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Department of Internal Diseases № 2

ACROMEGALY

METHODOLOGICAL MATERIALS

the main professional educational program of higher education - a program of a specialist in a specialty 31.05.01 General medicine

Vladikavkaz

Methodical materials "Acromegaly" are intended for training students of 5 courses (9 semester) therapeutic Faculty of FSBEA in the Sogma of the Ministry of Health of Russia in the discipline of Endocrinology.

Compilers:

Associate Professor of the Department of Internal Diseases No. 2, Ph.D. Z.T. Tsabolova

Associate Professor of the Department of Internal Diseases No. 2, Ph.D. A.B. Kusova

Reviewers:

Head of the Department of Internal Diseases No. 1 Sogma, D.M. Totrov I.N.

GL Doctor GBUZ "Republican Endocrinological Dispensary" Ministry of Health of RSO-Alania Fidarova M. Yu.

Introduction

Acromegaly is a heavy neuroendocrine disease caused by chronic hyperproduction of growth hormone (somatotropin, STG). Most often, the disease acromegaly is marked between 20 and 40 years, but its development is observed both over the age of 50 and aged between 10 and 15 years.

A million people accounted for from 50 to 70 cases of acromegaly diseases. 3-4 repeated cases are recorded annually. However, an accurate figure of the prevalence of this disease is difficult to indicate due to the fact that the time from the appearance of the first signs of acromegaly to establish an accurate diagnosis ranges from 5 to 15 years. Not revealed by a clear interconnection of the incidence of acromegaly with the floor, although many authors indicate a greater predisposition of women to this disease.

When analyzing anamnetical data, more than half of the patients noted the appearance of signs of the disease against the background of complete health, about 180/0 of patients bind the beginning of the disease with the preceding brain trauma, about 5% of women - with repeated abortions and childbirth, in patients with acromegaly in history, chronic sinusites and Otitis with frequent exacerbations.

Acromegaly is characterized by progressive disability and reduction of life expectancy. Mortality among patients with acromegaly exceeds ten times those in the control population. Approximately 50% of the untreated patients are dying under the age of 50. The main causes of increased mortality and reduce life expectancy are complications that develop under this disease: cardiovascular pathology, diabetes and its complications, diseases of the respiratory organs, malignant newly evidence of the gastrointestinal tract and some others. In turn

Timely diagnosis and adequate treatment of this disease makes it possible to reduce the mortality rate of 2-5 times.

If the disease occurs in childhood or in adolescence, when there is no echiphysis occurrence, there is an excess proportional increase in the skeleton bones in length, which leads to a significant increase in the linear growth of the subject. Such clinical syndrome was called giantism. If such patients are not subjected to timely treatment, then after completion of the puberty period, they develop all typical symptoms of acromegaly.

Etiology and pathogenesis

Currently, it is assumed that the following main etiopathogenetic mechanisms of chronic excess production hormone products are expected.

In 95% of cases, this is the primary excess secretion of the growth hormone of the adenoma pituitary. Histomorphological analysis of such adenses according to the Kazakhs that they can be a dense or rare-produced somatotropic adenoma, mixed adenoma of somatotrophic and lactotrophic cells, a mammosomatotropin, plurigormonal adenoma, also carcinoma from somatotrophic cells.

Currently, it is believed that the development of the pituitary aden is a multi-stage process in which primary genetic changes cause unregulated monoclonal expansion of mutated cells. Hypotalamic hormones and local growth factors play the role of promoters of further growth. The final phenotype of the pituitary tumor is the result of the interaction of activating and braking genetic mutations with local hypothalamic endocrine and paracryn growth factors.

Intensifying cell mutations include activation of fine protocoen. The protoncogen - the normal cellular cell involved in controlling cell proliferation and differentiation, which in the event of mutation is activated, which can lead to tumor transformation. Mutant alleles of protoncogens are dominant, and they are able to transform cells, despite the simultaneous expression of a normal allele. Thus, in 40% of the periods producing the pituitary aden, the Mutation of the alpha-subunit-protein is the most common mutation with this type of aden. In this case, this mutation is very rarely encountered with other types of pituitary tumors: Nag - <10%, corticotropine - <6%.

The frequency of this mutation also has an ethnic dependence: it is most rarely found in the Japanese population (less than 10%). The resulting Mutation GSP-oncogen causes the suppression of the activity of guanosyntrifosphate on the alpha subunit of the adenylate cyclic-dependent stimulating G-protein. This leads to persistent adenylate cyclase, which simulates the constant activation of somatolyberin receptors and leads to the autonomous secretion of the STG and the hyperplasia of somatotrophs.

It is believed that permanent activation of adenylate cyclase contributes to the receptors expressed in somatotrofam, a transduction defect, which leads to the inhibitation of adenylate cyclase.

Studies did not reveal correlations between the presence of GSP mutation and age, gender, the size of the tumor or the circulating level of STG and IRF-1.GSP-expression tumors according to the data of morphological analysis are dense-grained, weakly invasive, the least aggressive STG-secreting tumors, extremely sensitive to the overwhelming effect. Somatostatina.

In the high-producing adenoma of the pituitary gland with a lower frequency, an increased activity and other cellular protoncogens were found, in particular, protein kinases with (RKS) - the enzyme of the calcium family and phospholipid-dependent protein kinases. RCC, being an important enzyme in the transmission of cellular signals in the pituitary, stimulates fraystrins that contribute to tumor development. Moreover, the invasive tumor growth is combined with the detection of mutation V3 of the region of the Alfa-Isoform of the RCC.

It is also not excluded the role in the pituitary tumorogenesis of mutations of a powerful oncogene - a gene transforming pituitary tumor (PTTG). Increasing the expression of this oncogene by more than 500/0 was noted in most of the STG-secreted pituitary aden, and the highest expression is- in active tumors with invasion into wedge-shaped bone. An increase in PTTG expression leads to a chromosome separation, leading to the loss or appearance of excess chromosome. Subsequent chromosomal aneuploidy can lead to the activation of protoncogenic or loss of heterozygousness of tumor-suppressor genes.

Tumor-suppressor genes normally limit the cell proliferation, adjusting the cell cycle and maintaining the stability of the genome, thus preventing the manifestation of tumor growth. The initiation of the growth of the tumor cell begins after both recessive alleles of the tumor-suppressor gene are lost or changed. Among the tumor-suppressor genes, with a high probability of playing a role in the genesis of pituitary tumors, in particular, somatotropin, are the gene of multiple endocrine neoplasia 1, the Retinoblastoma gene and some of the CDK1 genes,

Maine 1-Sundar is associated with a genome overwhelming a tumor growth localized on the LLQ13 chromosome. Allel deletion involving LLQ13 has been demonstrated both in somatotropynes derived from patients with Main-1-syndrome and in 16% sporadic somatotropynes.

The Ratinoblastoma gene (RB) is normally adjusting the cell cycle and plays an important role in controlling cell differentiation and survival. In a number of malignant and invasive pituitary tumors

The loss of heterozygosity (LOH) is revealed close to RB locus on the chromosome 13q. Loss LOH Lokus 9P21 CDKN2A-gene and low P16 expression are also found in pituitary tumors. Thus, there are still single genes from a large number of already studied (about 8,000 thousand), involved in the pathogenesis of pituitary tumors. The molecular mechanism leading to the transformation of the pituitary cell remains unknown yet.

Very rarely (<2%) Hyperfunction of growth hormone can be caused by the STG-secreting tumor of an extraposable localization. The latter can be detected in the throat, pancreas, light, ovaries, mediastinum. The mechanism of its occurrence is presumably similar to the STG-producing pituitary adenome.

In less than 3% of all cases, acromegaly arises due to the increased secretion of somatolyberin, leading to the hyperplasia of somatotrophs, followed by the formation of the polyclonal adenoma of the pituitary gland. Such a pathological excessive secretion of somatraliberin may arise in the case of the development of both hypothalamus tumors (Gamartoma, Ganglionevrom) and ectopyanisomoliberin-producing tumors. The latter can be represented by carcinoid located in bronchi, gastrointestinal tract, pancreas; Tumor islets of Langerhans, as well as small-cell lung cancer.

Finally, it is assumed to the existence of Somatolyberin Hypothalamus hypothalamus due to inflammatory processes in the central nervous system (arachnoiditis, etc.), as a possible cause - the development of acromegaly.

The growth hormone produced in excess induces increased secretion of growth factors (somatomedians), mainly IRF-1 (somatomedin C), which is produced in the liver, as well as local products of growth factors in various tissues, including bones and cartilage. Under the influence of growth factors in soft tissues, mucopolysaccharides are deposited, including glucosaminoglycans, hyaluronic acid and chondroitin-sulfate; There is an increase in collagen products, the proliferation of the cartilage, which ultimately leads to growth and thickening of soft tissues, cartilage and bones and explains the emergence of the main clinical symptoms of the disease. Recent studies indicate a very probable role of local products of IRF-binding proteins, in particular, protein-3 in the stimulation of osteoblasts and chondrocytes.

Clinic

The clinical picture of acromegaly is very diverse, which is due to the involvement in the pathological process of many organs and systems at a given disease (Table 1, 2). The most vivid clinical manifestation of acromegaly is the change in appearance (Fig. 2). So, patients note the enlargement of the nose, lips, language, thickening of the skin, abrupt arcs. Diasthemia arises (expanding interdental intervals), prenatamism (outstanding the lower part), especially the lower jaw, which leads to a disruption of bite. Increase in the size of the limb: brushes, fingers, feet, and mainly in width, which forces patients to change gloves, rings, shoes. In the enlarged limbs frequent paresthesia, numbness of the fingers. In 35-43% of patients developing the Syndrome of the Carpal Channel due to the compression of the median nerve in the wrist area by changed soft tissues.

A characteristic symptom is a headache, often constant, exhausting, whose frequency is 60-86%. The pressure rendered to the surrounding tissue is not the only cause of headaches. The genesis of the latter has not yet been fully studied. The increased activity of sweat and sebaceous glands leads to increased sweating, the appearance of oily seborrhea, Vulgaris Assna, which causes a specific unpleasant smell of the body. Changes occur in peripheral nerves, in particular, segmental demyelinization of small-diameter nerve fibers, which is confirmed by the results of the biopsy. This process, most likely, determines the emergence of such clinical symptoms as paresthesia, as well as a decrease in peripheral reflexes, surface tactile and pain.

Despite hyperfunction of muscle fibers, leading to an increase in muscle mass, many patients are worried about fast fatigue, weakness, abruptly reduced abdication, tolerance to physical exertion. The latter is associated with developing almost 50% of patients with proximal myopathia, confirmed by the results of electromyography. Approximately 62-75% of patients are disturbed by pain in the joints, the spine on the type of radicular, which is associated with the development of arthropathy, up to osteoarthritis, as well as the deformation of the skeleton by the type of pathological kyphosis. Excessive products of collagen inside the tendons cause an additional destabilization of the joints. The permanent stimulation of Osteoblasts leads to degenerative changes in the okolosserts. At the same time, an increase in the size of the articular space is revealed (in the late stages - decrease), angular deformations of joints, osteophytes, observation of articular surfaces, osteosclerosis, subchondral cysts, an increase and calcification of rib-cartilaginous joints. Thickening voice ligaments and expansion of sinuses leads to the appearance of a low coarse voice. Women often appears Girsutism, Laktori; In 32-87% of them, there are violations of the menstrual cycle, more often by type of oligo and amenorrhea; 27-46% of men note a decrease in libido and potency. In 4-

5.2% of patients, there is a violation of vision, manifested as a decrease in the severity and restriction of fields, up to full blindness. The appearance of these symptoms is characteristic of the larger adena of the pituitary gland and is due to the suprasellary increase in the tumor, which squeezes the crossover of the visual nerves located on the front surface of the pituitary gland. In connection with the foregoing, the patient shows an ophthalmic examination, including perimetry, which allows to identify a mono- or bi-imperial hemianopia with / without central cattle, atrophy of optic nerves, pupil defects.

The significant spread of the pituitary tumor laterally in cavernous sinuses can lead to a violation of the function (paresa) of the III, IV, V and VI pairs of cranial brain nerves, parts of which are held in cavernous sinuses. It can be clinically manifested by ophthalmoplegia, ptosis, dysfunction of pupils, pains in the course of a trigeminal nerve, a decrease in reflexes. With a significant suprasellular proliferation of the tumor, the ventricle is possible, leading to an increase in intracranial pressure and the appearance of edema of the nipple of the optic nerve.

One of the serious complications for acromegaly is the case of the side of the cardiovascular system. So, in 25-50% of patients, arterial hypertension is recorded, which is 3-4 times more often than in the population. The genesis of the development of arterial hypertension in acromegaly studied is not enough, however, it is believed that the main predisposing factor is the delay in sodium and water in the body. Characteristic is the increase in the heart and the development of heart failure. Cardiomegaly is one of the manifestations of splanegalia characteristic of this disease. The mass of myocardial is directly proportional to the duration of the disease and can reach 1300 g. The cause of cardiomegali development is the concentric hypertrophy of the heart muscle and the increased synthesis of the connective tissue.

The development of myocardial hypertrophy, arterial hypertension also contributes to the development of the left ventricle.

Over time, dystrophic changes are developing in hypertrophied myocardium, leading to the development of so-called acromegalcardiomyopathy, which is confirmed by the emergence of changes in electrocardiograms, as well as the results of autopsy. In particular, 88% of patients independently of age are detected by diffuse changes in myocardium, impaired blood supply, heart rate disorders up to a complete histological study of the myocardium of dead patients in 93% of cases reveals myocardial hypertrophy, in 85% - interstitial fibrosis and in 59% of cases - lymphomonuclear myocarditis .

Metabolic disorders, microangiopathy, hypoxia, etc. resulting from acromegaly, hypoxium, and so on. Heart damage is often exacerbated by the addition of atherosclerosis of coronary arteries, which is found up to 20%. Gradually progressing, myocardiodistrophy leads to the development of heart failure and is often the cause of death. The lesion of the pulmonary system is also a serious problem of patients with acromegaly. Due to the growth of the jaws and soft tissues of the language and the epiglotes, 60% of patients are mostly male, obstructive night apnea is developing. Progressive kifoscolyosis leads to the development of restrictive pulmonary diseases. As a result, the mortality from respiratory disruption in patients with acromegaly exceeds such as a turn as compared with the control population.

And finally, the incidence of neoplasms in patients with acromegaly exceeds such in the overall population more than 2 times. The biopsy results indicate the predominance of intestinal adenomatous polyps, as well as colon cancer.

The chronic excess secretion of growth hormone also leads to pronounced metabolic shifts. These include the development of violations of carbohydrate, lipid and mineral exchanges.

The frequency of hydrogen exchange disorders reaches 54%, the share of diabetes is accounted for up to 25%. The main distinguishing feature of diabetes with acromegaly is resistance to traditional methods of treatment and, in particular, to insulin therapy.

Studies have shown that the degree of increase in growth hormone, the duration of the disease, the age of patients, hereditary predisposition, features do not affect the frequency and degree of violations of carbohydrate metabolism. It has also been established that the latter are not associated with the exhaustion of the secretory ability of β-cells, hyperproduction of glucagon, as well as a violation of the operation of insulin-specific receptors. It is assumed that at the heart of the carbohydrate exchange disorders under the acromegaly, there are changes in the central regulation of the secretion of insulin and glucagon in combination with the glucose protein vehicle in the post-receptor level, as well as with a violation of the formation of metabolic active insulin forms. All patients with acromegaly show shifts in lipid metabolism, positively correlating with the degree of violation of carbohydrate metabolism. In particular, the shift of the lipoprotein plasma spectrum is noted towards α-lipoproteins, a higher content in the blood of cholesterol, nage, ketone bodies and especially triglycerides. The level of the latter is statistically significantly different from the norm. The emergence of

hyperitriglyceridemia is due to a decrease in the activity of hepatic triglyceride-orpoproteinlipase.

Changes in mineral exchange are characterized by a violation of phosphorous calcium exchange. In particular, the increased reabsorption of phosphorus in the kidney nephron tubes is arising, which leads to hyperphosphatems of approximately 48% of patients. The increase in the activity of 1-α-hydroxylase kidney causes an increase in blood in the blood of 1.25 hydroxyvitamin D and calcium, which, in turn, contributes to the stone formation in the kidneys in 6-12.5% of patients.

Increasing the secretion of the HPS adenoma can cause violation of the functions of other adenogi disease departments, in particular gonadotrophs, corticotrophs and thyrotrophs, which, in turn, leads to a violation of the functional state of peripheral endocrine glands: gonad, thyroid gland and adrenal glands.

As mentioned above, in women suffering from acromegaly, disturbances of the menstrual cycle often arise, infertility. At the same time, 2/3 patients are detected by Lactera. The latter in a significant percentage of cases is also found in patients with acromegal men.

The main cause of the symptoms described above is hyperprolactinemium detected in 40-80% of cases. The latter is also the main cause of the decline in libido and potency in men, patients with acromegaly. At the same time, part of women with hyperprolactinemia may possibly lacker, which is explained by low levels of estrogen necessary to start the lactation process. The presence of lackers in women with a normal level of prolactin is probably due to the prolactically similar effect of growth hormone.

The appearance of hyperprolactinemia can be due to various reasons, the main of which is the presence of a mixed adenoma of a pituitary gland, consisting of somatotrophic and lactotrophic cells, secreting STS and prolactin (PRL), or the MammaSomaturropin. As a result of hyperprolactinemia, a reliable reduction in the level of gonadotropins and testosterone is noted. In the absence of timely treatment, the clinical picture of secondary hypogonadism is gradually developing.

In 30-97% of cases, an increase in the thyroid gland with / without nodes formation is found, which is explained by the direct stimulating effect of IRF-1 on the gland fabric. Histological analysis indicates a predominance (69%) of the colloid proliferating goiter. At the same time, autoimmune thyroiditis, papillary cystadenoma, microfollicular adenoma take place.

In most cases, structural changes in the gland are accompanied by a euticoid state. The hypothyroidism clinic, confirmed by laboratory data, is developing either in the case of massive nodes formation, especially against the background of autoimmune thyroiditis (primary hypothyroidism), or when the tumor of the thyrotrophic pituitary is reduced, leading to a decrease in the secretion of the thyrotropic hormone (TSH) (secondary hypothyroidism). It is possible to combine these processes. Head of scientists also explains the decline in TSH secretion by increasing the secretion of somatostatin by a hypothalamus induced by a high level of STG.

Thyareotoxicosis with acromegaly is rarely observed. So, the frequency of primary thyrotoxicosis, according to various authors, ranges from 2 to L%. Single patients with secondary thyrotoxicosis are described, which is a consequence of the Hyperproduction of TSH mixed adenoma pituitary.

The function of the adrenal glands in patients with acromegaly, as a rule, is not violated. However, according to literature data, up to 20% of patients may have secondary adrenal insufficiency due to the compression of the tumor mass of corticotrophs and reducing the secretion of ACTG at large, most often extrasellular substallopinomes. At the same time, in the first years of the disease, the symptoms of hyperfunction are possible, followed by the depletion of adrenal cortex and the development of hypocorticism phenomena.

In a morphological study in the adrenal glands, the hyperplasia of the cortical cell cells is noted, in some cases adenoma and cystic rebirths. It is extremely rare the combination of acromegali and sickness of Itsenko-Cushing.

Diagnosis and Differential Diagnosis

As follows from the very names of the disease, the most vivid clinical manifestation of acromegaly is the change in appearance, and if patients have characteristic complaints, the diagnosis is often no doubt. However, it is absolutely not difficult to be limited to the results of clinical examination. Only a complete laboratory and instrumental examination allows you to properly diagnose, determine the degree of activity of the disease and adequate therapeutic tactics.

The diagnostic algorithm of acromegaly includes a radiographic survey of the skull in the lateral projection, spine, brushes, stop. The latter allows you to identify not only explicit or indirect signs of the pituitary adenoma, but also other radiographic signs characteristic of this disease (Table s). Significant changes in the acromegaly undergoes the structure of soft foot tissues, which is manifested by the thickening of the connecting and intestinal partitions and extensions. In connection with this,

an important additional diagnostic x-ray indicator is the magnitude of the thickness of the soft tissues of the foot (TMTS), highly correlating with the level of growth hormone. The method of determining this indicator is as follows. It is made by the side shot of the foot. The X-ray bundle is centered on the middle point of the line connecting the medial ankle with the lower foot surface. Next to the line connecting the front and rear heal bone proof, the line parallel to it relative to the lower edge of the heel bone. From the point of intersection of this line with the lower edge of the heel bone, a perpendicular line is performed to the plantar surface of the foot. This line is the size of TMTS. The norm in men is up to 21 mm, in women - up to 20 mm. Unlike healthy individuals, this indicator in acromegaly does not depend on body weight and age. There is also no dependence on the duration of the disease acromegaly.

However, the radiographic study does not allow determining the size, the nature of the propagation of the pituitary adenoma, the degree of involvement in the pathological process of the Latero and Supacesellian structures, which you need to know when determining the subsequent therapeutic tactics. In this regard, all patients need CT (computed tomography) or MRI (magnetic resonance imaging) of the brain and the region of the Turkish saddle. As experience shows, CT should be carried out with mandatory contrast. In this case, the optimal method of visualizing the adenoma of the pituitary gland, especially in combination with the cystic component, "empty" Turkish saddle, as well as in the case of microenomes, is definitely MRI. The ability to conduct a study in three mutually perpendicular projections (sagittal, axial and frontal) makes it possible to obtain additional information about the anatomy-topographic features and changes in the selayal area, more accurately determine the degree of involvement in the laateroselle structures. The lack of radiation load and the possibility of using this method is multiple times especially valuable for dynamic observation of pituitary tumors against the background of the treatment. Additional use of quantitative MRT parameters allows for clear differentiation between proliferative processes in a pituitary and cystic changes, to reliably prove the "empty" Turkish saddle.

Currently, various diagnostic markers of acromegaly (Table 4) have been applied in world practice. The main in the laboratory diagnosis is to study the secretion of growth hormone (somatotropic hormone, STG). Traditionally, the diagnosis of acromegaly is based on the identification of chronically elevated levels of this hormone. In the majority of patients with acromegaly, basal levels of growth hormone range from 5 to 40 ng / ml, in a very small percentage of cases reaching 100-300 ng / ml. At the same time, from 30 to 53% of patients, only a moderate or insignificant increase in the level of STGs have. Moreover, almost 17% of patients

with basal levels of growth hormone are within normal values. Studying the character of the secretion of STGs under acromegaly showed that it is distinguished by a pronounced pulsation: the same patient can be fixed in a rapid rise in the level of blood hormone level from 5-10 ng / ml to 50-80 ng / ml for 20-40 minutes . On the other hand, multiple measurements have shown that healthy persons also have similar pulsations, in particular, the basal levels of the STG range from 0.2 to 20-40 ng / ml (5-10 pulses per day). Moreover, it is often possible to see patients with clinical signs of active acromegaly, in which in the random broken blood sample, the level of the STG will be less than 1.5 ng / ml. In addition, there are a number of states and diseases in which there may be a false increase in the level of the HDS of an empty stomach. These include: pain, stress, insulin-dependent diabetes, chronic kidney disease, malnutrition, long starvation, etc. (Table 5). Considering the foregoing, the experimental value of the STG is not informative due to the frequent coincidence between healthy persons and patients with acromegaly. In other words, the one-time definition of the basal level of growth hormone cannot both confirm and eliminate the diagnosis of acromegaly, especially in cases of the so-called "soft" acromegaly, when there are minimal clinical manifestations of the disease.

STG:
- basal or random
- every 10 minutes within 24 hours
Test with thyaroliberin and somatolybering
IRF-1-binding protein-s
Somatolyberin in blood
STH in blood from lower cavernous sines
HDP in the Daughty urine

The optimal is frequent (every 10-20 minutes within 24 hours) determining the level of STH blood, which allows you to clearly differentiate healthy individuals from patients with acromegaly. Normally, 75% of the samples, the content of growth hormone is determined at the level of the lower limit of the sensitivity of the method, in 25% of the samples are allowed high values of the level of STG (secretory peaks at midnight, early morning clock). In the active stage of the acromegaly, the level of STG in serum is constantly increased within 24 hours. Integrated daily levels of growth hormone in each patient exceed normal values 2-100 times, and sometimes more. Unfortunately, this study is almost very difficult to fulfill

Table 5.

The reasons for the increase in hardware, not caused by the acromegaly

Pain
Pregnancy
Publit period
Stress
Chronic kidney disease
Diseases of the heart
Diabetes
Long fasting
Bad food, malnutrition

Currently, in everyday practice, the maximum propagation was obtained by the use of oral glucose-tolerant test (OGTT), since the reception of glucose (75 grams) causes a decrease in the level of STGs up to minimally determined in 94% of healthy individuals, but not in patients with acromegaly. When conducting a test, the blood fence is carried out on an empty stomach, as well as every 30 minutes within 2-3 hours after receiving glucose. At the active stage of the acromegaly, the test is considered positive if there is no reduction in the growth hormone below 1 ng / ml. This reaction is noted in most patients. Moreover, up to 30% of persons with this disease have a paradoxical rise of the level of STGs in response to hyperglycemia. The problem occurs when the test is carried out in patients with minimally pronounced clinical signs of acromegaly, basal level of STGs from 1 to z ng / ml. Thanks to technical progress, new "super-sensitive" techniques have been created, in particular immunoluminometric and fluorometric methods with sensitivity up to 0.005 ng / ml, actually defining the basal level of growth hormone in normal persons. Preliminary results in healthy persons showed that young women during the OGTT level of the HDP decreases below 0.2 ng / ml, in young men - below 0.1 ng / ml. Further expansion of research with the inclusion of patients with acromegaly will eventually allow the use of OGTT to diagnose "soft" acromegaly.

Currently, it is shown that the use of previously used test used with Tyrolyiberin (V / in 500 μg) does not carry additional information in the diagnosis of acromegaly. Moreover, Tyrolyberin can stimulate the emission of STGs in many people who do not suffer from acromegaly: with decomposed diabetes, starvation, kidney and liver diseases, depression, psychosis, many healthy young women. The test is recommended to apply in the postoperative period with doubts in the

radicality of surgical intervention. Obtaining test results similar to preoperative may indicate the presence of residual adenomatous tissue.

Somatolyberin test (100 μg in / c) is also not valuable both in the diagnosis of standard-producing adenomes and in the diagnosis of Somatolyberin ectopic products.

Relatively recently it was proposed to be used as a new "integrator" of the STG secretion, the value of the blood content of the IRF-1-binding protein-s, the production of which is induced simultaneously hormone growth and IRF-1. However, a number of studies indicate a partial coincidence of the results between the firstly identified patients with acromegaly and healthy persons. It is believed that the detection of elevated levels of IRF-1-binding protein-3 confirms the presence of Hyperproduction of STS in the patient, but the obtaining of normal levels of this protein does not exclude the diagnosis of acromegaly. Determining the level of this protein is recommended to be carried out in border cases when there is a combination of positive OGTT with respect to the suppression of STGs with a minimally elevated level of IRF-1.

The only indication of the Somatolyberin level in the blood serum is suspected of its ectopic products, which is based on the absence of MRI signs of the pituitary adenoma and the identification of volumetric education in the chest or abdominal cavity in a patient with a clinical picture of acromegaly. With a given disease, somatolyberin levels exceed 300 pg / ml, whereas in all other cases, including the hypothalamic hyperproduction of somatolyberin, its level is less than 50 pg / ml. The literature presents 50 cases of acromegaly due to ectopic products of somatolyberin.

It is also proposed to use the determination of the content of growth hormone in the night or daily urine. The studies indicate a good correlation between the data indicator and the content of STG and IRF-1 in the blood. Additional information is required regarding the reliability of this marker. Most likely, it will be useful as a screening test or monitoring the activity of the disease.

Determination of the content of STGs in the blood flowing from the lower cavernous sines is shown in cases where it is necessary to clarify the localization of microenomes due to the lack of its clear MRI signs, or in case of suspected pituitary hyperplasia. As a rule, combined with intravenous administration of somatolyberin.

According to many authors, the best diagnostic marker confirming the chronic hyperproduction of STGs is the level of IRF-1 in the blood plasma. Such a statement is based on a number of factors (Table).

Table

Advantages of IRF-1 as a diagnostic marker in comparison with STG

IRF-1 is ultimately responsible for most clinical manifestations of acromegaly	
IRF-1 level reflects the average level of STS for the previous day	IRF-1 level reflects the average level of STS for the previous day
IRF-1, unlike STG, is not subject to fluctuations for a short period of time due to the long period of half-life	
Even a slightly elevated level of STGs is accompanied by a high level of IRF-1	

Thus, in contrast to the level of hardware, a single definition of the IPF-1 level can actually be used for differential diagnosis of persons with normal and pathological secretion of STG. For the correct interpretation of the obtained IRF-1 level results, it is necessary to remember a number of provisions: 1 - the connection between the growth hormone and the IRF-1 is mutually logarithmic. In particular, at the level of STGs more than 20 ng / ml, the IRF-1 content curve is presented in the form of a "plateau". Perhaps this level of STG is as efficient in terms of liver ability to synthesize IRF-1. To a certain extent, this makes it possible to explain the similar activity of the disease with significantly distinguishing levels of STG; 2 - IRF-1 level depends on gender and age, as well as on the nature of nutrition. A false reduction in the level of IRF-1 (up to a normal value corresponding to this sex and age) is possible in case of malnutrition of any origin, starvation, severe liver diseases.

Currently, the international consensus has developed clear criteria for the exception of acromegaly (Table 7).

Table 7.

Criteria exclusion of acromegaly

Random level STG <ng / ml
Normal IRF-1
Minimum level of hardware on the backdrop of OGTT <1 ng / ml (2,7med / l)
The average integrated level of STS per day <2.5 but / ml

The diagnostic algorithm in order to determine the Far Medical Tactics also includes the determination of the level of prolactin to address the issue of the treatment of dopamine agonists; Determination of the function of peripheral endocrine glands to solve the issue of the need for substitution hormone therapy, as well as an assessment of the state of view, both acute and fields.

The differential diagnosis of acromegaly should be carried out with such diseases as the syndrome of multiple endocrine neoplasia (Men-1-syndrome), hypothyroidism, pachidermoperity, PEDGET disease, McCune-Albright syndrome, and acromegaloidism.

The clinical picture of acromegalia with the development of adenoma can be a manifestation of Men-1-syndrome, for which the presence of hormonally active parathyroid glands, islands of the pancreas, and sometimes tumors of the lungs. The identification of family cases of acromegaly also indicates the presence of Mainic Syndrome.

In hypothyroidism, the changes, skin, skin, voices are possible with acromegaly. The diagnosis is excluded when a decrease in the function of the thyroid gland is detected in combination with normal levels of STG.

A rare family disease, known as Paidermoperity, may be mistaken for acromegaly, as it is characterized by rude features of the face, thickening of the skin and hypertrophic osteoarthropathy. Identifying normal levels of STGs of both basal and when conducting functional tests, the absence of signs of the adenoma of the pituitary gland rejects the diagnosis of acromegaly.

In the disease of the Pedge, the proximal departments of long tubular bones are thickening, their arcuate curvature, an increase in the skull due to the thickening of the bones of the arch and base. However, there are no characteristic of the acromegal changes in the soft tissues, the region of the Turkish saddle, the normal content of the STG in the blood is determined. There is a minor number of persons with external similar signs of acromegaly in combination with a normal level of hardware. This is the so-called acromegaloidism.

For a rare McCune-Albright syndrome, in addition to the clinical picture of acromegaly, a specific triad is also characterized: a polystotic fibrous dysplasia, premature puberty, specific pigment spots of pale-coffee-colored.

TREATMENT

As the rich world experience of making patients with acrytale, all patients with a verified diagnosis, even with a very soft manifestation of the disease, except for

very rare cases, when there are related diseases that cause a severe patient's patient with an unfavorable life forecast should be treated and very active.

The main objectives of treatment are the elimination of clinical symptoms of the disease, the normalization of STG and IRF-1 secretion, the elimination of the source of excess production STGs (Table 8).

Table 8 Treats of acromegal treatment

Elimination of clinical symptoms of the disease
Normalization of STG and IRF-1 secretion
Elimination of the source of excess production STG

Currently, the main methods of treatment are surgical (in most cases transfenoidal and very rarely transcraniacadenectomy), drug and radial (Table 9).

Table 9.

Methods of treatment of acromegaly

1. Surgical (transcraniac and transpanenoidal identityectomy)
2. Rade (remote gamma therapy, protonotherapy, gamma knife)
3. Medical (somatostatin analogues, dopamine agonists, growth hormone receptor antagonists)

The main factors determining the treatment method are: a state of view, the size and nature of the growth of adenoma, the level of growth hormone, the age of the patient, the presence of concomitant pathology. Sometimes the doctor is forced to choose one or another type of treatment, given the desire of the patient (Table 10).

The effectiveness of treatment is estimated at a certain strict criteria established in May 2000 on the basis of a consensus of 68 leading neuroendocrinologists and neurosurgeons of the world (Table 11).

Currently, for estimating the effectiveness of long-term therapy, the consequence of the "safe" level of the STG is additionally introduced. The magnitude of this indicator was obtained as a result of an epidemiological multicenter retrospective study conducted on a cohort of 1362 patients with acromegaly. This study showed that if the level of STG after therapy was less than 2.5 ng / ml, the overall mortality rate was not different from that in the overall population.

Table 10.

The main factors determining the choice of treatment method

1. Condition of view
2. Dimensions and character of the growth of adenoma
3. Growth hormone level
4. The age of the patient
5. The presence of severe concomitant somatic violations
6. Patient desire

Standing adenomectomy is the primary method of treating acromegaly, especially in cases where there are signs of chiasmal syndrome, indicating the compression of the pituitary nerve tumor. The degree of vision reduction depends on the duration of the preceding compression of the visual nerves and the degree of severity of the atrophy of the disks.

The method of operational intervention is determined by the dimensions of the adenoma and the characteristics of its distribution.

The main advantage of operational intervention is the speed of the effect. In the case of a successful (radical) operation, the early postoperative period is noted normalization of the HPG response to the administration of glucose (a decrease of less than 1 ng / ml), as well as the normalization of the IRF-1 level in a few weeks.

Table 11.

Criteria of remission acromegaly

Remissance Criteria Remissions	Remissance Criteria Remissions
Full remission - Activity signs of activity	Full remission - Activity signs of activity
-Stong basal <2.5 but / ml	-Stong basal <2.5 but / ml
-Mimnal level of hardware on the backdrop of OGTT <1 ng / ml	-Mimnal level of hardware on the backdrop of OGTT <1 ng / ml

The results of operational intervention varies significantly and are determined by many factors. In particular, one of the main is the size and nature of the spread of the adenoma. Thus, the presence of an endosellalar localization tumor in a patient makes it possible to achieve remission in 78-88% of cases, while in the case of extrasellular adenoma, especially gigantic, this chance is practically reduced to zero (Table 12). The lack of effect on operational intervention can also be due to invasion into a solid brain shell of STG-producing adenomatous cells, the

frequency of which reaches 43%, with the occurrence of true relapse. Repeated operation is needed only if it is a real chance of complete disposal of the adenoma.

Significantly affects the outcome of the operational intervention, the degree of technical neurosurgical equipment, in particular the use of endoscopic control, neuronavigation; Intra processing hormonal analysis and MRI control, as well as experience, neurosurgeon qualifications (Table 13).

Table 12.

The results of transphenoidaladenectomy with acromegaly

Table 13.

Terms of successful operation

In the case of a qualified neurosurgeon, postoperative complications arise in less than 2% of cases. These include: visual disorders, meningitis, deadly outcome. Such complications as nasal lyingvorea, unacceptable diabetes, hyponituitarism, have no more than 5% of patients. If the surgical intervention is made by a surgeon of insufficient qualifications, the percentage of complications increases by 3-4 times. Considering the foregoing, all patients in the postoperative period need an additional examination in order to eliminate hypocituitarianism and, if necessary, in adequate and timely correction, as well as the control examination of a neurologist, an oculist and otolaryngologist, which is an important condition for further successful rehabilitation.

For almost 100 years, radiation therapy is used as a method for the treatment of pituitary diseases. For the first time Beclere A. in Paris, and GramaGna in Venice, in 1909, applied this type of treatment with acromegaly. The most common types of radiation therapy are gamma therapy and proton therapy. Traditional remote gamma therapy is carried out by a static or rotational method. Several irradiation fields are used: the front, oblique and two laterals in order to maximize the dose concentration in the field of pituitary and minimal in the surrounding tissues. The usual dose of irradiation is 45-50 Gray in the form of 25 fractional doses. Dose daily dose - 1.8 Gray 5 days a week for 5 weeks. Protonotherapy is carried out by a multiply-convergent method with 15-25 fields in the left temporal area by the method "Nutrole" in a dose of 50-80 Gray, as a rule in one session.

Previously used, currently these types of radiation therapy due to their significant drawbacks, on the one hand, and improving surgical techniques and types of drug therapy, on the other, occupy the third place in the treatment of acromegaly. The

main drawbacks are the first, the remoteness in the time they produce effects and, second, --- complications.

So, in the case of gamma therapy, the inhibiting effect on the STG and IRF-1 secretion arises no earlier than in 2 years from the moment of radiation. In particular, the "safe" level of STGs (less than 2.5 ng / ml) can be obtained in 36% of patients after 2 years from the moment of radiation, in 44% - after 5 years and in 59% of patients in 10 years. Regarding the normalization of the IRF-1 level, the following results were obtained: after 3 years - in 27% of patients, after 7 years - in 53% and after 10 years - 56% of persons. According to other data obtained in the analysis of the results of gamma therapy in 560 patients with observation periods from 5 to 15 years, the normalization of the IRF-1 level was achieved only in 199 people (36%). At the same time, in studies with a duration of the observation period of less than 7 years, the efficiency was 29% (61 people out of 210), with the duration of Katamneza for more than 10 years this indicator increases to 39% (138 people from 350). However, with an increase in time from the moment of radiation therapy, the number of monitoring patients, and the number of patients with a surveillance duration of 15-20 years is no more than a total, thereby limiting the ability to analyze. Moreover, patients without remission of the disease die prematurely, while for long-term observation, only patients are preserved for long-term criteria, which in turn creates a distorted, false optimistic opinion on the effectiveness of radiation therapy. In the case of protonotherapy, the beginning of the suppressive effect is observed in 6-8 months from the moment of irradiation, in terms of 3 to 8 years old in 46% of patients, a significant decrease in the level of hardening with its full normalization in 39% of persons.

Hypopituitarism is the most frequent, later complication of radiation therapy. It is assumed that this is a consequence of the defeat of the hypothalamus. All researchers indicate the emergence of newly identified cases of hypocituitarism in a significant number of patients. The frequency of this complication depends on the magnitude of the fractional dose (more than 2 Gray), as well as the preceding surgical intervention. The degree of hypocitutarism is positively correlated with the duration of the post-radiation period: after 10 years, 50-60% of patients have new manifestations of hypocituitarism, requiring the use of substitution hormone therapy.

In addition to the above complications with a lesser frequency, the brain vessels arises, which increases the risk of stroke 2-4 times and significantly increases the mortality rate compared both with the overall population and patients who have not received this type of treatment. Moreover, the dependences of this indicator from

the levels of STG and IRF-1, the size of the tumor, its distribution beyond the Turkish saddle or the presence of hypocituitarism is detected. In 1-2% of cases, the development of induced malignant brain tumors is possible, as well as the temporal epilepsy, the defeat of the visual nerves, the appearance of the "empty" syndrome of the Turkish saddle. There are assumptions that radiation therapy can lead to neuropsychological changes, violation of CNS cognitive functions: reduced memory, depression, etc. However, there is a sufficient amount of research using special psychometric tests in perfectly controlled patients on substitution hormone therapy, including growth hormone .

In connection with the foregoing indications for these types of treatment, it is very limited. Gamma therapy as the primary treatment method is applied only with the impossibility of adenomectomy due to the lack of a specialized neurosurgical service or a categorical refusal of the patient. As an additional method with aggressive pituitary tumors with invasion into the surrounding structures, including cavernous sines and even temporal fractions, in case of incomplete removal of adenoma, especially in combination with an unfavorable histological picture in order to suppress further cell proliferation and Hyperproduction of the STG. Protonotherapy is changing as a primary treatment method with a pituitary adenoma to 1.5 CV diameter in people to 55 years with relatively low activity (STG level of no more than 20 ng / ml).

Radiation therapy is also shown to patients resistant to therapy analogues of somatostatin, or when there are serious contraindications to these types of treatment.

Contraindications for carrying out radiation therapy are: 1) the close arrangement of the adenoma to the crossover of the visual nerves, especially in the presence of defects of the fields of view, since sweep therapy arises, capable of aggravating existing impairment of vision. In the presence of such an adenoma arrangement before the planned irradiation, perfect is the conduct of surgical treatment (adenomectomy) in order to remove the suprasellular tumor component; 2) the presence of the "empty" Turkish saddle.

Due to the deferred effect of radiation therapy after irradiation, all patients need to appoint drug therapy for a long period.

In recent years, it has found the application of a new method of radiation therapy Stereotactic radiosurgery (linear acceleration technique and gamma-knife).

Its mainly difference from remote gamma therapy - the ability to send a very large dose to a narrow focusing beam to a clearly bounded zone (plot), which

significantly reduces the number of complications and increases the efficiency of this type of radiation therapy. Thus, according to a number of researchers, the remission of the disease can be achieved in 54% of persons 6 years after irradiation. At the same time, the frequency of the development of hypocituitarianism does not exceed 7%. However, as shown by the analysis of the remote results of this type of irradiation in 270 patients in terms of observation from 6 months to 10 years, the normalization of the IP-1 level was achieved only in 90 patients (33%). A comparative analysis of similar cohort on the duration of the katamnese (from 2 to 10 years) indicates the practical identity of the result: 33% (77 of 232 people) in the group of patients who received stereotactic radiosurgery as a treatment method (99 of 341) in the group, Received gamma therapy. Further accumulation of experience is required to develop clear indications for this type of radiation therapy.

A feature of the state after radiation therapy is the development of post-empty hyperprolactinemia, the frequency of which in the case of gamma therapy is two times higher than after the proton therapy (52 and 23% of patients, respectively). The purpose of small doses of dosphamine agonists leads to the normalization of the content of prolactin.

Currently, three grams of drugs are used as drug treatment with acromegaly: dopamine agonists, long-term commercial analogues of somatostatin and anthonomists of growth hormone receptors.

Dopamine agonists are used in the treatment of patients with acromegalia since 1972 due to the ability to bind to the dopamine receptors of the 2nd type at the level of the pituitary gland and cause the suppression of the STG secretion from the part of patients with acromegaly. The accurate mechnas action remains unclear. As the 30-year-old clinical experience has shown, the most ancient dopamine-bromocriptine agonist is capable of calling the level of HDM less than 20% of patients and less than 10% of patients with the normalization of the IRF-1 level. Increasing the dose Preparations above 20 ng / ml does not cause an increase in its action. In addition, only single patients bromocriptine causes a slight decrease in the size of the pituitary tumor. Currently, practically does not apply in the global practice of treating acromegaly, especially as mototherapy.

The selective D2-dopamine agonistvinagolide (norprolac) compared with Bromocriptine has a more pronounced effect on the SHG suppression, as well as smaller side effects, due to the absence of stimulation of D1-dopamine receptor. The drug causes normalization of the level of STS and IRF-1 not more than 40% of

patients. Doses of preparation-0.3 mg per day (0.15 mg * 2 times a day), a dose increases to 0.6 mg per day.

The new dopamine agonist Kabergoline created in recent years has a longer period of action (up to -2 hours) and a much smaller number of side effects than quinagolide bomocripsis. In doses of 1 to 3.5 mg (on average - 1.75 mg) per week or 0.5 mg daily Cabergolin therapy causes a decrease in the level of IRF-1 in 47-67% of patients, and its normalization in 28-50% of cases . The maximum effect is noted in the case of a mixed pituitary aden (SGG and prolactin-secreting). The degree of the degree of functional activity of adenomv, in particular the original IRF-1 level. Studies have shown that the optimal effect is noted at the initial level of IRF-1 no more than 750n / ml. Unlike bromocriptine, Cabergolin therapy causes varying degrees a decrease in the size of the pituitary adenoma in 16-20% of cases, and in the presence of a mixed adenoma - up to 50% of the initial volume of the tumor.

Thus, the indication to the appointment of therapy with dopamine agonists is the presence of a mixed (STG-prolactin-secreted) pituitary adenoma with moderate functional activity. The drug can be recommended to patients who are not sensitive to somatostatin analogues or abandoned them. Possible combination of therapy with dopamine agonists with somatostatin analogues.

About 30 years ago, a hypothalamic factor was opened, which is a 14-amino acid cyclic peptide, regulating the secretion of growth hormone, named later than somatostatin. In addition to suppressing the secretion of growth hormone, somatostatin inhibits many physiological functions in other organs by autocrine, paracryne and / or nervous regulation, all the effects of somatostatin are carried out through specific membrane receptors. The presence of somatostatin receptors is demonstrated in many organs, in particular in various areas of the brain, adenogipophysis, pancreas, mucous membrane of the gastrointestinal tract, organs of the immune system. The ability of somatostatin inhibit the functional activity of various organs served to use it as a therapeutic agent under hyperfunction. In most human tumors formed from tissues and target organs for somatostatin, somatostatin receptors with high density are detected. 5 subtypes of somatostatin receptors are identified. In most stage-producing pituitary aden, the subtype of the 5th (up to 81%), subtypes of the 2nd and 3rd approximately in 45% of cases are expressed. Significantly met subtypes 1st and 4th.

The practical use of natural somatostatin is impossible in view of its very short half-life (less than a minute), as well as the occurrence of post-infusion hypersecrection of hormones of the ricochet effect.

Thanks to the successes of pharmacology, a long-term activity of natural somatostatin (octreotide, Lanreotide, Sandostatin-LAR) was created.

Octreotide (Sandostatin, SMS-201995) is the first analogue of somatostatin, used in clinical practice from the mid-1980s. It has a high affinity for Ksomatostatin receptors of the 2nd subtype, in its high-inhibiting activity exceeds a native hormone in 45 times. In a daily dose of 100 μg, 3 times a day subcutaneously causes normalization of the level of STG and IRF-1, respectively, in 50 and 40% of patients, significantly reducing the secretion of this hormone in 85% of patients. As a large number of studies have shown, an octreotide therapy leads to a rapid pronounced clinical effect. Improving the general condition occurs after a few days from the start of treatment. In 95% of patients significantly decreases the degree of manifestation of such clinical symptoms, as a headache, swelling sweating, arthralgia, general weakness.

In recent years, a prolonged form of octreotydasandostatin-LAR, as well as the Lanreotide (Somatulin) has been created. The conclusion of the medication into special microspheres from the poly-DL lactid-khikcolide-glucose polymer causes their features of pharmacokinetics, so that the amount of injections, unlike Sandostatina, is not three per day, and only 2-3 per month (30 mg in / m - one Injection) In the case of somatulin and one injection in 28 days (10-30 mg in / m) in the case of Sandostatin-LAR.

In the chemical structure of the Lanreotide, the presence of a group of 3- (2-NaFTYL) -D-ALA outside the ring led to a higher selectivity with respect to somatostatin receptors compared to nativesomatostatin and slow enzyme splitting. The duration of the PR lanereotide is achieved by means of the fact that the Lanreotide is placed on the surface and inside the biodegradable microspheres. Immediately after injection, the drug is released from the surface of the microspheres, which is accompanied by a rapid rise in the concentration of the Lanreotide in the blood 2 hours after the introduction and the subsequent slow decrease in its level for about 48 hours, then the gradual release of the Lanreotide from the microspheres occurs as they are biological decay, What is accompanied by a new climb of blood concentration and preservation of the hunch of at least 1 ng / l for the 9-14th day after injection.

When the sandostatin-lar is introduced, the concentration of the drug also fresses due to the release with the surfacerrofer, then decreases and remains at a low level for 7 days with a new level lift for 7 days, followed by the preservation of the high concentration of the drug for 28-42 days.

Therapy analogs of somatostatin leads to the opposite development of violations by the cardiovascular system: a significant regression of symptoms of acromegalicardiomyopathy, a decrease in systemic arterial hypertension, left-oscillage hypertrophy, improves functional hemodynamic parameters. The frequency of night apnea is reduced.

Treatment of somatostatin analogues also leads to a rapid improvement in the activities of the cardiovary pulmonary system during physical exertion, a decrease in the risk factors for cardiovascular diseases and a decrease in the thickness of intimamedia carotid arteries. Achieving a steadily normal level of IRF-1 and STG suppression below 1 ng / ml for 1 year Against the background of therapy Sandostatin-Lar leads to almost complete restoration of the myocardial function of the left ventricle.

One of the meaningful properties of the analogues of the somatostatin is their ability to cause a decrease in the size of the pituitary adenoma. Studies have shown that somatostatin inhibits the proliferation of both normal and tumor cells. The antiproliferative effect of somatostatin is associated with the activation of somatostatin receptors, while the various mechanisms are involved depending on the subtype and tissue-target, the cell cycle, and the induction of apoptosis. The activation of Somatostatin receptors of subtype 1, 2, 4, and 5 most likely leads to a violation of the cell cycle, while the subtype 3 - stimulates the processes of apoptosis. In addition, the antiproliferative effect of somatostatin may be due to its indirect effects on the products of growth factors. The invincon, the inhibitory effect of somatostatin on anti-genesis is not excluded. Thus, on several cellular models, a direct suppression of endothelium cell growth was demonstrated, the effect is possible by reducing the level of growth factor of the endothelium of vessels. Preliminary therapy of patients with octreotide leads to a decrease in the Ki 67 - nuclear protein index expressed only in mitotically active labels, which was found in an immunohistochemical study of remote adenomes and increases the number of cells in the G1 and M-period. This effect was absent in adenomas of patients who did not receive therapy with this drug in the preoperative period.

Reducing the dimensions of the pituitary adenoma is most likely due to the result of this antiproliferative action. A significant reduction in the size of the tumor is considered to be reduced by 10-25%. The results of the therapy of somatostatin analogues (sampling, somatulin and sandostatin-lar) 921 patients with acromegaly in 36 studies duration from 1 month to 4.5 years have shown a decrease in the size of the pituitary tumor in 382 people (42%). On average, the size of the tumor decreased by 50%. At the same time, patients who were in primary drug therapy

were 52% in patients. When applying the analogues of somatostatin as an additional therapy, the result is much worse: 21% (52 people out of 248). At the same time, only 20 of 921 patients (2.2%), an increase in the size of the tumor was noted. Thus, on the background of therapy, the analogues of moomastotathyathinetically in all patients (97.8% of cases) can prevent further tumor growth, and often reduce its size, which prevents possible complications due to the "mass effect" and is an essential argument in favor of the appointment of these drugs as medication therapy acromegaly. In assessing the possible prognostic factors for reducing the tumor size, a negative effect of previously conducted therapy is established, with such factors such as the initial volume of the tumor. Dynamics of hormonal indicators, scintigraphy data with labeled radioisotope, practically do not affect the degree of this effect.

A comparative assessment of the effectiveness of various analogues of somatostatin indicates the advantages of Sandostatin-LAR (octreotide-LAR) regarding the impact on the size of the tumor as as primary, so additional therapy.

Recent studies on the comparative efficacy of Lanreotidasandostin-LAR showed that the introduction of Sandostatin-Lar once every month is much more effectively in relation to the reduction in the level of STG IRF-1 than the Lanreotide 2-3 times a month.

So, in 3 independent studies it was shown that the therapy of sandosgatin-lar once 1 time per month in a dose of 20-30 mg is intramuscularly more effective in terms of SHG and IRF-1 suppression than somatulin in a dose of 30 mg intramuscularly 1 time in 7-14 days. In particular, in the work of N. Turner with co-authors in the treatment of 10 patients, it was shown that therapy of the Lanreotide leads to the normalization of the IRF-1 in patients, while Sandostapsh-Lar therapy increases this indicator to 70%. The average value of the STG was significantly lower on the therapy of sandostatin-LAR than the Lanreotide ($P = 0.037$) with a reliably higher maximum SHG suppression ($p < 0.02$). In the study of K. Cozzi with co-authors, 12 patients with acromegaly revealed the pronounced efficiency of somatulin therapy for 6-24 months with a significant decrease in the level of STG ($P < 0.02$) and IRF-1 ($p < 0.00001$) relative to the original . At the same time, the subsequent 6 months of therapy sandostatin-lar was given to a further significant decrease in these indicators ($p < 0.05$ in comparison with somatulin). In a multicenter European study, (R. Chanson et al.) That therapy of the Lanreotide 125 patients for an average of 27 months leads to the achievement of a safe level of STG (up to 2 ng / ml) and less than 1 ng / ml, respectively, in 54% and 14% of patients with increasing data of indicators up to 68% and 35%, respectively, on the background

of a 3-month-old level. The number of patients reached the normal level of IRF-1 increased from 48% to 65%.

Therapy analogs of somatostatin leads not only to a significant regression of clinical symptom of acromegaly, but also provides stable hormonal control.

Increasing the duration of therapy Sandostatin -LR for more than 3 years leads to an increase in the level of IRF-1 in 79% of persons, which completely coincides with the results of radical surgical treatment in the case of endosellala aden. A direct correlation dependence of the duration of therapy with analogues of somatostatin and the degree of decrease in IRF-1 was revealed. Moreover, it is not excluded that the long-term therapy of sandostatin-LAR can lead to a change in the biological activity of the HOL molecule.

Sandostatin-LAR therapy is recommended to be carried out according to a specific scheme.

In the process of treatment, such side effects such as diarrhea, meteorism, abdominal pain, steato seater, nausea can develop for a long-term analogues of somatostatin. Moreover, these effects are most pronounced in obtaining the first injection, with duration of treatment after 6 months, the frequency of side effects is reduced by 3-7 times. In addition, asymptomatic stones in the bustling bubble, stagnation of bile, the expansion of the bile duct can appear.

The effectiveness of therapy with analogues of somatostatin with acromegatia does not depend on the floor of the patient, the previous surgical or radiation treatment. In some studies, the best control was achieved in patients with low source hormonal indicators and / or in elderly patients. With the help of regressive analysis, it was shown that the level of STG / IRF-1, respectively, after 3-6 months of therapy is the most accurate prognostic factor for the final outcome of therapy, more accurate than the basal level of STG / IFR-1 prior to the start of therapy, the duration of observation or dose drug.

The main conditions for the effectiveness of treatment with analogues of somatostatinate the number and type (SSTR-2 and / or SSTR-5) of somatostatin receptors and resistance to the therapy can be due to mutations of these receptors. That is why patients who respond to the inhalation by one analogue of somatostatin, in most cases also respond well for treatment by another finish, although there are some exceptions. Studies on the visualization of the pituitary gland with the use of Staradio of the LameCTreotide did not reveal factors to predict the response to the treatment of somatostatin analogues.

Somatostatin analogues are currently the preparations of the first line in the medication treatment of acromegaly. It is used in the event of unsuccessful surgical intervention and radiation therapy as additional therapy, especially if the patient is insensitive to the therapy of dopamine agonists or they are absolutely contraindicated. Unlike dopamine agonists, they are effective means as the primary treatment method, especially in elderly, weakened patients. Finally, due to the ability to cause a reduction in the size of the pituitary tumor, they are an effective means of preoperative preparation (Table 15).

Table 15.

The possibilities of using Sandostatin-Lar with acromegaly

Preoperative preparation
Primary therapy of patients who refused operation or having contraindications
Therapy in the postoperative period in the event of the ineffectiveness of surgical treatment
Treatment of patients after radiation therapy before reaching its result

Since the beginning of 2000, a fundamentally new drug - Pegvisant (Somavert), which is a gential analogue of an endogenous growth hormone with 9 mutations, a growth hormone antagonist, entered the practice of treating acromegaly. The determining functional features of the Pegvisanta molecule is the replacement of glycine to alanine at position 120 in the binding area (site) 2, blocking binding with the receptor. At the same time, eight amino acid substitutions in the field of binding (site) 1 significantly increase affinity of the antagonist molecule to the receptor. Conformational changes arising due to this restructuring lead to a disorder of the binding of an antagonist molecule with a receptor, which in turn causes a violation of the receptor dimerization process and induction of synthesis and the IRF-1 secretion. This allows you to prevent the peripheral effects of an excess STG at the cellular level, regardless of the presence of somatostatin or dopamine receptors in the pituitary tumor.

Pegvisant therapy after 2 weeks from the moment of administration of the drug leads to a significant regression of clinical symptoms, a decrease in the level of IRF-1 by 75% of the initial, after 3 months to the normalization of this indicator in

82%, and in 12 months in 97% of patients with dose correction drug in the process of treatment.

One of the most important effects of Pegvisanta is its ability to correlate various metabolic disorders, which are always available in patients with acromegaly and are the main cause of their disability and increased mortality. In particular, this drug leads to the elimination of hyperinsulin and a decrease in insulin resistance, which is a factor in the risk of developing cardiovascular diseases. Pegvnesant restores lipid metabolism, as well as leptin levels and bone remodeling indicators.

Applied at a dose of 10-30 mg subcutaneously daily.

Side effects are minimal. Can manifest itself to redness at the injection site, minor nausea (up to L0% of patients). During the first month of treatment, there is a significant increase in the level of HTH in blood serum, correlating with a dose of the administered drug without a significant subsequent increase, despite the continuing therapy. There are data on isolated cases of minor continued growth of adenoma against the background of therapy with this drug, mainly in persons who have not received radiation therapy. There are instructions on 6 cases of a significant increase in transaminase level (ALT and AST) in a few weeks of therapy, while 4 patients have come spontaneous normalization of the ongoing pegging therapy by Pegvisanta, in 2 - normalization after discontinuation of treatment. Against the background of treatment in 7-16% of cases, antibodies are noted to STGs in a low titer, as well as antibodies to Pegvisanta, without a negative impact on the degree of normalization of IRF-1. Considering the above, when therapy is prescribed by Peregvisanta, control of the dimensions of the pituitary adenoma (1 time in 6 months), liver functions (1 time per month). Control of IRF-1 levels must be carried out every 4-6 weeks with a possible dose correction of the drug. The initial dose is 10 mg per day, the maximum daily dose of 30 mg.

Despite the high efficacy of the drug, due to the insufficient study of its safety and the action of the pituitary tumor, the testimony for its use is: 1-- Lack of efficiency of somatostat's analogues with a period of treatment by them at least 3 months; 2 - preservation of pronounced side effects after 6 or more months of therapy analogs of somatostatin, despite their clinical and hormonal efficiency. Summarizing the above, the algorithm for treating acromegaly can be represented in the form of the following scheme (Fig. 7).

Symptomatic therapy of acromegaly is determined in each particular case and depends on the nature of the degree of involvement in the pathological process of a particular body or body system (correction of changes from the cardiovascular

system, musculoskeletal system, metabolic disorders, treatment of radiation therapy complications).

The forecast depends on the timeliness of identifying the success of the treatment of acromegaly.

Prevention of this disease does not exist.