Pharmacology and Occupational Diseases, Ryazan State Medical University, Ryazan, Russian Federation.]
ORCID ID 0000-0001-6726-1756,
Researcher ID B-1773-2017.

DOI: 10.23888/PAVLOVJ2018261117-132

Цитировать: Жулидова А.Ю., Дубинина И.И. Акромегалия и коморбидные состояния. Новые возможности диагностики и лечения (обзор литературы) // Российский медико-биологический вестник имени академика И.П. Павлова. 2018. Т. 26, №1. С. 117-132. doi: 10.23888/PAVLOVJ2018261117-132.

To cite this article: Zhulidova A.U., Dubinina I.I. Acromegaly and comorbid conditions. New possibilities of diagnosis and treatment (literature review). *I.P. Pavlov Medical Biological Herald.* 2018;26(1):117-32. doi: 10.23888/PAVLOVJ 2018261117-132.

Принята в печать/Accepted: 31.03.2018