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Basic Mechanisms of Development, Diagnosis and Treatment of Acromegaly

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Abstract: Acromegaly is a serious disorder caused by excess production of somatotropic hormone (STH) due to pituitary tumour. This leads to increased production of insulin-like growth factor 1 (IGF-1) by the liver, resulting in tissue effects of STH. Tumour size plays a role in hormone control, with larger tumours responding worse to treatment. In about 70-80% of patients with acromegaly, the tumour extends beyond the Turkish saddle, making treatment more difficult. Excess production of STH and IGF-1 has deleterious effects on the body, affecting systemic, metabolic and potentially leading to neoplastic consequences. These factors contribute to reduced life expectancy and mortality, which is 2-3 times higher in patients with acromegaly.

Acromegaly is a neuroendocrine disease caused by excessive secretion of growth hormone (somatotropin) in individuals who have not completed their normal growth. It results in abnormal growth of bones, cartilage, soft tissues, and internal organs, as well as disruptions in cardiovascular, pulmonary, endocrine, and metabolic functions.

Gigantism, on the other hand, is a neuroendocrine disease caused by excessive growth hormone secretion in children and adolescents, leading to proportional growth of skeletal bones and significant increase in height. If not treated in a timely manner, individuals with gigantism may develop symptoms of acromegaly after puberty. Both conditions are characterized by the excessive secretion of growth hormone and the subsequent effects on the body's growth and functioning.

Epidemiology. Acromegaly is a rare hormonal disorder that primarily affects individuals between the ages of 20 and 40, but can occur at any age. The prevalence of acromegaly is estimated to be around 50-70 cases per 1 million population, with 3-4 recurrences each year. However, determining the exact prevalence rate is challenging due to the variability in the time it takes to diagnose the disease, which can range from 5 to 15 years. While the incidence of acromegaly does not show clear gender differences, women may have a higher predisposition to the condition. Many patients experience a sudden onset of symptoms, despite being in good health. Risk factors associated with acromegaly include a history of head trauma, multiple abortions and childbirth in women, as well as chronic sinusitis and otitis media. Acromegaly can lead to progressive disability and a shortened life expectancy, with a mortality rate ten times higher than the general population. Complications such as cardiovascular disease, diabetes, respiratory problems, and gastrointestinal malignancies contribute to this increased mortality. However, early diagnosis and appropriate treatment can significantly reduce mortality by 2-5 times.

Classification. The most common classification is according to the etiological principle.

In addition, according to the degree of activity distinguish:

active stage (phase) of the disease;

stage (phase) of remission.

By the nature of the course distinguish:

progressive; torpid.

Etiology and pathogenesis. Chronic growth hormone overproduction is commonly caused by pituitary adenomas, with various subtypes identified through analysis. The development of these adenomas involves genetic alterations that result in the unregulated expansion of mutated cells. Hypothalamic hormones and local growth factors contribute to further growth. One specific activating mutation found in somatotropic adenomas is a mutation in the alpha subunit of the G-protein, leading to autonomous growth hormone secretion and hyperplasia. Other genetic mutations, such as in the RAS alpha isoform and PTTG oncogene, may also contribute to pituitary tumor growth. Loss or alteration of tumor suppressor genes can initiate tumor cell growth. In some cases, acromegaly and gigantism can be caused by ectopic secretion of growth hormone or somatoliberin from tumors in various locations. Inherited syndromes can also be associated with acromegaly. Pituitary tumors come in different sizes, ranging from microadenoma to macroadenoma, with various subtypes.

Clinic - Acromegaly is a complex disease affecting multiple organs and systems, resulting in a variety of clinical symptoms. One of the most noticeable changes is physical transformation with enlargement of facial features and limbs. Patients may experience paresthesias, carpal tunnel syndrome and headaches. Other effects include increased sweating, acne, and changes in peripheral nerves. Despite increased muscle mass, patients often experience rapid fatigue and weakness. Joint and spinal pain associated with the development of arthropathies is common. X-rays show degenerative changes in the joints. Other symptoms include thickening of the vocal cords, low voice, hirsutism and impaired lactation in women. Men may experience decreased libido and potency. Visual disturbances may occur due to optic nerve compression. Cardiovascular complications such as arterial hypertension and cardiomegaly are common. Lung damage, restrictive lung disease, and increased mortality from respiratory disease are also risks. Metabolic disorders, including diabetes mellitus, may occur. Overall, acromegaly has a wide range of symptoms and potential complications affecting various body systems.

A **diagnosis** of pituitary adenoma requires specialized tests to confirm the condition. Skull x-rays are used to detect signs of a pituitary tumor, while the thickness of soft tissues in the foot can indicate levels of STH hormone. CT or MRI scans provide detailed images of the pituitary adenoma and its surrounding structures. Laboratory evaluation of STH secretion is crucial, with fasting STH levels often elevated in acromegaly cases. Regular monitoring of blood STH levels is recommended to differentiate healthy individuals from acromegaly patients. Alternative diagnostic methods include measuring blood levels of STH and IGF-1, as well as an ophthalmologist examination of the eye fundus. Confirmation of the diagnosis requires STH levels above 0.4 ng/mL in the basal state and above 1 ng/mL during an oral glucose tolerance test, with elevated IGF-1 levels relative to age and sex. Additional investigations may include measuring other hormone levels, ultrasounds of the thyroid and pelvic organs, chest radiography, ECG, ECHO, glycemic profile, and blood biochemical analysis. In cases of suspected ectopic STH production, MRI or CT scans of the thoracic and abdominal organs are necessary.

Treatment for acromegaly is essential for all patients, regardless of the severity of symptoms. The main goals of treatment are to alleviate symptoms, normalize growth hormone secretion, and eliminate the excess production of growth hormone. Various treatment options are available, including surgery, radiation therapy, and medication. The choice of treatment depends on factors such as the patient's vision, adenoma size, growth hormone levels, age, presence of other diseases, and patient preference.

A study found that if post-treatment growth hormone (GH) levels were less than 2.5 ng/mL, the mortality rate was similar to that of the general population. Adenomectomy, specifically for cases of optic nerve compression, is the primary treatment for acromegaly. Visual recovery depends on the duration and severity of compression. Successful surgery can lead to normalization of GH and IRF-1 levels. The success of surgical interventions depends on factors like adenoma size and spread. Skilled neurosurgeons who utilize techniques like endoscopic monitoring and neuronavigation have lower

complication rates. Postoperative follow-up with specialists like neurologists, ophthalmologists, and otolaryngologists is crucial for successful rehabilitation and correction of complications.

Radiation therapy has been a treatment option for pituitary gland diseases for a long time. Two common types of radiation therapy are gamma therapy and proton therapy. Gamma therapy concentrates radiation on the pituitary gland area while minimizing damage to surrounding tissues, and is used when surgery is not possible. Proton therapy, on the other hand, is the primary treatment for pituitary adenomas in younger patients with smaller tumors. Radiation therapy may also be used for patients who cannot be treated with somatostatin analogs. However, radiation therapy has some contraindications such as proximity to the optic nerve junction or an empty Turkish saddle. Long-term drug therapy is needed after radiation therapy. Another form of radiation therapy called stereotactic radiosurgery delivers a high dose of radiation to a specific area, reducing complications. Hyperprolactinemia is a common side effect of radiation therapy but can be managed with dopamine agonists. In acromegaly treatment, three classes of drugs are used: dopamine agonists, somatostatin analogs, and growth hormone receptor antagonists. Dopamine agonists have been used since 1972 but have limited success in normalizing hormone levels or reducing tumor size. Currently, bromcriptine is rarely used in acromegaly treatment.

Conclusion. Excessive production of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) can have detrimental effects on the body, leading to systemic and metabolic issues as well as potential neoplastic consequences. This condition, known as acromegaly, reduces life expectancy and increases mortality rates. Treatment for acromegaly usually involves taking medications to lower growth hormone levels, surgical removal of the pituitary tumor, or inhibiting its growth, depending on the severity and cause of the disease. The effectiveness of therapy is evaluated by monitoring the levels of growth hormone and IGF-1 at regular intervals, as well as conducting MRI scans after specific time periods. Since acromegaly cannot be prevented, timely detection and successful treatment are crucial for a favorable prognosis.

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